THE SIGNIFICANCE OF PAIN IN KNEE JOINT LOADING DURING WALKING

PhD Thesis by Marius Henriksen
The Parker Institute
Frederiksberg Hospital
Denmark

This thesis is submitted for the degree of Doctor of Philosophy (Ph.D.) at
The International Doctoral School in Biomedical Science and Engineering
at
Aalborg University
Denmark
December 2006

PREFACE

The present thesis is based on three papers listed below (referred to by roman numerals in the text). The original papers are attached. The studies have all been carried out at The Parker Institute and The Laboratory of Functional Anatomy, The Institute of Medical Anatomy ,University of Copenhagen during the period from 2004-2007.

I

Henriksen M, Simonsen EB, Graven-Nielsen T, Lund H, Danneskiold-Samsøe B, Bliddal H
Impulse-forces during walking are not increased in patients with knee osteoarthritis. *Acta Orthopaedica* 2006; 77(4): 650-656.

II

Henriksen M, Simonsen EB, Alkjær T, Lund H, Graven-Nielsen T, Danneskiold-Samsøe B, Bliddal H
Increased joint loads during walking – A consequence of pain relief in knee osteoarthritis. *The Knee* 2006; 13: 445-450.

III

Henriksen M. Alkjær T, Lund H, Simonsen EB, Graven-Nielsen T, Danneskiold-Samsøe B, Bliddal H
Experimental quadriceps muscle pain impairs knee joint control during walking. *Submitted*

ACKNOWLEDGEMENTS

The making of this PhD thesis has been a challenging, exciting and educational experience, which would have been impossible without the help and support from many people, whom I would like to thank.

First of all I would like to express my gratitude to my supervisor and mentor *Hans Lund* for his never ending enthusiastic help, supervision and belief in my success. Our discussions on all aspects of science have been invaluable in my time as a Master and PhD student. Even in the most frustrating and discouraging periods of my work, *Hans* has been a source of encouragement and renewed hope. A special expression of gratitude also goes to the director of The Parker Institute, *professor, dr. med. Bente Danneskiold-Samsøe* for giving me the opportunity to pursue my goals. The efforts of *professor, dr. med. Bente Danneskiold-Samsøe* have provided me the optimal conditions and facilities to conclude my thesis. Also *professor, dr. med. Henning Bliddal* deserves a special acknowledgement for his seemingly endless wisdom in all scientific, medical and related disciplines, which I have benefited from on many occasions.

My thankfulness also goes to *Erik B. Simonsen* for inviting me in to *The Laboratory for Functional Anatomy, Biomechanics and Motor Control,* which has been the framework for the experimental part of this thesis. *Erik B. Simonsen* introduced me to the fascinating world of biomechanical movement analysis; my mission could not have been completed without his skilled and expert supervision. For her friendly and supportive aid in the dark basement of the Panum Institute and for exciting and interesting discussions *Tine Alkjær Eriksen* is thanked. *Tine* is always ready to lend me a hand in times of despair and her efforts are priceless. The completion of this thesis would not have been carried out with such efficiency without her personal and professional contributions. Although we are separated by geography, my supervisor at the Center for Sensory-Motor Interaction (SMI), Aalborg University, *Thomas Graven-Nielsen,* has shown great excitement and interest in my studies, and I want to thank him for this and for his valuable input.

The studies on which this thesis is based would have been impossible to perform without the generous financial support of *The Oak Foundation, Danish Physiotherapy Association, Copenhagen Hospital Corporation, The Danish Rheumatism Association* and *Sahva Legater* towards whom I am also very grateful. Similarly, none of the studies would have been conducted without the participation of my *patients* and *volunteers* – thank you all for your patience and tolerance.

Finally, my deepest admiration and love goes to my beautiful and loving wife *Lisbeth* and my princess daughter *Kamille* for bringing all the good things in life to my attention and for taking my mind off my work at home.

Thank you.

INTRODUCTION

The reasons why the interplay between the biomechanics of walking and pain / pain relief is of interest in the description of knee OA are several. Firstly, pain is the central symptom in knee OA (Felson 2005; Bellamy 2002; Creamer et al. 2000; McAlindon et al. 1993) and pain therapy is thus the aim in most treatments of the disease. Secondly, biomechanical joint loadings during walking are under strong suspicion as a pathogenetic factor in knee OA (Sharma et al. 2006; Felson et al. 2004). Thirdly, pain is a strong sensory input with the potential to alter the neuromuscular function as reflected in the biomechanical joint loadings. Finally, pain can be considered as having a protective function causing adaptive biomechanical changes in order to reduce potentially harmful and / or painful joint loadings and it is conceivable that the gait changes associated with knee OA are compensatory due to the pain.

Therefore, pain relief may act negatively on the underlying disease by decreasing or eliminating the protective signals, with subsequent inappropriately altered movement strategies; e.g. different joint mechanics during walking. Similarly, the experimental introduction of pain in an otherwise healthy subject may evoke compensatory changes in the locomotion pattern, which may be comparable to those observed in subjects suffering from "real" pain in e.g. knee OA patients. However, the effects of pain and pain relief on joint loadings during walking are not fully understood.

Hypotheses

The hypotheses of the thesis are:

- Patients with painful knee OA walk with altered knee joint loadings compared to healthy reference subjects.
- Knee joint pain relief in knee OA patients affects the joint loading during walking.
- Experimental muscle pain in healthy subjects affects the joint loading during walking.

Aims

The aims of this PhD project were:

1) To compare knee joint loadings in knee OA patients to those of a healthy reference group, 2) to evaluate the effect of local pain relief via intra-articular lidocaine injection on knee joint loadings in patients with knee OA and 3) to evaluate the effect of experimental quadriceps muscle pain on joint loadings in healthy subjects.

KNEE OSTEOARTHRITIS

Epidemiology

Osteoarthritis (OA) of the knee is the most common form of joint disease and the prevalence of both radiographically evident and symptomatic knee OA has been reported to be higher than 9.5% (corresponding to more than 300.000 persons in Denmark), with females having higher prevalence than males (11.4% vs. 6.8%) (Felson et al. 1987). The gender difference in prevalence has recently been emphasised in a meta-analyses, which provides evidence for a greater risk in females for prevalent and incident knee OA (Srikanth et al. 2005). The meta-analysis also reported that females tend to have more severe knee OA radiographically assessed than males and that the gender differences increase with age >55 years (Srikanth et al. 2005).

Of the three joint compartments that combine to form the knee joint (the lateral tibiofemoral compartment, the medial tibiofemoral compartment, and the patellofemoral compartment), the medial compartment is the most common site of knee OA (Ledingham et al. 1993), presumably as a reflection of the distribution of loading with the majority of the load being placed on this compartment (Schipplein et al. 1991).

Aetiology & Pathogenesis

The fundamental aetiology of knee OA is unknown, and it has been suggested that knee OA is the final common pathway in a group of overlapping disorders of diverse aetiologies, but with similar biological and clinical outcomes (Felson et al. 2000).

Pathogenetically, knee OA is characterised by structural changes in and around the knee joint. The predominant structural changes are the loss of cartilage and the formation of osteophytes. These changes are easily demonstrated radiographically, and objective measures of disease severity are based on the amount of joint space loss (a reflection of cartilage loss) and the presence of osteophytes (Kellgren et al. 1957). Furthermore, the subchondral bone scleroses in the early phases of OA and this process, possibly involving microfractures, has been suggested to be pathogenetic factors in the process of cartilage degeneration (Burr et al. 2003).

In addition to these structural “hard-tissue” changes, a number of changes in articular and periarticular soft-tissue occur with knee OA. These include synovial hyperplasia (Kristoffersen et al. 2006; D'Agostino et al. 2005; Abramson 2004) and joint effusions (de Miguel et al. 2006; D'Agostino et al. 2005). Although knee OA is not classified as an inflammatory disease, a common sign of knee OA is synovial inflammation (Abramson 2004), detected using ultrasonography

(Kristoffersen et al. 2006; D'Agostino et al. 2005). In addition, Magnetic Resonance imaging as well as arthroscopical inspection of the knee joint have also provided insights to the presence of inflammation in knee OA (Loeuille et al. 2005).

The clinical presentation of knee osteoarthritis

Symptoms

Pain is the most common and predominant feature of the clinical representation of knee OA (Felson 2005). According to the 1986 diagnostic criteria recommended by the American College of Rheumatism the presence of knee pain is required for the clinical diagnosis knee OA (Altman et al. 1986). Consequently, pain is the target for most treatment modalities, and their influence on the pain is the key factor in the evaluation of effect (Bellamy et al. 1997). The cartilage of the joint has no nerve supply and the origin of pain in knee OA is not clearly illuminated; the relationship of pain with other important physiological variables is worthy of investigation in order to establish a foundation for treatment optimisation.

Other clinical features of knee OA include *joint stiffness, swelling and deformation* (Hunter et al. 2006; Jackson et al. 2004).

Functional impairments

Knee OA is the single greatest cause of functional impairment among adults (Woolf et al. 2003). There are two types of physical functional measures: Individual subjective assessments of physical function (self-reported) and objective measures of performance. Self-reported measures of physical function specific to knee OA can be obtained via the Western Ontario and McMaster Osteoarthritis Index (WOMAC) (Bellamy et al. 1988). The Index is self-administered and using 24 questions assesses the three dimensions of pain (5 questions), disability (2 questions) and joint stiffness (17 questions) in knee (and hip) osteoarthritis. WOMAC is widely used in the evaluation of knee osteoarthritis and it is a valid, reliable and responsive measure of disease status (Roos et al. 1999), which has been used in diverse clinical and interventional environments (Bellamy 2002).

The objective measurements commonly used to assess functional status in knee OA, include the Six-Minute Walk Test (Guyatt et al. 1985) and Timed Up & Go Test (Podsiadlo et al. 1991). It has been shown that self-reported functional impairments are only moderately correlated to objective performance tests (Maly et al. 2006) indicating that different aspects of functional impairments are assessed by the subjective and objective measures.

A substantial number of knee OA patients (63%) report episodes of knee joint instability, such

as giving way, buckling etc. (Fitzgerald et al. 2004). Knee instability is a functional impairment not incorporated in the self-report based questionnaires, such as the WOMAC. It is indicated that knee instability is an important symptom of knee OA and that knee instability significantly impairs physical function beyond what can be explained by contributions of other impairments such as reduced muscle strength, pain and decreased range of motion (Fitzgerald et al. 2004). This indicates that the causes of functional impairments, such as knee instability, are not fully illuminated by standard clinical tests, and that detailed and objective evaluations of functional activities, such as walking, may provide valuable information on this matter.

Pain

The taxonomy subcommittee of the International Association for the Study of Pain (IASP) (Merskey et al. 1979) has defined pain as

> *"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."*

Important notes were made to this definition, namely that

> *"Pain is always subjective."* and further *"…(pain) is also always unpleasant and therefore also an emotional experience."*

Additionally it was noted that

> *"This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause."*

This means that there is a distinction between the sensation of pain and the neural activity in nociceptive afferents. Pain intensity is a subjective sensation, and a mismatch is not uncommon between the amount of pain (sensation) and the degree of injury or disease (nociception). Therefore, it is not surprising that pain intensity may be only weakly correlated to physiological variables in chronic pain conditions.

Nevertheless, pain is the cardinal symptom in knee OA, and pain intensity needs to be assessed in standardised and quantitative manners in both experimental and clinical research. In basic neurophysiological research, where the neural activity in the nociceptive afferents is of special interest, measurements of nociceptive activity in human experiments would require invasive test methods with various ethical problems attached to them. The acquisition of such data is practically impossible, and human experiments must therefore rely on the subjective rating of pain intensity.

Rating pain intensity

Pain intensity is usually measured using a Visual Analogue Scale (VAS) or a Verbal Rating Scale (VRS) (Huskisson 1974). These modalities have been compared and have been shown to be highly correlated (Ohnhaus et al. 1975; Woodforde et al. 1972), but it has been indicated that the VAS is a more precise tool for the reflection of the subjective sensation (Ohnhaus et al. 1975), and the usage of the VAS is the more common one.

Pain mechanisms in osteoarthritic knees

The nerve fibres carried by the articular nerves are group II, III and IV afferents and sympathetic efferents (Schaible et al. 1993). The group II afferents have corpuscular endings located in the capsule, ligaments, menisci and periostum; but not in the synovium and cartilage. The group III and IV afferents terminate in free nerve endings widely distributed throughout most of the articular tissues and constitute the articular nociceptive system, except for the cartilage per se (Johansson et al. 1991).

In the healthy joint, the group II afferents are mainly activated by non-noxious mechanical stimuli of the joint, whereas group III and IV afferents primarily are activated by noxious mechanical stimuli (Schaible et al. 1993). It should be noted that a significant proportion of the group III (24%) and IV (36%) afferents are so-called mechanoinsensitive fibres that are not activated by mechanical stimuli (neither noxious nor non-noxious) (Schaible et al. 1993). However, although joint afferents also mediate proprioception (Solomonow et al. 2001; Johansson et al. 1991), the main sensation that is ascribed to a joint is pain (Schaible et al. 1993).

Apart from pain originating from intracapsular structures, also periarticular tissue, e.g. muscles, can be the source of pain (Felson 2005). Similar to joint nociception, muscle pain is mediated by group III and IV muscle afferents (Graven-Nielsen et al. 2001; Mense 1993), and muscle pain is characterised as diffuse. However, periarticular involvement is often overlooked as the source of knee OA pain (Merritt 1989).

In the presence of joint inflammation, hyperalgesia and spontaneous pain (pain at rest) often develop, meaning that painful stimuli evoke stronger than normal pain, and that pain is perceived during stimuli that normally are insufficient to elicit pain. This is caused by peripheral sensitisation of the sensory units and by central sensitisation of spinal neurons (Schaible et al. 2002).

Peripheral sensitisation

Once joint inflammation is present, the joint group III and IV afferents develop a long-lasting sensitisation to mechanical stimuli, enhancing the afferent nociceptive input to the spinal cord. Importantly, enhanced responses are seen in both high-threshold and low-threshold nociceptive afferents (Schaible et al. 2002). This implies that movements within the physiological range of motion activate nociceptive afferents, and that physiological movements become painful in inflamed joints. An additional feature of group III and IV sensitisation is that many of them have been found to exhibit persistent discharges when the joint is kept in resting positions (Schaible et al. 1985). This provides the spinal cord with tonic afferent inputs, which may be the neural basis of pain during rest. Moreover, it has been shown that the proportion of group III and IV mechanoinsensitive receptors are "silent nociceptors", which become mechano-sensitive following inflammation, and thus the quantity of nociceptive input to the spinal cord is additionally increased (Schaible et al. 1993).

Central sensitisation

Plastic changes within the neural organisation of the spinal cord occur during development of joint inflammation (Schaible et al. 1993). This will ultimately lead to alterations in the spinal processing of the afferent inputs and in turn also cause changes in the spinal output (e.g. ascending signals and motor activity). The spinal cord neurons become hyperexcitable, causing increased responsiveness to noxious stimuli via lowered thresholds in the spinal neurons (Schaible et al. 2002). This leads to increased sensitivity or reduced thresholds to non-noxious pressure onto 1) the inflamed joint and, with some delay, 2) also onto adjacent and even remote non-inflamed tissue (e.g. ipsilateral muscles and even movements of the contralateral knee); the latter indicating that spinal neurons expand their receptive fields (Schaible et al. 1993). The increased excitability is due to long-term changes in the post-synaptic receptor sensitivity caused by ongoing barrage from group II, III and IV afferents (Schaible et al. 1993). These mechanisms indicate that the nociceptive input is amplified in the spinal cord when a joint is inflamed.

Nociceptor-motor interaction

The interaction between sensory input from the joints and the motor output to the muscles controlling the joint movements is not well understood. In the healthy subject the α-motor neurons are known only to be influenced weakly by joint afferents, whereas the effects of joint afferents on the γ-motor neuron system are so potent that even subtle joint mechanoreceptor activity induce

major changes in the muscle spindle responses (Solomonow et al. 2001; Johansson et al. 1991). However, it is generally agreed that joint pain always influences motor performance, and studies have shown that during joint inflammation, joint nociception have marked effects on the α-motor neurons (Schaible et al. 1993). However, no unequivocal data about the excitatory and inhibitory effects of nociception on the α-motor neurons have been reported.

The apparently potent effects of joint nociception on α- and γ-motor neurons makes it conceivable that an ongoing barrage of nociceptive input could be the neural basis of decreased muscle function and neuromuscular control seen in knee OA (Hortobagyi et al. 2005; Childs et al. 2004) and other painful knee joint disorders (Arvidsson et al. 1986).

Muscle pain has been shown to modulate motor neuron excitability (Schomburg et al. 1999; Johansson et al. 1993). Spatial facilitation occurs between group III, IV and Ib (mediated from Golgi tendon organs) afferents, and this facilitation may decrease the reflex sensitivity in agonistic muscles (Schomburg et al. 1999). Furthermore, it has been shown that the excitability of the spinal motor neuron pool (Le Pera et al. 2001; Wang et al. 1999) and cortical motor neurons (Le Pera et al. 2001) is decreased by experimental muscle pain. It has been proposed that the effects of muscle pain on muscle activity depend on the functional role of the painful muscle in the movement (Sterling et al. 2001; Lund et al. 1991). In the pain adaptation model, Lund et al. proposed that pain reduces muscle activity in muscles with synergistic function (Lund et al. 1991) and it has been shown that experimental muscle pain causes reorganisation of synergistic muscle activity during both dynamic and static contractions (Ervilha et al. 2005; Schulte et al. 2004). The synergistic inhibition indicates that central neural control mechanisms are involved in the altered motor activity and movement pattern. This is also indicated in studies of experimental muscle pain, where pain caused reduced maximal voluntary contraction forces without impairment of the contractile apparatus (Farina et al. 2005; Graven-Nielsen et al. 2002).

Current perspectives on biomechanical factors in knee OA

There is increasing agreement that knee OA is biomechanically driven (Andriacchi et al. 2004; Dieppe 2004) and caused by aberrant biomechanical factors acting on the knee within the context of a systemic susceptibility (Hunter et al. 2006; Andriacchi et al. 2006). The term ”biomechanics” refers to ”*the forces acting upon and within a biological structure and the effects produced by such forces*” (Nigg 1994). The fulcrum of the biomechanical factors in initiation and progression of the disease is joint loadings and it is generally accepted that joint loadings are in fact associated with the pathogenesis of knee OA (Andriacchi et al. 2006; Mundermann et al. 2005a; Mundermann et al. 2005c; Andriacchi et al. 2004; Felson et al. 2000; Sharma et al. 1998).

Joint loadings during walking

Knee joint loadings are largest, and thus potentially harmful to the knee, during weight bearing activities. Particularly the knee joint loadings during walking are of interest in this context, because walking is the most natural way of human locomotion and causes repetitive joint loadings. Walking is a biomechanical condition of relatively high loading, and its repetitive and cyclic nature associates it with the pathogenesis of knee OA (Andriacchi et al. 2006; Jackson et al. 2004; Hurwitz et al. 2001; Collins et al. 1989; Folman et al. 1986). Mechanical overload causes micro damage in the subchondral bone leading to bone remodelling (Burr 2004). This remodelling increases the bone density (Hurwitz et al. 2001; Hurwitz et al. 1998), thereby decreasing its efficiency as a shock absorber. Thus, the joint cartilage is subjected to increasing dynamic stresses as a consequence of repetitive, everyday physical activities and may suffer from gradual failure, which ultimately leads to the destruction of the tissue (Muir et al. 2006; Burr et al. 2003).

During walking, the knee joint is exposed to compressive loadings that can be separated into at least two different categories, depending on the origin of the loadings: 1) Rapidly applied *impulse-forces* occurring at heel strike, caused by the abrupt deceleration of the body’s centre of mass and 2) *dynamic joint loadings* generated by the combined forces of body weight, joint reaction forces and active muscular joint compression. Overweight is a significant factor in the development of knee OA (Felson et al. 1988) as well as symptoms in the established disease (Bliddal et al. 2006). However, experimental data are lacking on a possible specific influence of weight changes on joint forces and will not be addressed in this thesis.

In this thesis, the analysis of *impulse-forces* is focused on the events occurring during the first few milliseconds following heel strike, whereas the *dynamic joint loadings* are analysed during the entire stance phase of walking. In the following, the generation of impulse-forces and the dynamic

loadings and their relevance to knee OA will be discussed.

Impulse-forces

Excessive impulsive-forces in the knee joint have been suspected as a co-factor in the development and progression of knee OA (Burr et al. 2003; Gill et al. 2003; Radin et al. 1982; Radin et al. 1978; Radin et al. 1973; Simon et al. 1972). The impulse-forces that are generated at heel strike are caused by the impact of the foot with the ground and the subsequent vertical deceleration of the body mass. These forces travel rapidly up the musculoskeletal system as a mechanical shock wave, often referred to as the "heel strike transient" (Whittle 1999; Kim et al. 1994). The transmission of these forces results in peak forces in the lower extremity joints (Collins et al. 1989). The peak forces are typically estimated by accelerometry (because force and acceleration are synonymous) and the normal range of heel strike peak accelerations measured at the tibial tuberosity are reported as 1.5–3 *g* (*g* = units of gravity) during walking (Voloshin 1988; Folman et al. 1986). If these peak forces are of sufficient magnitude and repetition, they have been shown to contribute to the development of degenerative joint diseases in animal experiments (Radin et al. 1982; Radin et al. 1978). However, the only data available to illuminate the coherence between the impulsive forces and development of osteoarthritis are from animal experiments (Radin et al. 1982; Radin et al. 1978). No human studies have yet demonstrated excessive impulse-forces as a pathogenetic factor in development of human knee OA to support the theory.

Dynamic joint loadings

The dynamic joint loadings are caused by the simultaneous actions of soft tissue, dynamic muscle contractions and external loads during the entire gait cycle, and reaches maxima during the stance phase. The dynamic knee joint loadings are generated by the sum of 1) the tibiofemoral reaction forces, 2) the muscle forces and 3) the forces in ligaments and other soft tissue (Shelburne et al. 2006). The tibiofemoral reaction forces are external forces mainly generated by bodyweight, whereas the muscle forces are generated by the knee muscles contracting to either accelerate the femur or tibia with respect to each other or to stabilise the knee joint. The ligament and soft tissue forces are mainly tensile, and because none of the major ligaments are placed in parallel with the joint surfaces, the ligament tension will contribute to joint compression. The dynamic joint loadings are estimated and calculated from biomechanical models, and reports of tibiofemoral joint loadings during normal walking in healthy subjects range from 2.4 to 6 times bodyweight (Study II & III) (Shelburne et al. 2006; Thambyah et al. 2005; Taylor et al. 2004; Costigan et al. 2002;

Kuster et al. 1997; Morrison 1968). Similar to the impulse-forces, these dynamic joint loadings have been suggested involved in the development and progression of knee OA (Baliunas et al. 2002). For example, a prospective longitudinal study demonstrated that increases in the varus moment, which reflects the dynamic load on the medial compartment (see later and figure 1), predicted radiographic OA progression at the six year follow up in patients with medial compartment knee OA (Miyazaki et al. 2002).

Biomechanical factors that influence joint loadings during walking

Normal function of the knee joint requires a high degree of mobility while sustaining high loads during normal activities such as walking. Therefore, the knee joint is vulnerable to changes in anatomical alignment, mobility and / or loss of intrinsic soft-tissue stability (passive or active). Although the biomechanical factors are highly interdependent, the significance of the individual factors, namely anatomical alignment, passive soft-tissue stability (laxity), dynamic stability and joint dynamics, in development and progression of knee OA are reviewed in the following.

Anatomical alignment

Knee alignment is defined as the position of the knee in reference to the ankle and hip joints (Sharma et al. 2001) and can be quantified as the angle made by the intersection of the femoral and tibial mechanical axes (Sharma et al. 2000). A varus aligned knee joint is a knee with a medially measured angle of the above-mentioned intersection less than 180°. A valgus aligned knee has an angle greater than 180°. Normal knee joints have neutral or slight varus (<1.5°) alignment (Moreland et al. 1987). Once a knee joint is malaligned (either in varus or valgus) the mechanics of the joint changes (Sharma et al. 2001). The load-bearing axis is represented by a line drawn from the femoral head to mid ankle, and in a varus knee this line passes medial to the knee joint centre and a varus moment arm is created. In contrast, the load-bearing axis in a valgus knee passes lateral to the joint centre. Thus, anatomical malalignment is a determinant of joint loadings (Andriacchi 1994) and the severity of varus and valgus alignment is correlated to radiographical narrowing of the medial and lateral tibiofemoral joint spaces respectively (Sharma et al. 2001).

Malalignment is a common feature of knee OA (Felson et al. 2004) and it seems to create a vicious cycle of increasing joint loadings. In fact, several studies have shown that malalignment is a potent risk factor for progression of knee OA (Teichtahl et al. 2006; Sharma 2004; Jackson et al. 2004; Hurwitz et al. 2002; Cerejo et al. 2002; Wada et al. 2001; Sharma et al. 2001; Sharma et al. 2000; Kellgren et al. 1957).

Knee joint laxity

Knee joint laxity is defined as abnormal rotation or displacement of the tibia relative to the femur. Knee joint laxity can cause abrupt displacements of the articular surfaces and alter congruity with subsequent increased local shear and compressive forces. In an unloaded knee joint, knee stability is provided by the ligaments, capsule, menisci and other non-contractile soft-tissues (Sharma et al. 1999b; Hsieh et al. 1976). The functional role of passive knee joint laxity may be that during dynamic situations, such as the stance phase of walking, individuals with lax knees experience lateral (varus) thrusts, which have been identified as a risk factor for progression of medial knee OA (Chang et al. 2004). However, reports on laxity in knee OA are not uniform. Some have reported increased varus-valgus laxity but no antero-posterior laxity (Lewek et al. 2004a; Sharma et al. 1999a; Sharma et al. 1999b). Others report increased antero-posterior but no varus-valgus laxity (Wada et al. 1996) and even decreased laxity is reported (Brage et al. 1994). This diversity in reports may be because dynamic stability of a lax knee joint could be of greater importance in this matter than passive laxity itself.

Dynamic stability

Dynamic knee joint stability is defined as the joint stability provided by the interactions between ligaments, capsule and other soft-tissues, bony congruity and tibiofemoral compression caused by muscle activity, gravitational and inertial forces (Andriacchi et al. 2006; Sharma et al. 1999b; Louie et al. 1987; Shoemaker et al. 1985; Markolf et al. 1981; Hsieh et al. 1976; Wang et al. 1974).

Especially muscular activity, and the proper coordination hereof, is of importance in preservation of dynamic stability (Olmstead et al. 1986; Pope et al. 1979; Markolf et al. 1978) as well as intact sensory-motor function and proper levels of muscle strength and endurance. Altered muscle activation patterns (Childs et al. 2004), impairments of sensory-motor functions (Lund H. et al. 2004; Hortobagyi et al. 2004; Pai et al. 1997; Sharma et al. 1997; Marks et al. 1993; Barrett et al. 1991) and reduced voluntary isokinetic quadriceps muscle strength (Lewek et al. 2004b; Hurley et al. 1997; Fisher et al. 1997a) have been shown in patients with knee joint OA. Increased intra-articular pressure, due to joint effusion, has been proven a source of reduced neuromuscular function (Torry et al. 2000; Jensen et al. 1993; Geborek et al. 1989; Spencer et al. 1984; Stokes et al. 1984).

It is thus conceivable that knee OA patients have less ability to control the joint forces during

walking, and that the OA knee joint is more vulnerable to destabilising forces. Thereby, the knee joint structures may be exposed to more violent and potentially harmful forces.

Joint dynamics during walking

The structural and neuromuscular factors come together when complex movements such as walking are performed. Thus, the general walking pattern may reflect knee OA risk factors. The neuromuscular control of walking includes, among other things, proper activation of the muscles in order to control and absorb both the impulse-forces and the dynamic loadings.

This has been demonstrated in a study where inhibited quadriceps function, through experimental paralysis, caused increased impulsive ground reaction forces at heelstrike during walking (Jefferson et al. 1990). Further, muscular fatigue has been shown to increase the impulsive loading of the musculoskeletal system during running (Voloshin et al. 1998).

The varus moment during the stance phase has gained special interest. The knee varus moment is an external force caused by gravity trying to adduct the knee joint into a varus position (as displayed in figure 1). The varus moment during walking has been shown to be determinant for medial compartment compression (Schipplein et al. 1991) and has become a biomechanical marker for risk of progression of medial compartment OA (Andriacchi et al. 2006; Andriacchi et al. 2004). “Higher than normal” varus moments have been reported for severe knee OA patients (Hurwitz et al. 2002; Baliunas et al. 2002) and it has been shown that increases in the varus moment are associated with increased risks of loosing joint space (Miyazaki et al. 2002). Furthermore, joint loadings have been shown to influence cartilage metabolism in healthy

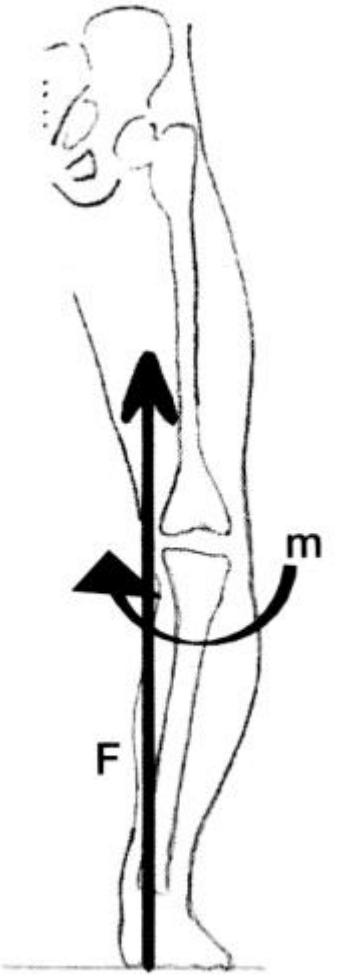


Figure 1. The varus moment (m) is a moment tending to adduct the tibia with respect to the femur, causing increased medial compartment compression. The varus moment may be estimated by means of the ground reaction force vector (F).

subjects, which provide additional support for the relationship between joint loadings and the biological response of cartilage to joint loadings (Mundermann et al. 2005b). Apart from the varus moment, other aberrant biomechanical variables during walking are present in knee OA. For example, reduced extensor moments in the stance phase are frequently observed (Kaufman et al. 2001; Fisher et al. 1997b) and altered mechanics of ankle and hip joints have also been reported (Mundermann et al. 2005a; McGibbon et al. 2002). It has been speculated that these changes in gait pattern are attempts to reduce the joint loadings. For example, reducing the knee joint extensor moments is an effective way of reducing joint loadings, since the extensor muscle force contributes significantly to the overall joint compression (Schipplein et al. 1991). However, reducing extensor moments is not costless because the knee extensor moment has been shown to have a significant role in the dynamic stability of the knee against varus deformations (Olmstead et al. 1986). Reduced extensor moments with unchanged varus moments may thus result in dynamic knee instability with unfavourable joint loadings as possible consequences.

Summary

Knee OA is a multi-factorial disease of epidemic-like proportions. The aetiology is basically unknown, but there is a general agreement (and accumulating evidence) that several aberrant biomechanical factors during walking are pathogenetic. However, the causal relationship between biomechanical factors and initiation and/or progression of knee OA remains to be fully clarified.

Knee OA is associated with a wide variety of symptoms, but among these, pain is the single most central one. Basic neurophysiological nociceptor-motor interactions have been described, while the link between knee osteoarthritic pain and biomechanics is not fully understood. Nevertheless, pain has the potential to affect the biomechanics of human movement, and this connection needs further investigation (Manetta et al. 2002).

METHODOLOGY

The biomechanical analysis of walking

In a gait analysis, the most interesting basic process is how the central nervous system adapts the motor performance of walking, and thereby alters the joint loadings, to knee OA and pain. This process is initiated as a neural activity in supraspinal centres, and ends in the generation of sequences of muscle activation patterns integrated with sensory feedback from muscles, joints and other receptors (e.g. nociceptors). Once the muscles are activated, tension develops which generates forces in, and moments about, the joints. These joint forces and moments either cause or resist movement of the skeletal segments and exert forces on the external environment. This approach is called a top-down approach and is based on a *cause-effect* relationship. In a gait analysis, the analyst estimates the *causes* based on measurements of the *effects*. The chain of events that must take place for walking to occur is illustrated in figure 2.

Because the goal of a gait analysis is to assess the *causes* of an observed walking pattern, measurements should be taken as high in the movement chain as possible. As the aim of the studies in this thesis is to evaluate knee joint loadings, the joint forces and moments generated

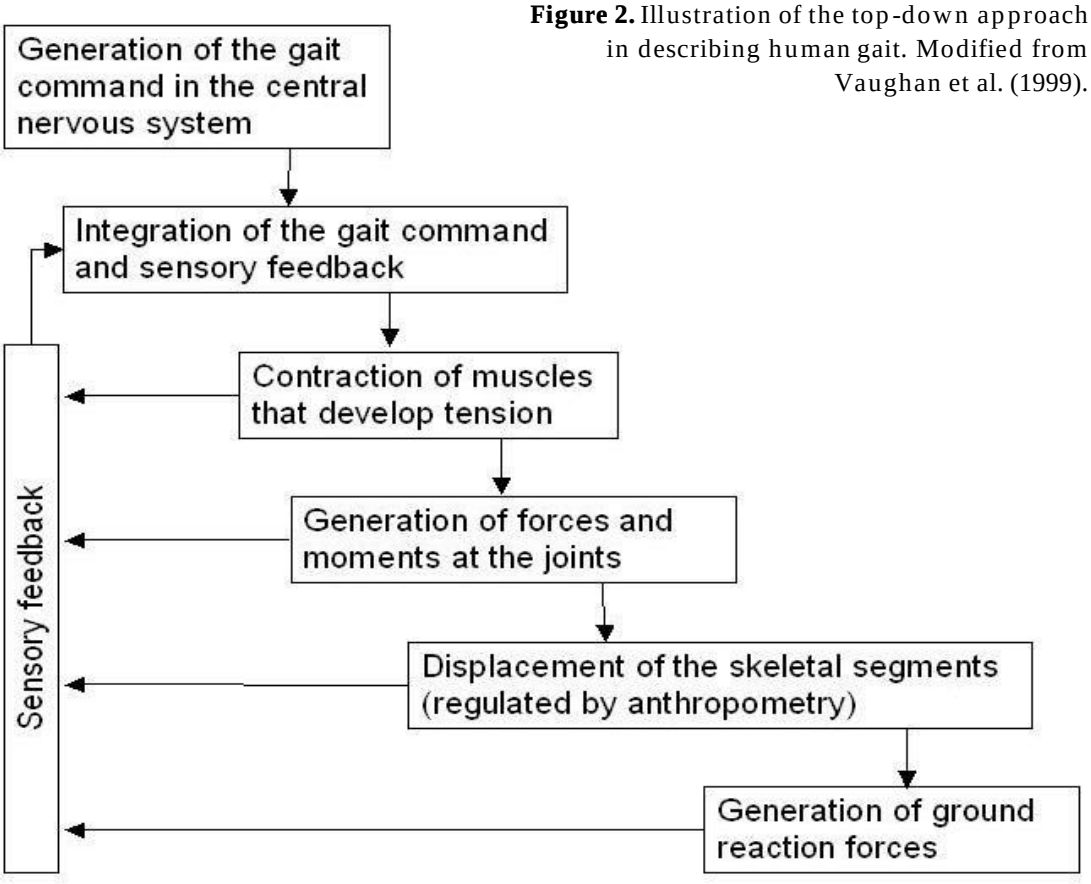


Figure 2. Illustration of the top-down approach in describing human gait. Modified from Vaughan et al. (1999).

during walking could be measured directly via transducers inserted into the joints. However, such measurements are fraught with methodological and ethical problems. This is why most gait analyses are based on an indirect approach called *inverse dynamics* (Nigg et al. 1994).

In inverse dynamics, the displacement of the lower extremity segments and ground reaction forces (*the effects*) are known in detail and the objective of the analysis is to determine the forces *causing* these effects. This is done by integration of body segment parameters (obtained by anthropometric measures), movement data (from video recordings) and ground reaction forces (from force platforms), yielding a biomechanical model of the walking subject. From the biomechanical model, three dimensional anatomical joint kinematics (joint angles) and dynamics (resultant joint forces and moments) can be calculated. A detailed description of the mathematics behind the analysis is not within the scope of this thesis but can be found elsewhere (Vaughan et al. 1999). A list of variables of interest extracted from gait analyses is given in table 1 at the end of this chapter.

The gait analysis procedure

In the experimental works of this thesis, the subjects were prepared for the gait analyses by placing reflective markers at anatomical landmarks on the subjects according to the marker set-up described by Vaughan et al. (Vaughan et al. 1999). During the walking trials, five digital video cameras recorded the movements. Two force platforms (OR6-5-1, AMTI, USA) measured the ground reaction forces. In Study I and II, all subjects walked at a predetermined walking speed of 4.0 km/h (~1.1 m/s). This speed was chosen as it was the average preferred walking speed of the participating patients. In Study III, the walking speed was fixed at 4.5 km/h (~1.25 m/s) as the study included healthy subjects alone. 4.5 km/h is considered within the range of normal walking speed (Andriacchi et al. 1977). The walking speed was measured by photocells, and a display provided the subjects with immediate visual feedback on their walking speed. The patients practiced the desired walking speed in several tests prior to the actual measurements.

EMG-assisted analysis

A limitation of inverse dynamics is that only the forces and moments exerted by muscle groups are assessed. If, however, the muscle activation pattern of specific muscles is to be assessed, electromyography (EMG) is needed in synchrony with the gait analysis. Such procedure is termed "EMG-assisted analysis", and was applied in Study III.

In synchrony with the gait analyses, surface EMG was recorded from the vastus medialis (VM),

vastus lateralis (VL), semitendinosus (ST) and biceps femoris (BF) muscles using a wireless EMG system (MQ8, Marq-Medical, Farum, Denmark).

The EMG signals were analysed by constructing linear envelopes (Winter 1990) normalised in amplitude to the EMG amplitude recorded during maximal isometric contractions. From the linear envelopes, peak and mean amplitudes were extracted as well as the integrated EMG in the following periods: during the 50 ms before heel strike, during the period of eccentric knee extensor muscle contraction and during the period of concentric knee extensor muscle contraction.

Gait analysis – outcomes and definitions

The Gait Cycle

The cyclic nature of the gait has brought about the term "the gait cycle", which is very useful for describing the temporal distribution of gait related events during walking. The gait cycle is basically divided into two main *phases*: The *stance* phase and the *swing* phase, which again is divided into phases named after the characterising events (Vaughan et al. 1999). Starting with the swing phase, the terminology most frequently used is:

1) Initial swing
2) Midswing
3) Terminal swing
4) Heel Strike
5) Loading response (or early single support)
6) Midstance
7) Terminal stance (or late single support)
8) Preswing
9) Toe Off

In Study I, only the heel strike events were analysed, whereas Study II focused on events taking place during the loading response and terminal stance phases. In Study III, the entire gait cycle was included, but emphasis was put on the loading response.

Joint angles

In this thesis, the sagittal plane joint angles were analysed. The reason for this was that the largest knee joint range of movement is in this plane. The joint kinematics have definitions equivalent to the anatomical definitions where a position of 0° reflects a fully extended knee joint and a neutral position of the hip joint. Negative joint angles express knee hyperextension, and

positive values reflect knee joint flexion. An illustrative example of the time course pattern of sagittal plane knee joint angles throughout a stance phase, including indications of events of interest in the stance phase, is shown in figure 3.

Forces and moments

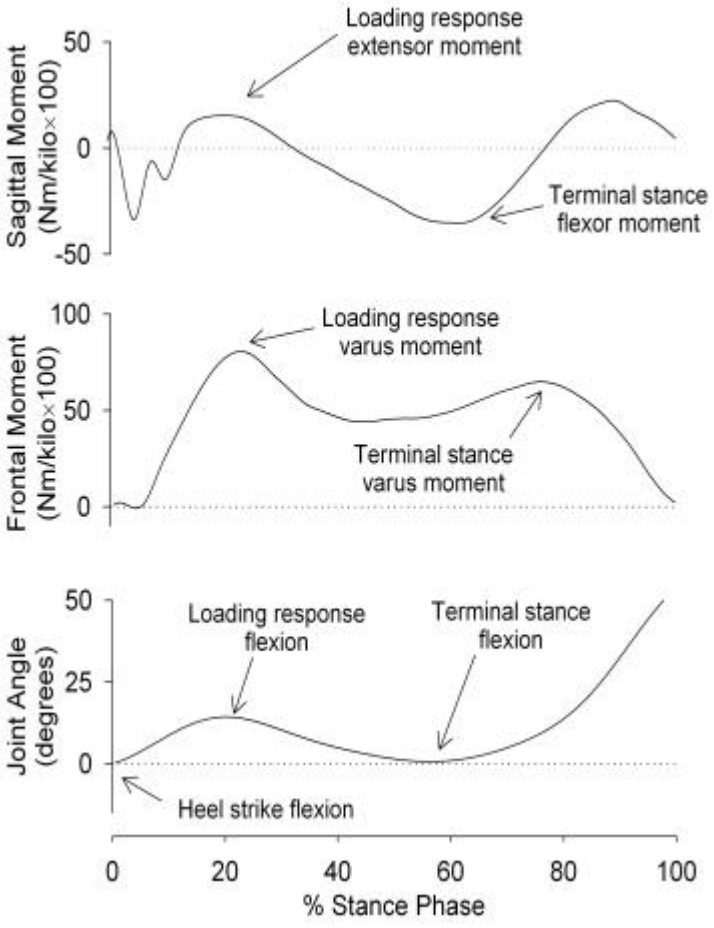
The joint forces and moments are particularly important because they provide insights into how the central nervous system adapts the function of the musculoskeletal system to compensate for any deficits.

Bearing in mind the top-down approach, the resultant joint moments are reflections of the moments generated by the muscles in order to achieve the observed movement, i.e. internally generated moments. However, due to differences in biomechanical approaches in the literature, confusion may occur as to whether the reported moments are generated internally or externally. To ensure clarity, attention is given to this matter in the following.

The rationale behind the usage of internal moments is the fact that movements are generated internally. Therefore a distinction between e.g. extens***or*** and extens***ion*** is important for the interpretation of the analysis. The extens***or*** is the internally generated moment, whereas the extens***ion*** is the externally generated moment. In this thesis the internal moments (i.e. –***or***) are reported.

One exception is the frontal plane knee joint moment, because no muscles can generate isolated abduct***or*** or adduct***or*** moment about the knee of significant magnitude (Shelburne et al. 2006). Perhaps this is why this moment is generally being reported as the external moment (-***ion***). To prevent confusion and facilitate readability, the

Figure 3. Illustration of typical time-course patterns of sagittal plane moment (top), frontal plane moments (middle) and knee joint angles (bottom).



frontal plane will be reported as varus / valgus moments in stead of internal abductor / adductor or external adduction / abduction. Thus, a varus moment = internal abductor moment = an external adduction moment and a valgus moment = an internal adductor moment = an external abduction moment.

The polarities of the moments are defined as follows:

In the sagittal plane, positive values represent net extensor moments and negative values represent net flexor moments. In the frontal plane, positive values represent net varus moments and negative values represent net valgus moments.

All joint moments were expressed as a percentage of the subject's bodyweight (Nm / kg×100) and it should be emphasised that the reported moments are net moments. This means that simultaneous exertion of muscle activity of e.g. flexor and extensor muscles will yield the resultant moment, i.e. the difference or the dominant moment, if any (Winter 1990).

Illustrative examples of the sagittal and frontal plane knee joint moments throughout a stance phase, including indications of the stance phase events of interest, are shown in figure 3.

As with all continuous data, there are inherent problems in extracting single measures for statistical analyses. Thus, turning points in the time-moment curves are extracted and used for statistical analyses and brief definitions of the extracted variables are given in table 1.

Estimation of impulse-forces

The impulsive forces are seen as a short spike of force in ground reaction force (GRF), immediately following the initial contact of the foot with the ground (see figure 4). This spike is called *the impulsive ground reaction force* (iGRF).

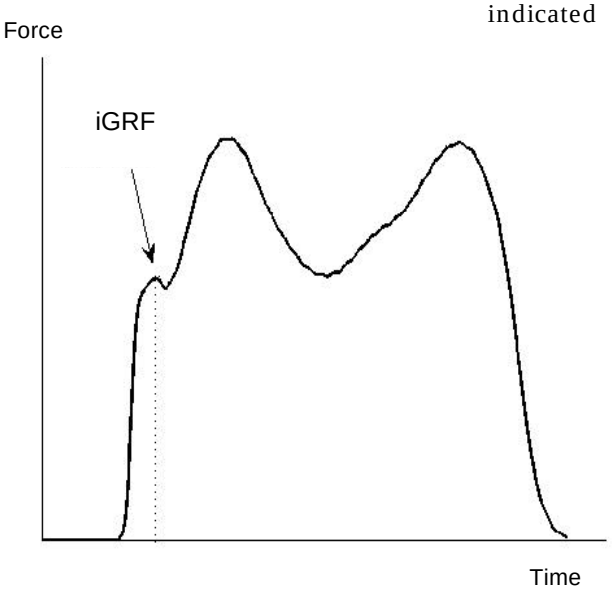
Because the iGRF is a reflection of an abrupt deceleration of the body, the subsequent mechanical shock wave can be assessed at higher levels of the body by means of body-mounted accelerometers as distinct peaks in the acceleration traces, called *shock wave accelerations*.

Measurement of impulsive Ground Reaction Forces (iGRF)

To assess the iGRF, the subjects of Study I walked across two force platforms (AMTI, OR6-5) mounted in the concrete floor in the basement of the building. The platforms measured three-dimensional ground reaction forces (GRF) at 1000 Hz, and tests showed that 90% of the frequency spectrum was contained between 0-28 Hz and 99% between 0-42 Hz. Thus, the selected sampling frequency of 1000 Hz was considered adequate and has previously been used to record iGRF (Gill et al. 2003).

Because the trajectory of the body's centre of gravity in the terminal swing phase is not necessarily vertical, but also has an antero-posterior component, the impulse force spike can be observed in both the vertical and antero-posterior ground reaction forces. By combining the force vectors from the antero-posterior and vertical directions, a sagittal plane GRF vector is constructed and the impulsive ground reaction force (iGRF) can be measured as the magnitude of the transient peak occurring a few ms following heel strike (see Figure 4). The iGRF was normalised to percentage of body mass and expressed in N / kg×100.

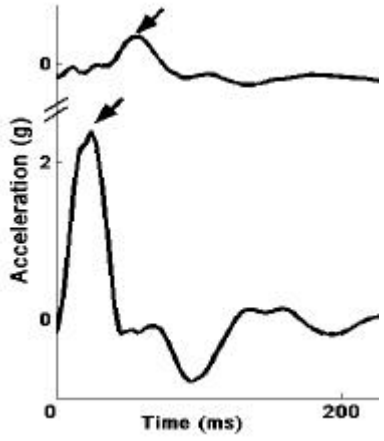
Figure 4. Illustration of the sagittal plane ground reaction force vector with the impulsive ground reaction force spike (iGRF)force spike indicated



Assessment of the shock wave

The most common way of evaluating the shock wave's transmission up through the musculoskeletal system is by using accelerometry. In previous studies, accelerometers have been attached to anatomical landmarks, either bone- or skin-mounted, the latter being the most preferable when considering ethical and practical circumstances. Most researchers have applied at least two accelerometers to evaluate the attenuation of the shockwave between two anatomical points (Flynn et al. 2004; Derrick et al. 2002; Mercer et al. 2002; Mizrahi et al. 2000; Voloshin et al. 1998; Johnson 1990). The most common accelerometer placements are at anatomical landmarks with superficial bony prominences. This is in order to diminish the contribution to the signal from soft tissue vibrations (Helliwell et al. 1989; Voloshin 1988; Pratt 1988; Johnson 1986; Wosk et al. 1985; Voloshin et al. 1982; Wosk et al. 1981; Voloshin et al. 1981a; Voloshin et al. 1981b).

Figure 5. Acceleration traces from the sacral (top) and tibial (bottom) accelerometers during the first 225 ms of stance. Arrows indicate the peak values extracted for analysis.



In Study I, linear accelerations in units of gravity (*g*) were measured at the tibial tuberosity and at the sacrum, using miniature tri-axial piezoresistent accelerometers (ADXL210E, Analogue Devices, USA) with natural frequencies between 75-100 Hz similar to previous reports (Shorten et al. 1992). The

tibial accelerometer was mounted with the vertical sensing axis aligned to the longitudinal axis of the tibia. The sacral accelerometer was mounted on the skin at S2-level, with the vertical sensing axis aligned to the cranio-caudal axis of the sacrum. Elastic Velcro straps, tightened to the subjects' limit of tolerance, were used to reduce vibrations from skin and soft tissue. The acceleration signals were recorded at 250 Hz. Previous investigations of skin-mounted accelerometers have shown that the heel strike shock wave accelerations during walking usually contains frequency components in the range of 25-30 Hz (Wosk et al. 1981), and skin mounted accelerometers have been proven a suitable tool for providing accuracy in the studies of mechanical signals resulting from heel strikes (Kim et al. 1993).

The static gravitational acceleration was removed from the tibial acceleration signal by calculating the 3D inclination of the tibia using Euler angles obtained from the gait analysis. The sacral acceleration signal was corrected for the gravitational component using an algorithm previously reported (Moe-Nilssen 1998a). Thus, dynamic accelerations along the longitudinal axis of the tibia and the cranio-caudal axis of the sacrum were obtained (see figure 5).

To asses the propagation of the shock wave caused by heel strike, peak accelerations of the corrected tibia and sacrum acceleration signals in a 100 ms window following heel strike were extracted Peak accelerations are reported in units of gravity (*g*).

Estimation of dynamic joint loadings

To assess the knee joint compressive forces, a previously published biomechanical model (Schipplein et al. 1991) was applied. The model assesses if the overall knee compression forces are sufficient to balance the varus moment, thereby keeping the joint closed laterally (figure 6). The overall knee compression forces are calculated as the vector sum of **a)** the intersegmental reaction forces resolved along the long axis of the tibia, **b)** the compression components of the active muscle group forces and **c)** the axial cruciate ligament forces. The hamstring and gastrocnemius complex constituted a flexor muscle group active when the sagittal knee joint moment favoured the flexors (i.e. negative moment) and the quadriceps muscle represented an extensor muscle group active when the sagittal moment favoured extensors (i.e. positive moment). The muscle forces were calculated by combining the sagittal plane joint moments with the muscle moment arms derived from a polynomium relating the knee joint angle to the muscle moment arms (Draganich et al. 1987). The axial cruciate ligament forces were estimated under the assumption that the cruciates only resist antero-posterior shear forces. The medio-lateral position of the tibio-femoral contact point is fixed at 25% of the knee joint diameter from the knee joint centre (Schipplein et al. 1991).

As long as the overall knee compression forces resist the frontal plane moment, no tension in lateral soft tissue is required, otherwise appropriate lateral tissue tension is introduced to avoid lateral joint opening. Lateral soft tissue tension indicates that the medial joint compartment supports all joint forces. The predicted values are presented as a proportion of bodyweight.

Limitations to this model must be considered. The model does not account for antagonistic muscle activity or differences in activation levels within the agonist muscle groups. Furthermore, the input parameters are derived from an inverse dynamics calculation, i.e. net moments. Thus, the predicted forces represent the lower boundaries. Another limitation may be that the cruciate ligaments only resist antero-posterior shear forces. However, it has been indicated that the lateral soft tissue is the most important structure in resisting a varus moment and that the cruciates' contributions are insignificant in this matter (Seering et al. 1980). In the model the lateral collateral ligament, capsule, passive and active tension in the iliotibial tract were lumped together as the lateral soft tissue. It should be emphasised that the tensor fascia latae is active in a large portion of the gait cycle (Vaughan et al. 1999) and that this may be of significant importance for knee joint stability. However, it is not possible to estimate the contribution of this particular muscle to the lateral soft tissue tension in an inverse dynamics analysis.

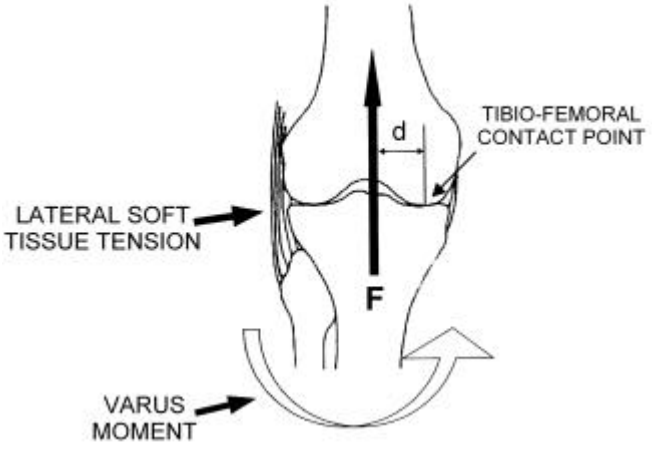


Figure 6. Graphical illustration of the mathematical model applied. The varus moment is balanced by the resultant knee compression force (F) acting over (d) to avoid lateral opening of the joint. If the resultant knee compression force was insufficient, tension in the lateral soft tissue was induced. Tension in the lateral soft tissue indicated that the resultant compression forces was supported by the medial compartment as the joint opens laterally until the lateral tissue is no longer slack. Modified from Schipplein (1991).

Pain – scoring and modulation

Scoring Pain

In Study I and II, the OA patients registered the knee joint pain intensity during walking. In Study III, the muscle pain intensity during walking was registered. Pain intensity was measured using a 100 mm Visual Analogue Scale (VAS) (Price et al. 1983) with end points of 0 mm = 'No Pain' and 100 mm = 'Worst imaginable Pain'.

Pain relief

Knee joint pain relief (analgesia) was induced by injecting 10 mL lidocaine (1%) into the suprapatellar bursa. The injections were ultrasound guided to ensure proper placement of the lidocaine bolus in the suprapatellar bursa (Qvistgaard et al. 2001).

Experimental Muscle Pain

Muscle pain was induced by intramuscular bolus injections of 1 ml sterile hypertonic saline (5.8%). The hypertonic saline injections result in an intense, short lasting (approximately 5 minutes) muscle pain (Graven-Nielsen et al. 1997). The injections were made into m. vastus medialis approximately 5 cm proximal and 5 cm medial to the medial corner of the patellar base. Injections of isotonic saline (0.9%) were used as control.

Table 1. Definitions of the variables of interest and in which study they are analysed.

Variable	Definition	Study
KNEE JOINT ANGLES		
Heel strike flexion angle	Knee joint angle at heel strike (0% stance phase)	I
Loading response flexion angle	Maximal knee flexion angle during the first half of the stance phase	II & III
Terminal stance flexion angle	Maximal knee extension angle during the last half of the stance phase	II
SAGITTAL PLANE KNEE MOMENTS		
Loading response extensor moment	Maximal extensor moment during the first half of the stance phase	II & III
Midstance flexor moment	Maximal flexor during the last half of the stance phase	II
FRONTAL PLANE KNEE MOMENTS		
Loading response varus moment	First peak varus moment occurring during the first half of the stance phase	II & III
Terminal stance varus moment	Second peak varus moment occurring during the last half of the stance phase	II & III
IMPULSE-FORCES		
Impulsive ground reaction force	Magnitude of the impulse-spike in the sagittal plane ground reaction force shortly after heel strike (first 10-20 ms)	I
Peak Tibial acceleration	Maximum acceleration measured at the tibial tuberosity shortly after heel strike (first 100ms)	I
Peak Sacral acceleration	Maximum acceleration measured at the sacrum shortly after heel strike (first 100ms)	I
DYNAMICS LOADINGS		
Loading response overall knee joint force	Maximum overall knee joint compression during the first half of the stance phase	II & III
Loading response medial compartment force	Maximum medial compartment compression during the first half of the stance phase	II
Terminal stance overall knee joint force	Maximum overall knee joint compression during the last half of the stance phase	II
Terminal stance medial compartment force	Maximum medial compartment during the last half of the stance phase	II

GAIT CHANGES IN KNEE OSTEOARTHRITIS

Joint Angles

Reports on kinematic characteristics in knee OA are not equivocal. The heel strike and loading response knee joint angles reported in Study I and II are equal in knee OA patients and healthy reference subjects, although a tendency towards increased flexion was observed, but the limited study sample (n=9), may have restricted the study. There is no general agreement between other studies that either report both more flexed (Childs et al. 2004; Baliunas et al. 2002), more extended (Hubley-Kozey et al. 2006; Astephen et al. 2005; Mundermann et al. 2005a) or equal (Mundermann et al. 2005a) knee joint angles in knee OA patients compared to healthy reference subjects.

The terminal stance knee joint angle reported in Study II were significantly more flexed in the knee OA patients compared to the reference group, but no other studies are available to confirm this.

Most studies, however, have not reported significant differences in the peak joint angles in knee OA patients, but report significantly reduced dynamic range of motion (ROM), defined as the knee joint excursion from heelstrike to the peak knee flexion angle during loading response (Bejek et al. 2006; Lewek et al. 2006; Lewek et al. 2004a; Manetta et al. 2002; Al Zahrani et al. 2002; Cheing et al. 2001; Messier et al. 1992; Stauffer et al. 1977).

Interestingly, one of the largest studies, in terms of participants (139 knee OA patients), reported no differences in knee joint kinematics between knee OA patients and healthy subjects (Kaufman et al. 2001). Although no correlation between disease severity and knee joint kinematics during walking has been presented, differences in study populations may account for the discrepant reports on this matter. Furthermore, most studies investigating knee joint kinematics during walking employ self-selected walking speeds during tests. Although such an approach may be desirable in terms of describing the “true” function of the patients, it also poses the risk of blurring the outcome of interest because walking speed per se affects knee joint angles (Lelas et al. 2003; Oberg et al. 1994; Kirtley et al. 1985). There may also be significant differences in preferred walking speeds between patients and healthy subjects. In Studies I and II, all subjects (patients and healthy) walked at a fixed walking speed of 4.0 km / h and thus the observed differences in knee joint kinematics are not caused by differences in walking speed.

In conclusion, there are no clearly defined changes in knee joint angles during walking associated with knee OA. Differences in gait analysis protocols and study populations may explain the differences in the observed knee joint angle measurements.

Impulse-forces and knee OA

There are very limited human data supporting the theoretical link between knee OA and impulsive joint loads. At present, Study I is the only available study of impulse-forces in knee OA patients. Impulse-forces at heel strike were measured as the impulsive ground reaction forces (iGRF) and peak axial accelerations of the proximal tibia and sacrum. No differences in impulse-forces between a knee OA group and a healthy group were demonstrated (Study I) (figure 7).

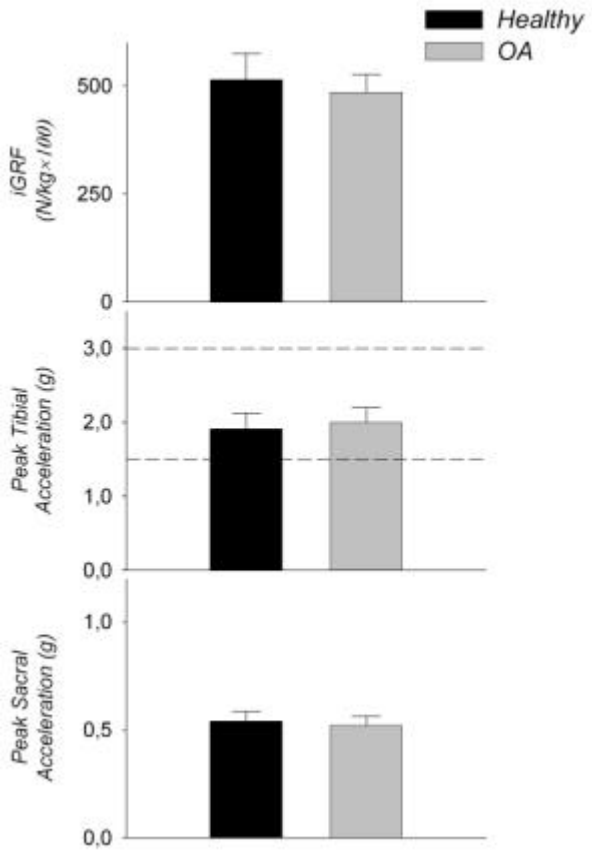


Figure 7. Group averages (±SE) of impulsive ground reaction forces (top), peak tibial (middle) and sacral (bottom) accelerations. Normal values for the tibial accelerations are indicated by horisontal lines. From Study I.

Walking speed has significant effects on the iGRF (Chen et al. 2003; Whittle 1999; Whittle 1997), tibial (Voloshin 2000) and trunk accelerations (Henriksen M. et al. 2004; Moe-Nilssen 1998a; Moe-Nilssen 1998b). Further, it has been suggested that age is positively correlated to the generation of impulse-forces (Robbins et al. 2001). Finally, different knee joint angles at heel strike have been proven determinant for the magnitude of the impulse-forces (Lafortune et al. 1996).

However, the included subjects (patients and healthy) in Study I did not differ with respect to walking speed, age or joint kinematics at heel strike. Additionally, the observed tibial peak accelerations are well within the normal range of 1.5 g – 3 g previously reported for healthy subjects (Voloshin 1988; Folman et al. 1986). Furthermore, the included patients were characterised as “mild” knee OA patients. Taken together, these factors weaken the causal connection between impulse-forces and knee OA.

The design of Study I was cross-sectional, and therefore no conclusions about the role of impulse-forces during walking in the development of knee OA can be made. However, the hypothesis has not been tested in knee OA patients before; and based on the results of Study I, the hypothesis that impulse-forces are elevated in OA patients needs to be revised.

In conclusion, there is no evidence of differences in impulse-forces between knee OA patients and healthy reference subjects.

Joint moments and knee OA

Several reports about knee joint moments in knee OA are available. Due to the connection between the varus moment and the compression forces in the medial joint compartment during walking (Schipplein et al. 1991), this particular moment has gained special attention. In fact, it has been shown that increases in the varus moment are associated with increased risks of loosing joint space (Miyazaki et al. 2002) emphasising the importance of the varus moment in disease progression. The time course pattern of the varus moment is characterised predominantly by a varus moment throughout the stance phase (see figure 3 and 8).

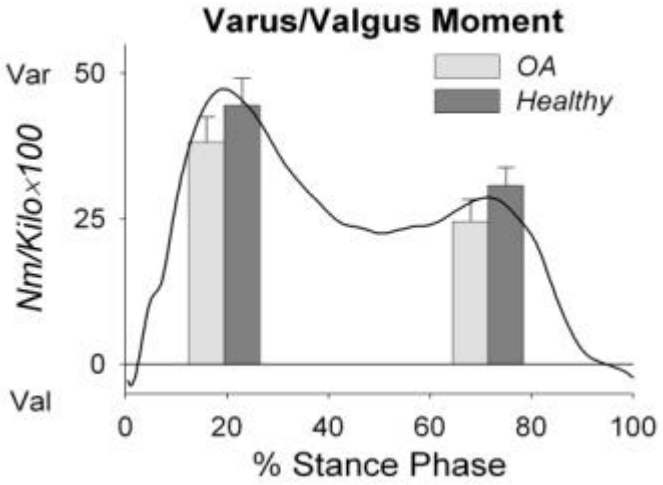


Figure 8. Illustration of a typical time-course pattern of the frontal plane knee moment during the stance phase of walking. Bars represent group averages (SE). No differences between the healthy and the knee OA group. From Study II.

In Study II, no differences in neither loading response nor terminal stance peak varus moment between the OA group and the reference group were found (figure 8); an observation different from a number of studies reporting increased varus moment in medial knee osteoarthritis (Astephen et al. 2005; Mundermann et al. 2005a; Lewek et al. 2004a; Hurwitz et al. 2002; Baliunas et al. 2002; Kaufman et al. 2001; Prodromos et al. 1985). Although no statistical comparisons were made between patients and a healthy reference group, one study showed reduced varus moment in the knee OA group (Shrader et al. 2004). However, in most studies the radiographic classification of the majority of the patients are “moderate” or “severe” as opposed to the study sample in Study II that had “mild” joint space narrowing. This difference in study groups most probably accounts for the different observations of the varus moments. Actually, it has been shown that patients with less-severe knee OA (Kellgren-Lawrence [K/L] grade = 2) and asymptomatic control subjects had similar peak varus moments, whereas patients with more-severe knee OA (K/L grade = 3) had significantly higher varus moments than healthy subjects and less-severe knee OA patients (Mundermann et al. 2005a; Mundermann et al. 2004; Wada et al. 2001; Sharma et al. 1998). These observations are supported in a study that shows that for every 1% increase in varus moment, there was more than six-fold increase in the risk of radiographic disease progression in the medial joint compartment over a six year period (Miyazaki et al. 2002).

Because of the positive correlations between varus moment and a) disease severity (Hurwitz et

al. 2000; Sum et al. 1997) and b) anatomical alignment (Hilding et al. 1995), it has been suggested that increased peak varus moments may not have a pathogenetic role in knee OA, but is rather an effect of morphological changes in the pathological knee joint (Mundermann et al. 2004). This may explain why no differences in varus moments between groups were observed in Study II, as the included patients were classified as "mild" knee OA.

The knee joint compression forces are proportional to the sagittal plane knee joint moments (Study III) and therefore these moments are of importance in assessment of knee joint loadings.

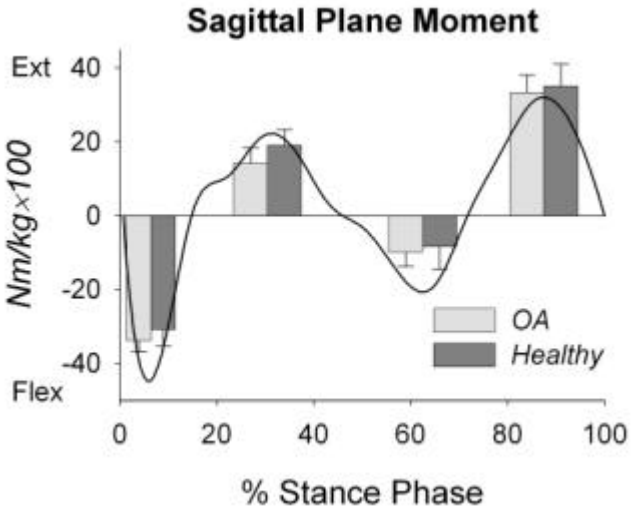


Figure 9. Illustration of a typical time-course pattern of the sagittal plane knee moment during the stance phase of walking. Bars represent group averages (SE). No differences between the healthy and the knee OA group. From Study II.

The time course pattern of the sagittal plane knee joint moment is characterised by an initial period of flexor moment followed by oscillations between extensor and flexor moment (see figure 3 & 9).

No differences in the sagittal plane moments between the knee OA group and the healthy reference group were observed in Study II. These observations are in agreement with previous studies (Messier et al. 2005; Mundermann et al. 2005a; Shrader et al. 2004; Baliunas et al. 2002). However, other studies report decreased extensor moments in the loading response (Lewek et al. 2006; Kaufman et al. 2001) and similar terminal stance flexor moments in knee OA compared to healthy subjects (Kaufman et al. 2001). One study has even reported larger peak extensor moments in a knee OA sample compared to healthy subjects (Schipplein et al. 1991).

The disagreement in the reported sagittal plane moments is likely to be accounted for by the inconsistent kinematics reported in the same studies because sagittal knee joint moments and knee joint angles are correlated (Alkjaer et al. 2003; Manetta et al. 2002; Baliunas et al. 2002). Furthermore, the walking speeds at which the gait is analysed influence the moment magnitudes significantly (Lelas et al. 2003; Oberg et al. 1994; Kirtley et al. 1985) which also may contribute to the variety of reported observations. Finally, and perhaps most importantly, the amount of pain experienced by the patients at the time of testing is generally not well accounted for, but certainly has a potential to affect the sagittal plane moments (Study III).

In contrast to the varus moments, the sagittal plane moment and disease severity are

uncorrelated (Mundermann et al. 2005a; Sharma et al. 1998). However, it is possible that the differences are caused by varying levels of pain in the different study samples, which is also uncorrelated to disease severity (Dieppe 2004; Creamer et al. 1999).

In conclusion, neither sagittal plane peak flexor / extensor moments nor frontal plane varus moments were different between knee OA and healthy reference subjects in Study II. The similarities in the sagittal plane moments between patients and healthy subjects are in accordance with the majority of other similar comparative studies, whereas the frontal plane varus moment results from Study II are probably explained by the mildness of the disease severity in the patient sample.

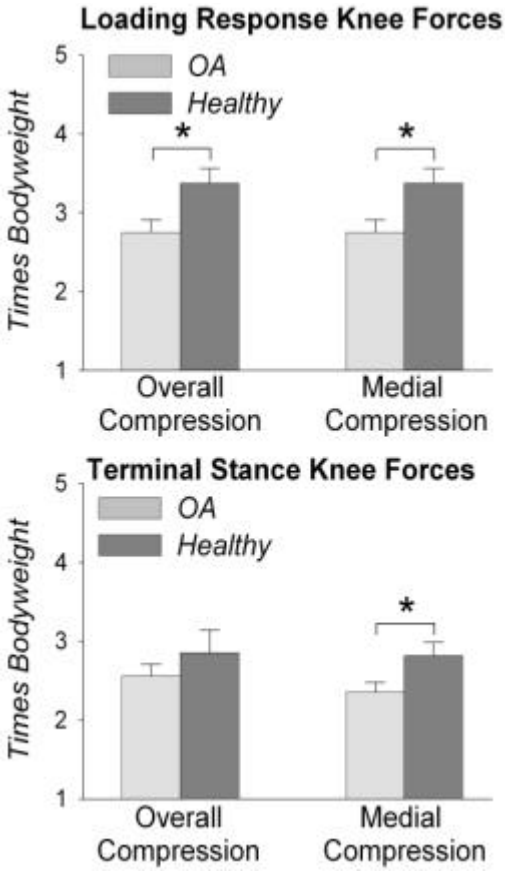
Dynamic loadings & knee OA

Few available studies estimate knee joint loadings during walking in knee OA patients. Most studies have assessed the joint loadings indirectly by means of the varus moment because it is determinant of medial compartment compression forces (Schipplein et al. 1991).

However, as demonstrated in Study II and III, the overall and medial knee joint compartment compressive forces are not determined by the varus moment alone, but also significantly by the sagittal plane moments. Therefore, conclusions about knee joint compressive forces based on the varus moment alone should be made with caution.

Study II has the advantage of presenting the varus moment along with estimates of the total compressive forces as well as the medial compartment compression forces. It was shown that the knee OA patients walked with less overall and medial compartment compressive knee joint forces compared to the reference group during loading response (See figure 10). These findings are partly confirmed by a previous study showing reduced compressive reaction forces in a knee OA group compared to a healthy reference group (Robon et al. 2000). However, when these results were adjusted for walking speed, the group difference disappeared (Robon et al. 2000). In another study that estimated the joint compression in a knee OA sample, the joint

Figure 10. Group averages (±SE) of overall and medial compartment knee joint compressive forces during loading response (top) and terminal stance (bottom). Asterisks denote significant differences at $p<0.05$. From Study II



forces did not differ between OA patients and healthy controls (Messier et al. 2005). Again, differences in walking speed between groups may account for this.

In conclusion, the notion that knee OA patients walk with greater joint loadings than healthy subjects is not consistently supported. Differences in gait analysis protocols and pain intensities are important confounders of the joint loadings, and these factors should be considered in future research.

Electromyographic changes

The sparsity of studies of electromyographic activity during walking is striking, especially because there is a strong suggestion that the neuromuscular system is impaired in knee OA (Brandt et al. 2006). The activation of the muscles surrounding the knee constitutes the essential way to control the external joint loads and generate the motion itself during walking. Therefore, altered muscle activation at the knee may interfere with normal generation of internal forces and alter the control of external forces, thus affecting both the local knee joint motion, dynamic stability and joint loadings as well as the walking pattern in general.

Few studies have investigated this, and the main findings are that patients with knee OA have prolonged muscular activity in quadriceps, hamstrings, gastrocnemius and tibialis anterior muscles compared to healthy subjects (Childs et al. 2004) (*Hammer C. et al,* unpublished data). It is possible that the muscle activation patterns are correlated to disease severity because the patients in the study by Childs et al. can be classified as moderate to severe (K/L = 2), and recent findings in a group of mild knee OA patients revealed prolonged quadriceps but not hamstring activity (*Hammer C. et al,* unpublished data). Also, increased co-contraction between quadriceps and hamstring muscles has been reported (Lewek et al. 2006; Hortobagyi et al. 2005; Lewek et al. 2004a) and it has been suggested that this increase is caused by reduced quadriceps activation and increased hamstring muscle activity (Hortobagyi et al. 2005).

Summary

Although the theory of impulse-forces and development and progression of knee OA is enticing, the human data provided in Study I questions the significance of these forces as having a pathogenetic role in knee OA. However, no conclusions about causality can be made without longitudinal studies.

While the varus moment is related to disease severity and pain, no such relationship exists between sagittal plane moments or kinematics and disease severity or pain. On the other hand, knee joint kinematics and sagittal plane moments are closely related, and differences in pain levels and gait analysis protocols may account for the diversity in the literature. The reported joint loadings are also dissimilar, with an overweight of reports of decreased joint loadings in knee OA. This is also most likely to be caused by variance in pain and walking speeds.

Nevertheless, if the varus moments are increasing with disease severity without concomitant increases in the sagittal plane moments and joint compression, the knee joint stability becomes compromised, and the gait changes associated with knee OA suggests instability causing aberrant distribution of the joint loadings in the knee joint. The notion of dynamic instability in knee OA is supported by evidence of altered muscle activity and increased co-contractions.

CHANGES IN JOINT LOADINGS ASSOCIATED WITH PAIN

The reasons that the interplay between the biomechanics of walking and pain / pain relief is of interest in the description of knee OA are several. Firstly, pain is the central symptom in knee OA. Secondly, biomechanical joint loadings are under strong suspicion as a pathogenetic factor in knee OA. Thirdly, pain is a strong sensory input with the potential to alter the neuromuscular function and thereby the biomechanical joint loadings. Finally, pain can be considered as having a protective function causing adaptive biomechanical changes in order to reduce potentially harmful and / or painful joint loadings, and it is conceivable that the gait changes associated with knee OA are compensations to pain. Therefore, a comparison is of interest between knee OA patients and healthy subjects with estimates of the possible effects of pain on the biomechanical outcome of interest. In view of this, the sparsity of studies assessing the effects of pain and pain relief on the knee joint dynamics is striking.

There are two ways of assessing the effects of knee pain on knee biomechanics during walking: Either by relieving pain in painful subjects (Study I & II) or by inducing pain experimentally in pain free subjects (Study III).

Impulse-forces and pain

The similar impulse-forces during walking in knee OA patients and healthy reference subjects reported (Study I) could be attributed to the presence of pain in the patient group. This is because pain has the potential to cause adaptive changes in the motor activity (Sterling et al. 2001; Lund et al. 1991) in order to reduce potentially harmful and / or painful joint loads. In such case, the impulsive ground reaction forces (iGRF) and shock wave accelerations would be less in a painful than in a pain-free condition, and increased impulse-forces would be expected following pain relief. However, pain relief in the knee OA group caused decreased peak tibial accelerations while the iGRF and the peak sacral accelerations were unaffected (Study II). The magnitudes of changes were not within clinically relevant ranges, suggesting that pain and pain relief have little or no effect on the impulse-forces during walking.

Although changed knee joint angles at heel strike also occurred following pain relief in the knee OA group (Study I), the joint angles reported were not different from those of the healthy subjects (Hurd et al. 2004; Kerrigan et al. 1998; Kirtley et al. 1985) neither during painful nor pain-free walking trials. The changes included increased extension of both hip and knee joint angles,

resulting in a functional lengthening of the leg. Increased knee joint extension has been shown to result in decreased tibial heel strike acceleration values (Lafortune et al. 1996), and the changes in joint kinematics and shock wave accelerations reported in Study I support this relationship.

The changes in heel strike kinematics and shock wave accelerations caused by pain relief were subtle (Study I), and the shock wave acceleration values reported in Study I are well within the reference range (Folman et al. 1986, Voloshin 1988), which also supports the notion of clinically insignificant differences between groups.

Dynamic loadings and pain

Introduction of experimental muscle pain (Study III) attenuated the peak knee extensor moments during the loading response (see figure 11). The attenuation is explained by a reduced quadriceps activation observed as decreases in the EMG activity in the vastus medialis and vastus lateralis muscles. The attenuated peak knee joint extensor moments during the loading response during experimental muscle pain is consistent with a report of decreased peak loading response extensor moments with increased pain in knee OA (Hurwitz et al. 2000). Further, the attenuated peak extensor moments in the loading response following experimental muscle pain (Study III) resemble those of knee OA patients reported by some authors (Study II) (Lewek et al. 2006; Kaufman et al. 2001). This supports the notion that reduced extensor moments and joint loadings may be compensatory reactions to pain (Hurwitz et al. 2000). In further support of this, local knee joint analgesia, via intraarticular injections of combined lidocaine and steroid, brought about increases in both extensor moments, varus moments and walking speeds (Shrader et al. 2004). Similarly, in a study of four weeks NSAID pain treatment of knee OA patients, increased peak loading response extensor moments and walking speeds were observed (Schnitzer et al. 1993). It was suggested that these changes represent a "normalisation" of the gait pattern, while at the same time increasing the dynamic loadings of the knee joint (Shrader et al. 2004). In Study II such "normalisation" in joint loads were observed in terminal stance, as an increase in the peak flexor

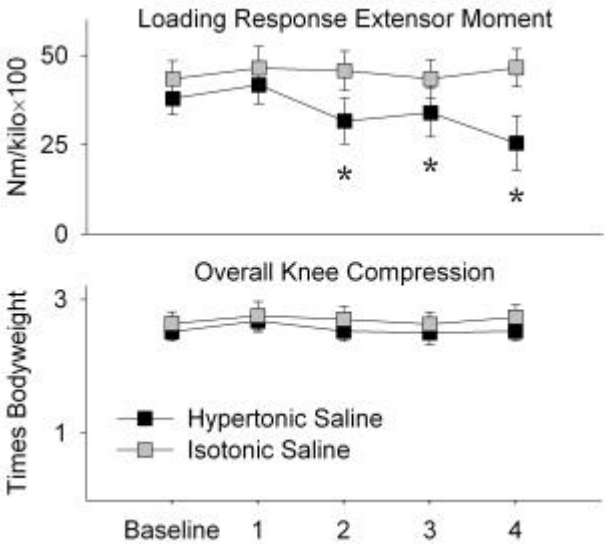


Figure 11. The loading response extensor moment (top) and overall knee compression (bottom). Asterisks denote significant differences between isotonic and hypertonic saline at $p<0.05$. Pain is present during sequence 2 and 3. From Study III.

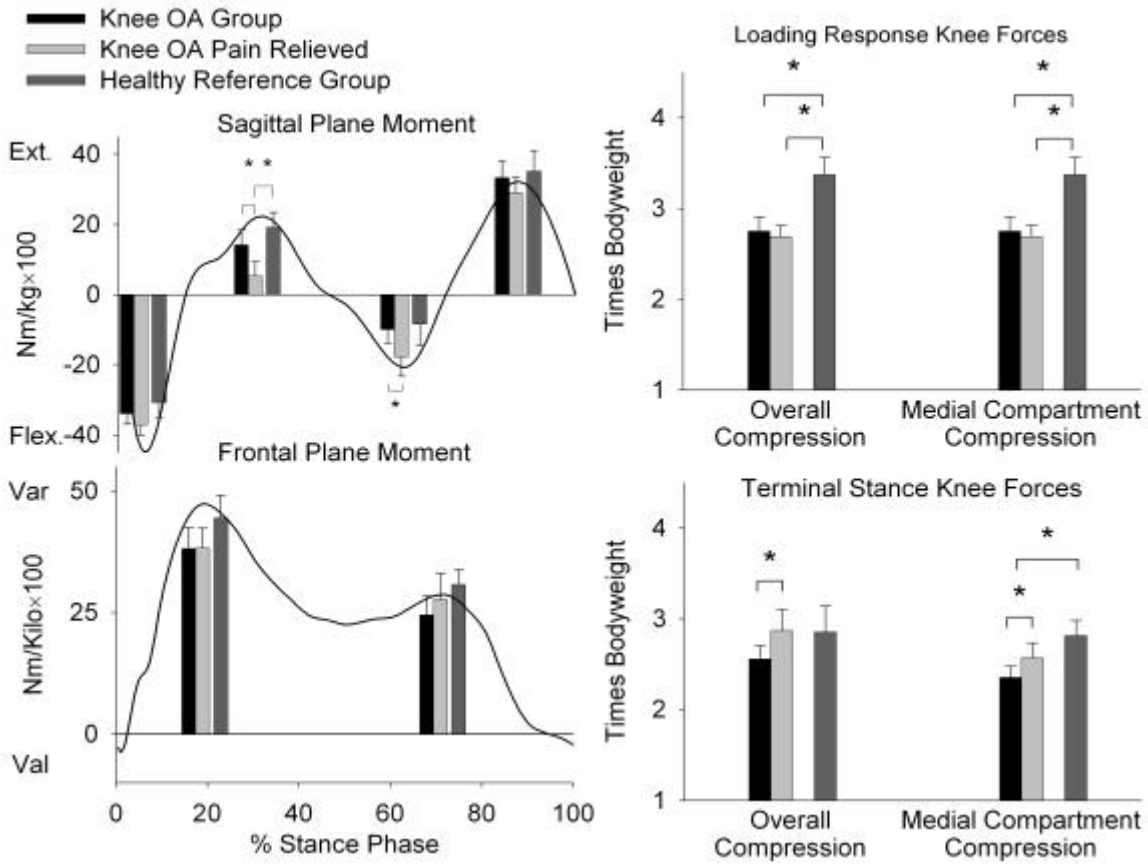


Figure 12. Left: Illustration of the effects of pain relief on the sagittal and frontal plane peak knee moments compared to the healthy group. Bars represent group averages (+ SE) of the peak values. Right: Group averages (+SE) of knee joint compressive forces during loading response (top) and terminal stance (bottom). Asterisks denote significant differences at $p<0.05$. From Study II.

moment and overall and medial compartment joint loadings to a level comparable to the healthy group (see figure 12).

It may therefore seem paradoxical that local knee joint analgesia (intra-articular lidocaine injections) in a knee OA group (Study II) resulted in reduced loading response peak knee extensor moments (see figure 12). Despite the attenuated peak extensor moments, the joint loadings were unaffected in this part of stance (Study II). However, while intra-articular lidocaine injections and experimental muscle pain are convenient means of assessing the effects of pain on the knee dynamics, any direct comparisons of the effects cannot be made. Further, they do not represent the extremes of two opposed clinical situations (painful and pain-free knee OA). This, because the pain modalities (i.e. analgesia and experimental pain) may not have 100% fidelity of clinical knee OA pain and its effects on knee joint dynamics. Although sagittal plane moments are not related to pain, it has been shown that pain changes are inversely correlated to changes in the peak varus moments (Hurwitz et al. 2000; Sum et al. 1997). However, neither pain relief (Study II) nor experimental muscle pain (Study III) caused changes in the peak varus moments, substantiating

the incomplete fidelity. Lidocaine injections effectively block all neural reception within the knee joint, including mechanoreception, which has been shown to have increased excitability in the presence of painful joint inflammation (Schaible et al. 2002). This implies that pain relief via intra-articular lidocaine injections does not only result in an isolated removal of nociception but also blocks non-noxious mechanoreception, which may affect the neuromuscular function. In addition, introduction of fluids into a knee joint could give rise to altered mechanoreception from intra-articular receptors because knee joint effusion affects the neuromuscular function of the knee muscles (Torry et al. 2000; Jensen et al. 1993; Geborek et al. 1989; Spencer et al. 1984; Stokes et al. 1984). However, because the relatively high lidocaine concentration (1%) blocks both pain mediating nerve fibres and many somatosensory fibres (Bonica 1984), neuromuscular changes caused by the unavoidable effusion caused by lidocaine injections are negligible (Spencer et al. 1984). Finally, although experimental saline induced muscle pain has proven useful in studying basic physiological aspects of human pain (Graven-Nielsen et al. 1997), it does not fully reflect clinical knee OA joint pain, providing a possible further explanation for the apparently illogical analogous effects of pain relief and pain induction. Nevertheless, the primary effect of intra-articular lidocaine injections is pain relief, and the experimental muscle pain bring about changes in the gait pattern similar to those observed in knee OA, validating the usage of the pain modalities.

The contradictory effects of pain relief on the loading response peak extensor moment reported in Study II and in (Shrader et al. 2004; Schnitzer et al. 1993), may be explained by the similar diversity in the observed knee joint angles, which again is dependent on walking speeds. Further, the prolonged pain relief caused by NSAID treatment (Schnitzer et al. 1993) differs from the short lasting and rapidly induced effect of the lidocaine injections: Lidocaine abolishes the pain in practically all subjects within seconds (Study II; (Shrader et al. 2004)), while NSAID has a more varying effect across subjects. Also, the knee OA symptoms flare during a month in a rather unpredictable way, causing variability in the pain relieving effects of the NSAID treatment, whereas the pain relief of lidocaine in Study II was confined to a few hours. Thus, it seems that selection of the patients, the current disease status (pain) and gait analysis protocols (walking speeds) may have great importance for the outcome of a study. Study I, II and III all have the advantage of having equal walking speeds between groups and pain conditions, making the effects of pain and pain relief easier to assess reliably.

In Study II, increased terminal stance peak flexor moments were observed following pain relief, causing increased joint loadings to a level comparable with healthy subjects (“normalisation”), (see

figure 12). The patients included in Study II were characterised as having less-severe knee OA, based on the radiographic evaluation and on the WOMAC scores. In another study of pain relief in predominantly less-severe knee OA patients, decreased pain also resulted in increased terminal stance peak flexor moments (Hurwitz et al. 2000). On the other hand, the introduction of experimental muscle pain (Study III) did not result in any biomechanical changes in terminal stance, supporting further that other factors than pain also affects the knee OA gait changes, and that experimental muscle pain is not a complete model of knee OA. In agreement with the idea that reduced joint loadings may be a compensation to pain, experimental muscle pain lead to reduced extensor moments in the loading response phase of stance (Study III). In both Study II and III, the extensor moments were reduced following pain modulation. Reduced knee extensor moments are traditionally interpreted as unloading of the knee joint, as higher extensor moments contribute to higher overall compressive forces in the knee joint (Schipplein et al. 1991). However, the estimated joint loadings forces were unaffected by the decreases in the extensor moments during the loading response of the stance phase in both Study II and III. There are several possible sources for this paradoxical observation: It could be a result of 1) antagonistic activity of the knee flexors, 2) increased axial reaction forces, 3) changes in the extensor muscles' moment arm due to changes in joint angles (Visser et al. 1990), 4) adoption of a quadriceps avoidance gait pattern or 5) simultaneous increases in the varus moment.

In Study II, the axial reaction forces and varus moments were unchanged, and none of the subjects adopted a quadriceps avoidance gait pattern following pain relief. Antagonistic muscle activity, increased moment extensor muscle arms due to kinematic changes or a combination of those must account for the unchanged joint loadings in the loading response. Unfortunately, the applied model does not allow the calculation of antagonistic muscle activity, and therefore antagonist muscle compression forces cannot be determined.

In Study III, the absence of group differences in joint loadings are explained by a complete quadriceps avoidance gait pattern in 4 of the 20 subjects (see figure 13 for an illustrative example).

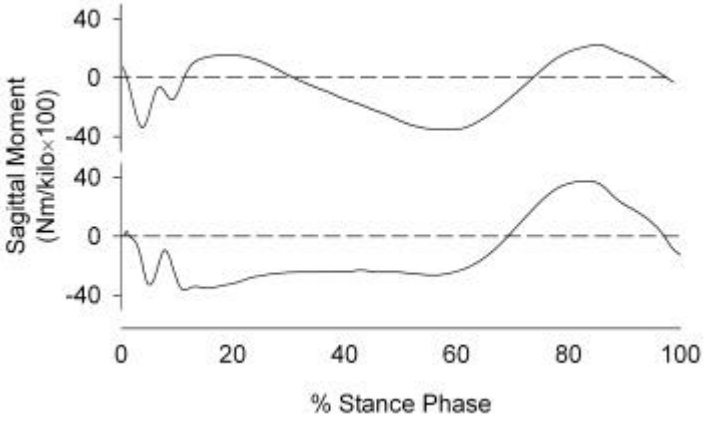


Figure 13. Graphical illustration of a normal (top) vs. a quadriceps avoidance (bottom) sagittal plane knee joint moment pattern. The normal moment pattern is characterised by oscillations between flexor (negative) and extensor (positive) moments. The quadriceps avoidance pattern is dominated by flexor moment in the first half of the stance phase. From Study III.

A quadriceps avoidance pattern is characterized by flexor moment dominance throughout the stance phase (Alkjaer et al. 2003; DeVita et al. 1998; Simonsen et al. 1997; Winter 1980). The flexor moment is exerted by the hamstring / gastrocnemius muscles that can compress the knee joint effectively, thus causing the group averages to remain unchanged (Study III), (see figure 11 & 14). Therefore, the results from Study III demonstrated that reducing the extensor moment per se is an effective strategy to reduce joint compression.

Pain relief also caused significantly less flexed knee joint angles in loading response (Study II), which, at least partially, explains the reduced extensor moments (Alkjaer et al. 2003). Experimental muscle pain did not cause kinematic changes (Study III).

The varus moment is believed to be determinant for medial compartment compression (Schipplein et al. 1991). However, while no changes in the varus moment following pain relief were observed in Study II, the medial compartment loadings in terminal stance increased following pain relief. This indicates that other biomechanical factors than the varus moments contribute significantly to the medial compartment loadings. Although not present in Study II, changes in pain is inversely correlated to changes in varus moment (Hurwitz et al. 2000; Sum et al. 1997) which is consistent with the inverse relationship between clinical symptoms (WOMAC) and peak axial knee joint reaction forces (Robon et al. 2000) and peak varus moments (Hurwitz et al. 2002). In addition, it has been shown that pain relief brought about increases in the varus moment to a level comparable to a healthy reference group (Shrader et al. 2004) although the walking speeds were also increased. This indicates that patients with worse clinical symptoms (pain) have lower varus moments and that pain causes adaptive changes in the movement pattern in order to lower the joint loadings. As pain is uncorrelated to disease severity (Dieppe 2004; Creamer et al. 1999) and negatively correlated to the varus moment (Hurwitz et al. 2000; Sum et al. 1997), it is indicated that pain is a protective signal, which by its presence causes compensatory changes in the gait pattern to reduce the joint loadings – irrespective of the disease severity.

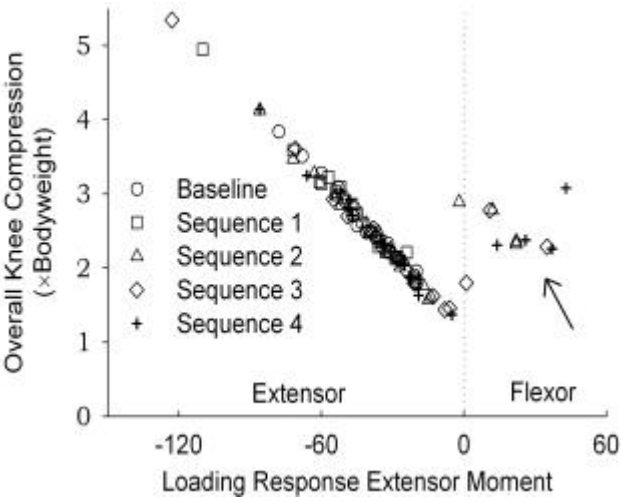


Figure 14. A scatter of individual sequence average loading response extensor moments vs. knee compression reveals that reducing the moment is an effective way of reducing compression. Due to a subgroup with flexor moments (arrow) the group average joint compression were unaffected by pain. From Study III.

An interesting observation was made in Study

III, where the effects of experimental muscle pain on both the joint dynamics and the EMG activity were sustained even after the pain was no longer present (see figure 11). This may indicate a reflexive inhibition of the extensor muscles at a spinal level persisting beyond the conscious pain perception. This is in accordance with previous observations showing that pain inhibition of muscle function still occurs when the pain is no longer present (Slater et al. 2003; Shakespeare et al. 1985). Similarly, the *neuromuscular activation model* suggests that the presence of pain initiates changes in motor control, and that these changes often are sustained beyond the acute pain phase (Sterling et al. 2001). While the peak varus moments were unaffected, the sustained attenuation of the extensor moments and quadriceps EMG activity post pain leaves the knee joint less stable (Louie et al. 1987; Pope et al. 1979; Markolf et al. 1978) and thus prone to injury.

The sustenance of synergistic muscle inhibition post pain indicates that the immediate adaptive response to muscle pain in motor activity and movement pattern is not as easily "un-adapted" once the nociceptive input is vanished. This could suggest that pain causes changes in the basic movement strategy. Another explanation could be a central adaptation to nociceptive inputs (Polianskis et al. 2002). This implies that the nociceptive signals from the periphery modulate motor circuits at spinal levels post pain without the nociceptive signals reaching consciousness to evoke pain sensation.

The symptoms of knee OA flare over a period of time, and the patients may even experience pain-free periods, especially in the early stages of the disease, which is certainly beneficial to the patients and an aim in most treatments. However, the results from Study III suggest that the reflexive muscle inhibition may persist in these pain-free phases, with a preservation of the dynamic instability. Without the protective pain sensation, a pain-free OA knee joint is even more prone to further damage, and pain relief may be a pathogenetic factor in disease progression. This has wide clinical implications. It has been shown that patients with knee OA have increased consumption of NSAIDs during a period with participation in a study of exercise (Bennell et al. 2005). By exercising and taking the medication at the same time, the knee joints of these patients might be exhibited to a double jeopardy. This could be one explanation for the indication of accelerated cartilage loss in NSAID treated knee OA patients (Reijman et al. 2005).

An interesting common feature of studies of knee OA and biomechanics is the poor relationship between the pain level and the biomechanical outcome of interest. No studies have presented correlations between the raw pain intensity and e.g. joint moments. This may be the reason why the effects of pain on biomechanics have gained limited attention in the literature. Only one study have shown a significant correlation between pain and biomechanical variables, and in that study

dichotomised pain scores were used (Hurwitz et al. 2000) in contrast to the frequently used VAS providing continuous data. The sustained alteration in the knee joint dynamics presented in Study III offers a possible explanation for the lack of correlation between pain intensity and gait biomechanics reported in the literature. Further, it is important to distinguish between nociception (neural activity) and pain sensation (conscious, subjective sensation), as these are not necessarily correlated. Thus, it seems that dichotomised pain ratings such as "presence / absence of" or "increase / decrease in" pain intensity are more determinant than the raw pain intensity score, e.g. obtained by VAS.

Summary

The insignificant effects of pain relief on the impulse-forces during walking in knee OA patients indicate that these forces are not important in the pathogenesis of knee OA (Study I). However, due to the cross-sectional study design, no conclusion about causality can be made before longitudinal data are presented.

The reported changes in dynamic joint loadings associated with pain relief (Study II) points in the same direction, namely that many of the gait changes observed in knee OA patients can be attributed to the presence of pain. The study of experimentally induced muscle pain (Study III) confirms this, because the changes caused by pain are similar to those observed in knee OA patients.

The reported effects of pain relief are not uniform, however. Differences in study protocols probably account for this. The major discrepancy between studies is the selection of self-selected or fixed walking speeds – and it should be clear now that walking speed is a major confounding factor in gait analyses. However, preferred walking speed is also a marker for functional ability (Andriacchi et al. 1977) and increases in preferred walking speed following an intervention has clinical relevance (Lindemann et al. 2006; Newman et al. 2006; Sonn 1996; Potter et al. 1995).

Nevertheless, the available studies on the effects of pain relief on joint loadings all indicate that pain relief may have detrimental effects on the OA knee joint, due to increased joint loadings.

The isolated effects of pain is difficult to estimate, however, but available data suggest that experimentally induced muscle pain in otherwise pain free and healthy subjects evokes gait patterns with similarities of those observed in knee OA patients. Introduction of pain in healthy subjects caused joint instability, and the effects were sustained even after the pain was no longer present. It is conceivable that this sustenance of biomechanical effects in post pain may have a pathogenetic role in the progression of knee OA.

CONCLUDING REMARKS

In this thesis, the impulse-forces and dynamic joint loadings were investigated in knee OA patients and in healthy reference subjects. The hypothesis that impulse-forces should be elevated in knee OA patients could not be confirmed, because similar impulse-forces at heel strike during walking were observed in a knee OA patient group and in a group of healthy reference subjects. The dynamic joint loadings were assessed during the loading response and terminal stance phases of the gait cycle and in both phases the dynamic joint loadings were lower in the knee OA group.

These observations could be attributed to the presence of joint pain in the patient group, because pain has the potential to alter motor activity and strategy. However, when relieving the patients' knee pain, only subtle changes in the impulse-forces were observed, and encompassed only slightly decreased peak tibial accelerations. Although the study was cross-sectional, the results indicate that the hypothesis of impulse-forces playing a role in knee OA pathogenesis needs to be revised.

The dynamic joint loadings increased following pain relief to a level comparable to that of the healthy reference subjects, suggesting that pain is a protective mechanism that causes changes in the movement pattern to reduce the joint loadings.

The induction of experimental muscle pain in healthy subjects brought about changes in the knee joint dynamics similar to those observed in knee OA patients under normal conditions (i.e. painful knees) indicating that pain is a protective mechanism causing adaptive movement changes. The drawback of these adaptations is that the knee joint becomes unstable. The adaptive changes persisted even after the conscious pain sensation was no longer present, suggesting that the reflexive muscle inhibition persists in pain-free periods, with a subsequent preservation of the dynamic instability. Without the protective pain sensation, a pain-free OA knee joint is even more prone to further damage, and pain relief may be a pathogenetic factor in disease progression.

These results show that clinicians face a dilemma in the conservative treatment of knee OA. While pain relief may cause increased dynamic joint loadings, which is under strong suspicion to be pathogenetic in disease progression, it appears that pain per se causes undesirable joint instability, with potentially detrimental biomechanical consequences.

Thus, improvement of the muscular function becomes crucial and should be included or prioritised as an important aim in treatment of knee OA – besides the obvious pain therapy. Further, the increased knee vulnerability during pain free periods should be emphasised to the patients as well as the clinical staff.

Knee OA may be biomechanically driven and caused by aberrant biomechanical factors acting

on the knee within the context of a systemic susceptibility (Andriacchi et al. 2004; Dieppe 2004). Ideally, future treatments should thus be able to relieve the patient's pain without exacerbating the disease. However, if new treatments that are effective with respect to pain relief while at the same time capable of neutralizing the potentially detrimental biomechanical effects of moving without pain is to be innovated, there is a need for better understanding of the interplay between musculoskeletal pain, motor performance and joint loadings.

Although extensive work is being carried out on how pain modulates the basic components of motor physiology, such as reflexes, the effects of pain on motor behaviour and performance during more composite and complex tasks, such as walking and stair climbing, need further investigation. The "normal" biomechanics of the knee joint is depending on proper function of many anatomical structures and muscles, all of which may be the source of knee OA pain and participate in development of aberrant or inapt movement patterns. However, the detailed role of pain in these structures on the biomechanics of the knee during functional every-day activities needs to be examined. Experimentally induction of pain in specific structures or localised structure-specific pain relief may be ways to illuminate this.

Although pain is recommended as an important "real end-point" in clinical studies, the interplay between the applied interventions, pain, the biomechanical outcomes and disease progression needs attention. Likewise, detailed studies of the long-term effects of pain relieving treatments on knee biomechanics and disease status are needed. More profound knowledge about the different aspects of the complex interplay between symptoms, signs and disease progression will hopefully lead to the design of better and more effective interventions in the future.

DANSK SAMMENFATNING (DANISH SUMMARY)

Ætiologien og patogenesen bag knæledsartrose er grundlæggende ukendt. Biomekaniske faktorer, inklusiv øgede mekaniske belastninger, nedsat neuromuskulær og sensori-motorisk funktion, er blevet forbundet med sygdommen, men en kausal sammenhæng er endnu ikke blevet fundet. Ikke desto mindre vil en svækkelse af en eller flere af disse biomekaniske faktorer påvirke patientens funktionsniveau i dagligdagsaktiviteter og bidrage til øget belastning af knæleddet.

Knæsmerter er et kardinalsymptom ved knæledsartrose, og smertebehandling er derfor formålet med de fleste behandlinger af sygdommen. Smerter ved bevægelse af knæleddet kan anses som havende en beskyttende funktion, der forårsager kompensatoriske ændringer i bevægemønstret mhp. at forhindre potentielt skadelige mekaniske overbelastninger under bevægelsen. Derved er det muligt, at smertelindring har en negativ effekt på sygdommen, da de beskyttende nociceptive signaler fra knæledet er dæmpet eller helt elimineret. Dette kan tænkes at medføre ændringer i bevægelsen med øgede ledbelastninger til følge. På lignende vis kan det tænkes, at eksperimentelle smerter hos raske personer vil medføre kompensatoriske ændringer i bevægemønstret, der er sammenlignelige med de bevægemønstre der observeres hos patienter med ”ægte” knæsmerter, såsom knæartrosepatienter. Dog er effekterne af smertelindring af patienter og eksperimentelle smerter hos raske på knæbelastningen ikke fuldt belyst, og de overordnede formål med denne afhandling var at sammenligne knæledsbelastningen under gang mellem en gruppe patienter med knæledsartrose og en gruppe raske personer, samt at undersøge effekten af eksperimentel smerte hos raske personer på knæledsbelastningen under gang.

I de første to studier (I & II), blev de impulsive kræfter, der opstår ved hælisættet under gangbevægelsen samt de dynamiske knæledsbelastninger under standfasen i en gruppe patienter med knæledsartrose sammenlignet med en gruppe raske personer. Det blev observeret, at patienternes impulsive knæledsbelastninger var sammenlignelige med raske personers, hvorimod de dynamiske standfasebelastninger var reduceret i patientgruppen. Dette indikerer, at de impulsive belastninger har ingen eller ringe betydning for ætiologien og patogenesen af knæledsartrose. Det kunne dog tænkes at observationerne var betinget af tilstedeværelsen af knæsmerter i patientgruppen, hvorfor denne gruppe også blev undersøgt efter en lokalanalgesi af de smertefulde knæled. Her blev det fundet, at impulsbelastningerne var stort set uændrede, hvorimod de dynamiske standfasebelastninger øgedes til et niveau, der er sammenligneligt med den raske gruppe. Således er det indikeret, at den nedsatte knæledsbelastning, der er observeret i patientgruppen, er en kompensatorisk strategi forårsaget af knæsmerter.

I det tredje studie (III) blev effekten af eksperimentelle muskelsmerter i m. vastus medialis på

standfasebelastningerne under gang undersøgt i en gruppe raske personer. De eksperimentelle smerter medførte ændringer i belastningsmønstret, der minder om de observerede belastningsmønstre i patientgruppen fra studie (II) under normale omstændigheder (dvs. smertefulde knæ). Dette indikerer yderligere, at smerter fungerer som en beskyttende mekanisme, der forårsager kompensatorisk aflastning af knæleddet. De kompensatoriske bevægemønstre medførte desuden funktionel instabilitet af knæleddet som følge af inhiberet muskelaktivitet. De observerede ændringer vedblev i op til 20 minutter efter den bevidste smerteopfattelse var forsvundet, hvilket indikerer, at den reflektoriske muskelinhibering også er til stede i smertefri perioder hos patienter med knæledsartrose. Uden de beskyttende smertesignaler bliver et smertefrit artroseknæ endnu mere udsat for yderligere beskadigelse som følge af uhensigtsmæssige og skadelige belastninger, og smertelindring kan således være en patogenetisk faktor i sygdomsprogressionen.

Resultaterne viser at klinikeren befinder sig i et dilemma mht. behandling af patienter med knæartrose. Medens smertelindring kan medføre øgede dynamiske knæbelastninger, der er under stærk mistanke som værende en patogenetisk faktor, kan smerte per se medføre uhensigtsmæssig instabilitet med potentielle skadelige biomekaniske konsekvenser til følge. Dette indikerer at forbedret/opretholdt muskelfunktion er afgørende og bør inkluderes som et vigtigt mål i behandling af knæartrose – udover smertelindringen som patienterne efterspørger. Derudover bør den potentielt øgede sårbarhed af knæleddet i smertefri perioder understreges overfor såvel patienter som klinisk rehabiliteringspersonale.

REFERENCES

Abramson SB. Inflammation in osteoarthritis. *J Rheumatol Suppl* (2004); 70: 70-76.

Al Zahrani KS, Bakheit AM. A study of the gait characteristics of patients with chronic osteoarthritis of the knee. *Disabil Rehabil* (2002); 24: 275-280.

Alkjaer T, Simonsen EB, Jorgensen U, Dyhre-Poulsen P. Evaluation of the walking pattern in two types of patients with anterior cruciate ligament deficiency: copers and non-copers. *Eur J Appl Physiol* (2003); 89: 301-308.

Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* (1986); 29: 1039-1049.

Andriacchi TP. Dynamics of knee malalignment. *Orthop Clin North Am* (1994); 25: 395-403.

Andriacchi TP, Mundermann A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. *Curr Opin Rheumatol* (2006); 18: 514-518.

Andriacchi TP, Mundermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. *Ann Biomed Eng* (2004); 32: 447-457.

Andriacchi TP, Ogle JA, Galante JO. Walking speed as a basis for normal and abnormal gait measurements. *J Biomech* (1977); 10: 261-268.

Arvidsson I, Eriksson E, Knutsson E, Arner S. Reduction of pain inhibition on voluntary muscle activation by epidural analgesia. *Orthopedics* (1986); 9: 1415-1419.

Astephen JL, Deluzio KJ. Changes in frontal plane dynamics and the loading response phase of the gait cycle are characteristic of severe knee osteoarthritis application of a multidimensional analysis technique. *Clin Biomech* (2005); 20: 209-217.

Baliunas AJ, Hurwitz DE, Ryals AB, Karrar A, Case JP, Block JA, Andriacchi TP. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. *Osteoarthritis Cartilage* (2002); 10: 573-579.

Barrett DS, Cobb AG, Bentley G. Joint proprioception in normal, osteoarthritic and replaced knees. *J Bone Joint Surg Br* (1991); 73: 53-56.

Bejek Z, Paroczai R, Illyes A, Kiss RM. The influence of walking speed on gait parameters in healthy people and in patients with osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* (2006); 14: 612-622.

Bellamy N. WOMAC: a 20-year experiential review of a patient-centered self-reported health status questionnaire. *J Rheumatol* (2002); 29: 2473-2476.

Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* (1988); 15: 1833-1840.

Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, Altman R, Brandt K, Dougados M, Lequesne M. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. *J Rheumatol* (1997); 24: 799-802.

Bennell KL, Hinman RS, Metcalf BR, Buchbinder R, McConnell J, McColl G, Green S, Crossley KM. Efficacy of physiotherapy management of knee joint osteoarthritis: a randomised, double blind, placebo controlled trial. *Ann Rheum Dis* (2005); 64: 906-912.

Bliddal H, Christensen R. The management of osteoarthritis in the obese patient: practical considerations and guidelines for therapy. *Obes Rev* (2006); 7: 323-331.

Bonica JJ. Local anaesthesia and regional blocks. In: Wall PD, Melzack R, editors. Textbook of Pain. Edinburgh: Churchill Livingstone, 1984. pp. 541-557.

Brage ME, Draganich LF, Pottenger LA, Curran JJ. Knee laxity in symptomatic osteoarthritis. *Clin Orthop* (1994); 184-189.

Brandt KD, Radin EL, Dieppe PA, van de PL. Yet more evidence that osteoarthritis is not a cartilage disease. *Ann Rheum Dis* (2006); 65: 1261-1264.

Burr DB. The importance of subchondral bone in the progression of osteoarthritis. *J Rheumatol Suppl* (2004); 70: 77-80.

Burr DB, Radin EL. Microfractures and microcracks in subchondral bone: are they relevant to osteoarthrosis? *Rheum Dis Clin North Am* (2003); 29: 675-685.

Cerejo R, Dunlop DD, Cahue S, Channin D, Song J, Sharma L. The influence of alignment on risk of knee osteoarthritis progression according to baseline stage of disease. *Arthritis Rheum* (2002); 46: 2632-2636.

Chang A, Hayes K, Dunlop D, Hurwitz D, Song J, Cahue S, Genge R, Sharma L. Thrust during ambulation and the progression of knee osteoarthritis. *Arthritis Rheum* (2004); 50: 3897-3903.

Cheing GL, Hui-Chan CW. The motor dysfunction of patients with knee osteoarthritis in a Chinese population. *Arthritis Rheum* (2001); 45: 62-68.

Chen WL, O'Connor JJ, Radin EL. A comparison of the gaits of Chinese and Caucasian women with particular reference to their heelstrike transients. *Clin Biomech* (2003); 18: 207-213.

Childs JD, Sparto PJ, Fitzgerald GK, Bizzini M, Irrgang JJ. Alterations in lower extremity movement and muscle activation patterns in individuals with knee osteoarthritis. *Clin Biomech* (2004); 19: 44-49.

Collins JJ, Whittle MW. Impulsive Forces During Walking and Their Clinical Implications. *Clin Biomech* (1989); 4: 179-187.

Costigan PA, Deluzio KJ, Wyss UP. Knee and hip kinetics during normal stair climbing. *Gait Posture* (2002); 16: 31-37.

Creamer P, Lethbridge-Cejku M, Hochberg MC. Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures. *J Rheumatol* (1999); 26: 1785-1792.

Creamer P, Lethbridge-Cejku M, Hochberg MC. Factors associated with functional impairment in symptomatic knee osteoarthritis. *Rheumatology (Oxford)* (2000); 39: 490-496.

D'Agostino MA, Conaghan P, Le BM, Baron G, Grassi W, Martin-Mola E, Wakefield R, Brasseur JL, So A, Backhaus M, Malaise M, Burmester G, Schmidely N, Ravaud P, Dougados M, Emery P. EULAR report on the use of ultrasonography in painful knee osteoarthritis. Part 1: prevalence of inflammation in osteoarthritis. *Ann Rheum Dis* (2005); 64: 1703-1709.

de Miguel ME, Cobo IT, Uson JJ, Bonilla HG, Martin ME. Clinical and ultrasonographic findings related to knee pain in osteoarthritis. *Osteoarthritis Cartilage* (2006); 14: 540-544.

Derrick TR, Dereu D, McLean SP. Impacts and kinematic adjustments during an exhaustive run. *Med Sci Sports Exerc* (2002); 34: 998-1002.

DeVita P, Hortobagyi T, Barrier J. Gait biomechanics are not normal after anterior cruciate ligament reconstruction and accelerated rehabilitation. *Med Sci Sports Exerc* (1998); 30: 1481-1488.

Dieppe PA. Relationship between symptoms and structural change in osteoarthritis. what are the important targets for osteoarthritis therapy? *J Rheumatol Suppl* (2004); 70: 50-53.

Draganich LF, Andriacchi TP, Andersson GB. Interaction between intrinsic knee mechanics and the knee extensor mechanism. *J Orthop Res* (1987); 5: 539-547.

Ervilha UF, Farina D, Arendt-Nielsen L, Graven-Nielsen T. Experimental muscle pain changes motor control strategies in dynamic contractions. *Exp Brain Res* (2005); 164: 215-224.

Farina D, rendt-Nielsen L, Graven-Nielsen T. Experimental muscle pain decreases voluntary EMG activity but does not affect the muscle potential evoked by transcutaneous electrical stimulation. *Clin Neurophysiol* (2005); 116: 1558-1565.

Felson DT. The sources of pain in knee osteoarthritis. *Curr Opin Rheumatol* (2005); 17: 624-628.

Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. *Ann Intern Med* (1988); 109: 18-24.

Felson DT, Goggins J, Niu J, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. *Arthritis Rheum* (2004); 50: 3904-3909.

Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, Kington RS, Lane NE, Nevitt MC, Zhang Y, Sowers M, McAlindon T, Spector TD, Poole AR, Yanovski SZ, Ateshian G, Sharma L, Buckwalter JA, Brandt KD, Fries JF. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* (2000); 133: 635-646.

Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* (1987); 30: 914-918.

Fisher NM, Pendergast DR. Reduced muscle function in patients with osteoarthritis. *Scand J Rehabil Med* (1997a); 29: 213-221.

Fisher NM, White SC, Yack HJ, Smolinski RJ, Pendergast DR. Muscle function and gait in patients with knee osteoarthritis before and after muscle rehabilitation. *Disabil Rehabil* (1997b); 19: 47-55.

Fitzgerald GK, Piva SR, Irrgang JJ. Reports of joint instability in knee osteoarthritis: its prevalence and relationship to physical function. *Arthritis Rheum* (2004); 51: 941-946.

Flynn JM, Holmes JD, Andrews DM. The effect of localized leg muscle fatigue on tibial impact acceleration. *Clin Biomech* (2004); 19: 726-732.

Folman Y, Wosk J, Voloshin A, Liberty S. Cyclic impacts on heel strike: a possible biomechanical factor in the etiology of degenerative disease of the human locomotor system. *Arch Orthop Trauma Surg* (1986); 104: 363-365.

Geborek P, Moritz U, Wollheim FA. Joint capsular stiffness in knee arthritis. Relationship to intraarticular volume, hydrostatic pressures, and extensor muscle function. *J Rheumatol* (1989); 16: 1351-1358.

Gill HS, O'Connor JJ. Heelstrike and the pathomechanics of osteoarthrosis: a pilot gait study. *J Biomech* (2003); 36: 1625-1631.

Graven-Nielsen T, Arendt-Nielsen L, Svensson P, Jensen TS. Experimental muscle pain:A quantitative study of local and referred pain in humans following injection of hypertonic saline. *Journal of Musculoskeletal Pain* (1997); 5: 49-69.

Graven-Nielsen T, Lund H, Arendt-Nielsen L, Danneskiold-Samsoe B, Bliddal H. Inhibition of maximal voluntary contraction force by experimental muscle pain: a centrally mediated mechanism. *Muscle Nerve* (2002); 26: 708-712.

Graven-Nielsen T, Mense S. The peripheral apparatus of muscle pain: evidence from animal and human studies. *Clin J Pain* (2001); 17: 2-10.

Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* (1985); 132: 919-923.

Helliwell PS, Smeathers JE, Wright V. Shock absorption by the spinal column in normals and in ankylosing spondylitis. *Proc Inst Mech Eng* (1989); 203: 187-190.

Henriksen M., Lund H., Moe-Nilssen R, Bliddal H., Danneskiold-Samsoe B. Test-Retest Reliability of Trunk Accelerometric Gait analysis. *Gait Posture* (2004); 19: 288-297.

Hilding MB, Lanshammar H, Ryd L. A relationship between dynamic and static assessments of knee joint load. Gait analysis and radiography before and after knee replacement in 45 patients. *Acta Orthop Scand* (1995); 66: 317-320.

Hortobagyi T, Garry J, Holbert D, DeVita P. Aberrations in the control of quadriceps muscle force in patients with knee osteoarthritis. *Arthritis Rheum* (2004); 51: 562-569.

Hortobagyi T, Westerkamp L, Beam S, Moody J, Garry J, Holbert D, DeVita P. Altered hamstring-quadriceps muscle balance in patients with knee osteoarthritis. *Clin Biomech* (2005); 20: 97-104.

Hsieh HH, Walker PS. Stabilizing mechanisms of the loaded and unloaded knee joint. *J Bone Joint Surg Am* (1976); 58: 87-93.

Hubley-Kozey CL, Deluzio KJ, Landry SC, McNutt JS, Stanish WD. Neuromuscular alterations during walking in persons with moderate knee osteoarthritis. *J Electromyogr Kinesiol* (2006); 16: 365-378.

Hunter DJ, Felson DT. Osteoarthritis. *BMJ* (2006); 332: 639-642.

Hurd WJ, Chmielewski TL, Axe MJ, Davis I, Snyder-Mackler L. Differences in normal and perturbed walking kinematics between male and female athletes. *Clin Biomech* (2004); 19: 465-472.

Hurley MV, Scott DL, Rees J, Newham DJ. Sensorimotor changes and functional performance in patients with knee osteoarthritis. *Ann Rheum Dis* (1997); 56: 641-648.

Hurwitz DE, Ryals AB, Case JP, Block JA, Andriacchi TP. The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain. *J Orthop Res* (2002); 20: 101-107.

Hurwitz DE, Ryals AR, Block JA, Sharma L, Schnitzer TJ, Andriacchi TP. Knee pain and joint loading in subjects with osteoarthritis of the knee. *J Orthop Res* (2000); 18: 572-579.

Hurwitz DE, Sumner DR, Andriacchi TP, Sugar DA. Dynamic knee loads during gait predict proximal tibial bone distribution. *J Biomech* (1998); 31: 423-430.

Hurwitz DE, Sumner DR, Block JA. Bone density, dynamic joint loading and joint degeneration. A review. *Cells Tissues Organs* (2001); 169: 201-209.

Huskisson EC. Measurement of pain. *Lancet* (1974); 2: 1127-1131.

Jackson BD, Wluka AE, Teichtahl AJ, Morris ME, Cicuttini FM. Reviewing knee osteoarthritis--a biomechanical perspective. *J Sci Med Sport* (2004); 7: 347-357.

Jefferson RJ, Collins JJ, Whittle MW, Radin EL, O'Connor JJ. The role of the quadriceps in controlling impulsive forces around heel strike. *Proc Inst Mech Eng* (1990); 204: 21-28.

Jensen K, Graf BK. The effects of knee effusion on quadriceps strength and knee intraarticular pressure. *Arthroscopy* (1993); 9: 52-56.

Johansson H, Djupsjobacka M, Sjolander P. Influences on the gamma-muscle spindle system from muscle afferents stimulated by KCl and lactic acid. *Neurosci Res* (1993); 16: 49-57.

Johansson H, Sjolander P, Sojka P. Receptors in the knee joint ligaments and their role in the biomechanics of the joint. *Crit Rev Biomed Eng* (1991); 18: 341-368.

Johnson GR. The use of spectral analysis to assess the performance of shock absorbing footwear. *Eng Med* (1986); 15: 117-122.

Johnson GR. Measurement of Shock Acceleration During Walking and Running Using the Shock Meter. *Clin Biomech* (1990); 5: 47-50.

Kaufman KR, Hughes C, Morrey BF, Morrey M, An KN. Gait characteristics of patients with knee osteoarthritis. *J Biomech* (2001); 34: 907-915.

Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* (1957); 16: 494-502.

Kerrigan DC, Todd MK, Della CU. Gender differences in joint biomechanics during walking: normative study in young adults. *Am J Phys Med Rehabil* (1998); 77: 2-7.

Kim W, Voloshin AS, Johnson SH, Simkin A. Measurement of the impulsive bone motion by skin-mounted accelerometers. *J Biomech Eng* (1993); 115: 47-52.

Kim W, Voloshin AS, Johnson SH. Modeling of heel strike transients during running. *Human Movement Science* (1994); 13: 221-244.

Kirtley C, Whittle MW, Jefferson RJ. Influence of walking speed on gait parameters. *J Biomed Eng* (1985); 7: 282-288.

Kristoffersen H, Torp-Pedersen S, Terslev L, Qvistgaard E, Holm CC, Ellegaard K, Bliddal H. Indications of inflammation visualized by ultrasound in osteoarthritis of the knee. *Acta Radiol* (2006); 47: 281-286.

Kuster MS, Wood GA, Stachowiak GW, Gachter A. Joint load considerations in total knee replacement. *J Bone Joint Surg Br* (1997); 79: 109-113.

Lafortune MA, Lake MJ, Hennig EM. Differential shock transmission response of the human body to impact severity and lower limb posture. *J Biomech* (1996); 29: 1531-1537.

Le Pera D, Graven-Nielsen T, Valeriani M, Oliviero A, Di L, V, Tonali PA, Arendt-Nielsen L. Inhibition of motor system excitability at cortical and spinal level by tonic muscle pain. *Clin Neurophysiol* (2001); 112: 1633-1641.

Ledingham J, Regan M, Jones A, Doherty M. Radiographic patterns and associations of osteoarthritis of the knee in patients referred to hospital. *Ann Rheum Dis* (1993); 52: 520-526.

Lelas JL, Merriman GJ, Riley PO, Kerrigan DC. Predicting peak kinematic and kinetic parameters from gait speed. *Gait Posture* (2003); 17: 106-112.

Lewek MD, Rudolph KS, Snyder-Mackler L. Control of frontal plane knee laxity during gait in patients with medial compartment knee osteoarthritis. *Osteoarthritis Cartilage* (2004a); 12: 745-751.

Lewek MD, Rudolph KS, Snyder-Mackler L. Quadriceps femoris muscle weakness and activation failure in patients with symptomatic knee osteoarthritis. *J Orthop Res* (2004b); 22: 110-115.

Lewek MD, Scholz J, Rudolph KS, Snyder-Mackler L. Stride-to-stride variability of knee motion in patients with knee osteoarthritis. *Gait Posture* (2006); 23: 505-511.

Lindemann U, Becker C, Unnewehr I, Muche R, Aminin K, Dejnabadi H, Nikolaus T, Puhl W, Huch K, Dreinhofer KE. Gait analysis and WOMAC are complementary in assessing functional outcome in total hip replacement. *Clin Rehabil* (2006); 20: 413-420.

Loeuille D, Chary-Valckenaere I, Champigneulle J, Rat AC, Toussaint F, Pinzano-Watrin A, Goebel JC, Mainard D, Blum A, Pourel J, Netter P, Gillet P. Macroscopic and microscopic features of synovial membrane inflammation in the osteoarthritic knee: correlating magnetic resonance imaging findings with disease severity. *Arthritis Rheum* (2005); 52: 3492-3501.

Louie JK, Mote CD, Jr. Contribution of the musculature to rotatory laxity and torsional stiffness at the knee. *J Biomech* (1987); 20: 281-300.

Lund H., Juul-Kristensen B, Christensen H, Bliddal H., Danneskiold-Samsoe B. Impaired proprioception of both knees and elbows in patients with knee osteoarthritis compared to healthy controls. Osteoarthritis and Cartilage 12 (Suppl B), S25. 2004.

Lund JP, Donga R, Widmer CG, Stohler CS. The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. *Can J Physiol Pharmacol* (1991); 69: 683-694.

Maly MR, Costigan PA, Olney SJ. Determinants of self-report outcome measures in people with knee osteoarthritis. *Arch Phys Med Rehabil* (2006); 87: 96-104.

Manetta J, Franz LH, Moon C, Perell KL, Fang M. Comparison of hip and knee muscle moments in subjects with and without knee pain. *Gait Posture* (2002); 16: 249-254.

Markolf KL, Bargar WL, Shoemaker SC, Amstutz HC. The role of joint load in knee stability. *J Bone Joint Surg Am* (1981); 63: 570-585.

Markolf KL, Graff-Radford A, Amstutz HC. In vivo knee stability. A quantitative assessment using an instrumented clinical testing apparatus. *J Bone Joint Surg Am* (1978); 60: 664-674.

Marks R, Quinney HA, Wessel J. Proprioceptive sensibility in women with normal and osteoarthritic knee joints. *Clin Rheumatol* (1993); 12: 170-175.

McAlindon TE, Cooper C, Kirwan JR, Dieppe PA. Determinants of disability in osteoarthritis of the knee. *Ann Rheum Dis* (1993); 52: 258-262.

McGibbon CA, Krebs DE. Compensatory gait mechanics in patients with unilateral knee arthritis. *J Rheumatol* (2002); 29: 2410-2419.

Mense S. Nociception from skeletal muscle in relation to clinical muscle pain. *Pain* (1993); 54: 241-289.

Mercer JA, Vance J, Hreljac A, Hamill J. Relationship between shock attenuation and stride length during running at different velocities. *Eur J Appl Physiol* (2002); 87: 403-408.

Merritt JL. Soft tissue mechanisms of pain in osteoarthritis. *Semin Arthritis Rheum* (1989); 18: 51-56.

Merskey H, Bonica JJ, Carmon A, Dubner R, Kerr FWL, Lindblom U, Mumford JM, Nathan PW, Nordenbos W, Pagni CA, Renear MJ, Sternbach RA, Sunderland SS. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. *Pain* (1979); 6: 249.

Messier SP, DeVita P, Cowan RE, Seay J, Young HC, Marsh AP. Do older adults with knee osteoarthritis place greater loads on the knee during gait? A preliminary study. *Arch Phys Med Rehabil* (2005); 86: 703-709.

Messier SP, Loeser RF, Hoover JL, Semble EL, Wise CM. Osteoarthritis of the knee: effects on gait, strength, and flexibility. *Arch Phys Med Rehabil* (1992); 73: 29-36.

Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. *Ann Rheum Dis* (2002); 61: 617-622.

Mizrahi J, Verbitsky O, Isakov E. Shock accelerations and attenuation in downhill and level running. *Clin Biomech* (2000); 15: 15-20.

Moe-Nilssen R. A new method for evaluating motor control in gait under real-life environmental conditions. Part 2: Gait analysis. *Clin Biomech* (1998a); 13: 328-335.

Moe-Nilssen R. Test-retest reliability of trunk accelerometry during standing and walking. *Arch Phys Med Rehabil* (1998b); 79: 1377-1385.

Moreland JR, Bassett LW, Hanker GJ. Radiographic analysis of the axial alignment of the lower extremity. *J Bone Joint Surg Am* (1987); 69: 745-749.

Morrison JB. Bioengineering analysis of force actions transmitted by the knee joint. *Biomed Eng* (1968); 3: 164-170.

Muir P, McCarthy J, Radtke CL, Markel MD, Santschi EM, Scollay MC, Kalscheur VL. Role of endochondral ossification of articular cartilage and functional adaptation of the subchondral plate in the development of fatigue microcracking of joints. *Bone* (2006); 38: 342-349.

Mundermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. *Arthritis Rheum* (2005a); 52: 2835-2844.

Mundermann A, Dyrby CO, Andriacchi TP, King KB. Serum concentration of cartilage oligomeric matrix protein (COMP) is sensitive to physiological cyclic loading in healthy adults. *Osteoarthritis Cartilage* (2005b); 13: 34-38.

Mundermann A, Dyrby CO, Hurwitz DE, Sharma L, Andriacchi TP. Potential strategies to reduce medial compartment loading in patients with knee osteoarthritis of varying severity: reduced walking speed. *Arthritis Rheum* (2004); 50: 1172-1178.

Mundermann A, King KB, Dyrby CO, Andriacchi TP. Biomarker for knee osteoarthritis (COMP) is sensitive to physiological cyclic loading in healthy adults. ISB XXth congress . 2005c.

Newman AB, Simonsick EM, Naydeck BL, Boudreau RM, Kritchevsky SB, Nevitt MC, Pahor M, Satterfield S, Brach JS, Studenski SA, Harris TB. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *JAMA* (2006); 295: 2018-2026.

Nigg BM. Biomechanics of the musculo-skeletal System. Chichester, England: John Wiley & Sons Ltd, 1994.

Nigg BM, van den Bogert AJ. Simulation. In: Nigg BM, Herzog W, editors. Biomechanics of the musculo-skeletal System. Chichester, England: John Wiley & Sons Ltd, 1994. pp. 551-566.

Oberg T, Karsznia A, Oberg K. Joint angle parameters in gait: reference data for normal subjects, 10-79 years of age. *J Rehabil Res Dev* (1994); 31: 199-213.

Ohnhaus EE, Adler R. Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. *Pain* (1975); 1: 379-384.

Olmstead TG, Wevers HW, Bryant JT, Gouw GJ. Effect of muscular activity on valgus/varus laxity and stiffness of the knee. *J Biomech* (1986); 19: 565-577.

Pai YC, Rymer WZ, Chang RW, Sharma L. Effect of age and osteoarthritis on knee proprioception. *Arthritis Rheum* (1997); 40: 2260-2265.

Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* (1991); 39: 142-148.

Polianskis R, Graven-Nielsen T, rendt-Nielsen L. Spatial and temporal aspects of deep tissue pain assessed by cuff algometry. *Pain* (2002); 100: 19-26.

Pope MH, Johnson RJ, Brown DW, Tighe C. The role of the musculature in injuries to the medial collateral ligament. *J Bone Joint Surg Am* (1979); 61: 398-402.

Potter JM, Evans AL, Duncan G. Gait speed and activities of daily living function in geriatric patients. *Arch Phys Med Rehabil* (1995); 76: 997-999.

Pratt DJ. Medium term comparison of shock attenuating insoles using a spectral analysis technique. *J Biomed Eng* (1988); 10: 426-429.

Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* (1983); 17: 45-56.

Prodromos CC, Andriacchi TP, Galante JO. A relationship between gait and clinical changes following high tibial osteotomy. *J Bone Joint Surg Am* (1985); 67: 1188-1194.

Qvistgaard E, Kristoffersen H, Terslev L, Danneskiold-Samsoe B, Torp-Pedersen S, Bliddal H. Guidance by ultrasound of intra-articular injections in the knee and hip joints. *Osteoarthritis Cartilage* (2001); 9: 512-517.

Radin EL, Ehrlich MG, Chernack R, Abernethy P, Paul IL, Rose RM. Effect of repetitive impulsive loading on the knee joints of rabbits. *Clin Orthop* (1978); 288-293.

Radin EL, Orr RB, Kelman JL, Paul IL, Rose RM. Effect of prolonged walking on concrete on the knees of sheep. *J Biomech* (1982); 15: 487-492.

Radin EL, Parker HG, Pugh JW, Steinberg RS, Paul IL, Rose RM. Response of joints to impact loading. 3. Relationship between trabecular microfractures and cartilage degeneration. *J Biomech* (1973); 6: 51-57.

Reijman M, Bierma-Zeinstra SM, Pols HA, Koes BW, Stricker BH, Hazes JM. Is there an association between the use of different types of nonsteroidal antiinflammatory drugs and radiologic progression of osteoarthritis? The Rotterdam Study. *Arthritis Rheum* (2005); 52: 3137-3142.

Robbins S, Waked E, Krouglicof N. Vertical impact increase in middle age may explain idiopathic weight-bearing joint osteoarthritis. *Arch Phys Med Rehabil* (2001); 82: 1673-1677.

Robon MJ, Perell KL, Fang M, Guererro E. The relationship between ankle plantar flexor muscle moments and knee compressive forces in subjects with and without pain. *Clin Biomech* (2000); 15: 522-527.

Roos EM, Klassbo M, Lohmander LS. WOMAC osteoarthritis index. Reliability, validity, and responsiveness in patients with arthroscopically assessed osteoarthritis. Western Ontario and MacMaster Universities. *Scand J Rheumatol* (1999); 28: 210-215.

Schaible HG, Ebersberger A, Von Banchet GS. Mechanisms of pain in arthritis. *Ann N Y Acad Sci* (2002); 966: 343-354.

Schaible HG, Grubb BD. Afferent and spinal mechanisms of joint pain. *Pain* (1993); 55: 5-54.

Schaible HG, Schmidt RF. Effects of an experimental arthritis on the sensory properties of fine articular afferent units. *J Neurophysiol* (1985); 54: 1109-1122.

Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. *J Orthop Res* (1991); 9: 113-119.

Schnitzer TJ, Popovich JM, Andersson GB, Andriacchi TP. Effect of piroxicam on gait in patients with osteoarthritis of the knee. *Arthritis Rheum* (1993); 36: 1207-1213.

Schomburg ED, Steffens H, Kniffki KD. Contribution of group III and IV muscle afferents to multisensorial spinal motor control in cats. *Neurosci Res* (1999); 33: 195-206.

Schulte E, Ciubotariu A, Arendt-Nielsen L, Disselhorst-Klug C, Rau G, Graven-Nielsen T. Experimental muscle pain increases trapezius muscle activity during sustained isometric contractions of arm muscles. *Clin Neurophysiol* (2004); 115: 1767-1778.

Seering WP, Piziali RL, Nagel DA, Schurman DJ. The function of the primary ligaments of the knee in varus-valgus and axial rotation. *J Biomech* (1980); 13: 785-794.

Shakespeare DT, Stokes M, Sherman KP, Young A. Reflex inhibition of the quadriceps after meniscectomy: lack of association with pain. *Clin Physiol* (1985); 5: 137-144.

Sharma L. The role of proprioceptive deficits, ligamentous laxity, and malalignment in development and progression of knee osteoarthritis. *J Rheumatol Suppl* (2004); 70: 87-92.

Sharma L, Hayes KW, Felson DT, Buchanan TS, Kirwan-Mellis G, Lou C, Pai YC, Dunlop DD. Does laxity alter the relationship between strength and physical function in knee osteoarthritis? *Arthritis Rheum* (1999a); 42: 25-32.

Sharma L, Hurwitz DE, Thonar EJ, Sum JA, Lenz ME, Dunlop DD, Schnitzer TJ, Kirwan-Mellis G, Andriacchi TP. Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. *Arthritis Rheum* (1998); 41: 1233-1240.

Sharma L, Kapoor D, Issa S. Epidemiology of osteoarthritis: an update. *Curr Opin Rheumatol* (2006); 18: 147-156.

Sharma L, Lou C, Cahue S, Dunlop DD. The mechanism of the effect of obesity in knee osteoarthritis: the mediating role of malalignment. *Arthritis Rheum* (2000); 43: 568-575.

Sharma L, Lou C, Felson DT, Dunlop DD, Kirwan-Mellis G, Hayes KW, Weinrach D, Buchanan TS. Laxity in healthy and osteoarthritic knees. *Arthritis Rheum* (1999b); 42: 861-870.

Sharma L, Pai YC, Holtkamp K, Rymer WZ. Is knee joint proprioception worse in the arthritic knee versus the unaffected knee in unilateral knee osteoarthritis? *Arthritis Rheum* (1997); 40: 1518-1525.

Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *JAMA* (2001); 286: 188-195.

Shelburne KB, Torry MR, Pandy MG. Contributions of muscles, ligaments, and the ground-reaction force to tibiofemoral joint loading during normal gait. *J Orthop Res* (2006); 24: 1983-1990.

Shoemaker SC, Markolf KL. Effects of joint load on the stiffness and laxity of ligament-deficient knees. An in vitro study of the anterior cruciate and medial collateral ligaments. *J Bone Joint Surg Am* (1985); 67: 136-146.

Shorten MR, Winslow DS. Spectral Analysis of Impact Shock During Running. *Int J Sport Biomech* (1992); 8: 288-304.

Shrader MW, Draganich LF, Pottenger LA, Piotrowski GA. Effects of knee pain relief in osteoarthritis on gait and stair-stepping. *Clin Orthop* (2004); 188-193.

Simon SR, Radin EL, Paul IL, Rose RM. The response of joints to impact loading. II. In vivo behavior of subchondral bone. *J Biomech* (1972); 5: 267-272.

Simonsen EB, Dyhre-Poulsen P, Voigt M, Aagaard P, Fallentin N. Mechanisms contributing to different joint moments observed during human walking. *Scand J Med Sci Sports* (1997); 7: 1-13.

Slater H, rendt-Nielsen L, Wright A, Graven-Nielsen T. Experimental deep tissue pain in wrist extensors--a model of lateral epicondylalgia. *Eur J Pain* (2003); 7: 277-288.

Solomonow M, Krogsgaard M. Sensorimotor control of knee stability. A review. *Scand J Med Sci Sports* (2001); 11: 64-80.

Sonn U. Longitudinal studies of dependence in daily life activities among elderly persons. *Scand J Rehabil Med Suppl* (1996); 34: 1-35.

Spencer JD, Hayes KC, Alexander IJ. Knee joint effusion and quadriceps reflex inhibition in man. *Arch Phys Med Rehabil* (1984); 65: 171-177.

Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage* (2005); 13: 769-781.

Stauffer RN, Chao EY, Gyory AN. Biomechanical gait analysis of the diseased knee joint. *Clin Orthop Relat Res* (1977); 246-255.

Sterling M, Jull G, Wright A. The effect of musculoskeletal pain on motor activity and control. *J Pain* (2001); 2: 135-145.

Stokes M, Young A. The contribution of reflex inhibition to arthrogenous muscle weakness. *Clin Sci (Lond)* (1984); 67: 7-14.

Sum J, Hurwitz DE, Janik RC, Dressander J, Andriacchi TP, Schnitzer TJ, Andersson GBJ. The Impact of Osteoarthritic Knee Pain on Dynamic Loads during Gait. *Gait Posture* (1997); 5: 173.

Taylor WR, Heller MO, Bergmann G, Duda GN. Tibio-femoral loading during human gait and stair climbing. *J Orthop Res* (2004); 22: 625-632.

Teichtahl AJ, Cicuttini FM, Janakiramanan N, Davis SR, Wluka AE. Static knee alignment and its association with radiographic knee osteoarthritis. *Osteoarthritis Cartilage* (2006); 14: 958-962.

Thambyah A, Pereira BP, Wyss U. Estimation of bone-on-bone contact forces in the tibiofemoral joint during walking. *Knee* (2005); 12: 383-388.

Torry MR, Decker MJ, Viola RW, O'Connor DD, Steadman JR. Intra-articular knee joint effusion induces quadriceps avoidance gait patterns. *Clin Biomech* (2000); 15: 147-159.

Vaughan CL, Davis BL, O'Connor JC. Dynamics of Human Gait. Cape Town: Kiboho Publishers, 1999.

Visser JJ, Hoogkamer JE, Bobbert MF, Huijing PA. Length and moment arm of human leg muscles as a function of knee and hip-joint angles. *Eur J Appl Physiol Occup Physiol* (1990); 61: 453-460.

Voloshin A. The influence of walking speed on dynamic loading on the human musculoskeletal system. *Med Sci Sports Exerc* (2000); 32: 1156-1159.

Voloshin A, Wosk J. Influence of artificial shock absorbers on human gait. *Clin Orthop* (1981a); 52-56.

Voloshin A, Wosk J. An in vivo study of low back pain and shock absorption in the human locomotor system. *J Biomech* (1982); 15: 21-27.

Voloshin A, Wosk J, Brull M. Force wave transmission through the human locomotor system. *J Biomech Eng* (1981b); 103: 48-50.

Voloshin AS. Shock absorption during running and walking. *J Am Podiatr Med Assoc* (1988); 78: 295-299.

Voloshin AS, Mizrahi J, Verbitsky O, Isakov E. Dynamic loading on the human musculoskeletal system -- effect of fatigue. *Clin Biomech* (1998); 13: 515-520.

Wada M, Imura S, Baba H, Shimada S. Knee laxity in patients with osteoarthritis and rheumatoid arthritis. *Br J Rheumatol* (1996); 35: 560-563.

Wada M, Maezawa Y, Baba H, Shimada S, Sasaki S, Nose Y. Relationships among bone mineral densities, static alignment and dynamic load in patients with medial compartment knee osteoarthritis. *Rheumatology (Oxford)* (2001); 40: 499-505.

Wang CJ, Walker PS. Rotatory laxity of the human knee joint. *J Bone Joint Surg Am* (1974); 56: 161-170.

Wang K, Svensson P, Arendt-Nielsen L. Modulation of exteroceptive suppression periods in human jaw-closing muscles by local and remote experimental muscle pain. *Pain* (1999); 82: 253-262.

Whittle MW. Force platform measurement of the heelstrike transient in normal walking. *Gait Posture* (1997); 5: 173-174.

Whittle MW. Generation and attenuation of transient impulsive forces beneath the foot: a review. *Gait Posture* (1999); 10: 264-275.

Winter DA. Overall principle of lower limb support during stance phase of gait. *J Biomech* (1980); 13: 923-927.

Winter DA. Biomechanics and Motor Control of Human Movement, Vol. 2 Wiley-Interscience, 1990.

Woodforde JM, Merskey H. Some relationships between subjective measures of pain. *J Psychosom Res* (1972); 16: 173-178.

Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* (2003); 81: 646-656.

Wosk J, Voloshin A. Wave attenuation in skeletons of young healthy persons. *J Biomech* (1981); 14: 261-267.

Wosk J, Voloshin AS. Low back pain: conservative treatment with artificial shock absorbers. *Arch Phys Med Rehabil* (1985); 66: 145-148.