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Tuomas Liikavainio

Biomechanics of Gait and Physical Function in Patients with Knee Osteoarthritis

Thigh Muscle Properties and Joint Loading Assessment

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UNIVERSITY OF
EASTERN FINLAND

TUOMAS LIIKAVAINIO

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ABSTRACT

The cause of osteoarthritis (OA) remains unknown but the mechanical aspects in the etiopathogenesis of this disease seem to be important. Knee OA does not only affect the articular cartilage but the other joint structures and periarticular muscles, and weakness in the thigh muscles may also be a risk factor for knee OA. The present series of studies were designed to examine the gait biomechanics and physical function of patients suffering from knee OA with a special emphasis on investigating the properties of the thigh muscles, and the usefulness of skin mounted accelerometers (SMAs) in assessing impact joint loading during walking. The objective and subjective physical function was investigated with a battery of physical function tests and questionnaires (WOMAC, RAND-36), respectively. In patients with knee OA, the altered muscle activation patterns during walking pointed to a disease specific neuromuscular compensatory mechanism. The SMAs proved to be practical and reproducible for use in the clinical environment for collection of data that may be used to estimate joint loads. The radiographic knee OA grade did not display a linear correlation with physical function, but passive knee motion, knee extension strength, and WOMAC subscales were related to the radiographic severity of the disease. The results highlight the effect of thigh muscle strength on physical function in patients with knee OA. Since the severity of radiographic knee OA clearly had adverse effects on functional ability at the later stages of the disease, it is important to assess the patient's physical function in detail when deciding on treatment policy in symptomatic knee OA.

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Medical Subject Headgings: Biomechanics; Electromyography; Exercise Test; Gait; Muscle Strength; Osteoarthritis, Knee; Quadriceps Muscle/rehabilitation; Questionnaires; Reproducibility of Results; Walking/physiology

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TIIVISTELMÄ

Nivelrikon syytä ei tunneta, mutta mekaanisten tekijöiden osuus nivelrikon etiopatogeneesissa näyttää olevan keskeinen. Polvinivelrikossa ei vaurioidu ainoastaan nivelrusto vaan sairauden patologiset muutokset kohdistuvat myös muihin nivelrakenteisiin sekä polviniveltä liikuttaviin lihaksiin. Toisaalta reisilihasten heikkous saattaa olla polvinivelrikon riskitekijä. Tässä väitöskirjatutkimuksessa tutkittiin polvinivelrikkopotilaiden kävelyn biomekaniikkaa ja toimintakykyä. Erityistä huomiota kiinnitettiin reiden lihasten ominaisuuksien tutkimiseen. Tarkemmin selvitettiin myös iholle kiinnitettävien kiihtyvyysantureiden käytettävyyttä kävelyn aikaisen niveleen kohdistuvan iskukuormituksen mittaamisessa. Fyysistä toimintakykyä mitattiin testipatteristolla ja subjektiivista toimintakykyä arvioitiin kyselykaavakkeilla (WOMAC ja RAND-36). Polvinivelrikkopotilaiden lihasaktiivisuusmallit olivat erilaiset kävelyssä verrattuna terveisiin kontrollihenkilöihin, mikä viittasi potilaiden käyttävän hermo-lihasjärjestelmän kompensaatiomekanismeja saman kävelysuorituksen toteuttamiseen. Kiihtyvyysanturit osoittautuivat käytännöllisiksi, ja niiden avulla voidaan arvioida toistettavasti nivelen iskukuormitusta kliinisessä työssä. Radiologinen polvinivelrikko ei ollut yhteydessä fyysisen toimintakyvyn kanssa, mutta passiivinen polvinivelen liikelaajuus, polven ojennusvoima ja WOMAC-kyselyn osiot korreloivat radiologisen polvinivelrikon vaikeusasteeseen kanssa. Tutkimuksen tulosten perusteella reisilihasten lihasvoiman merkitys toimintakyvylle on keskeinen polvinivelrikkopotilailla. Koska fyysinen ja subjektiivinen toimintakyky näyttää olevan alentunut selvemmin vasta radiologisesti vaikeaa polvinivelrikkoa sairastavilla, on tärkeää selvittää potilaan toimintakyky ennen kuin päätetään oireisen polvinivelrikon operatiivisesta hoidosta.

Luokitus: WE 348

Yleinen suomalainen asiasanasto (YSA): biomekaniikka, kävely, lihakset, luotettavuus, nivelrikko, polvet, toimintakyky

To Riitta, Siiri, Amanda, and Iisak

But the Lord said to me, "Do not say, 'I am too young.' You must go to everyone I send you to and say whatever I command you.

Jeremiah 1:7

Q.D.B.V.

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Kangosjärvi, May 2010

Tuomas Liikavainio

List of Original Publications

The present thesis is based on the following original publications* which are referred to by their Roman numerals.

I Liikavainio T, Isolehto J, Helminen HJ, Perttunen J, Lepola V, Kiviranta I, Arokoski JPA, Komi PV. Loading and gait symmetry in level and stair walking in asymptomatic subjects with knee osteoarthritis: Importance of quadriceps femoris in reducing impact force in heel strike. The Knee 2007; 14 (3): 231-8.

II Liikavainio T, Bragge T, Hakkarainen M, Jurvelin JS, Karjalainen PA, Arokoski JPA. Reproducibility of loading measurements with skin mounted accelerometers during walking. Archives of Physical Medicine and Rehabilitation 2007; 88 (7): 907-15.

III Liikavainio T, Bragge T, Hakkarainen M, Karjalainen PA, Arokoski JP. Gait and muscle activation changes in men with knee osteoarthritis. The Knee 2010; 17 (1): 69-76.

IV Liikavainio T, Lyytinen T, Tyrväinen E, Sipilä S, Arokoski JP. Physical function and properties of quadriceps femoris muscle in men with knee osteoarthritis. Archives of Physical Medicine and Rehabilitation 2008; 89 (11): 2185-94.

*Some unpublished data are also presented.

Contents

Abbreviations

A-P	antero-posterior
ASI	absolute symmetry index
a_z	axial acceleration
BF	biceps femoris muscle
BMI	body mass index, subject's mass divided by the square of height (kg/m^2)
BW	body weight
EMG	electromyography
F_x, F_y, F_z	ground reaction forces in the antero-posterior, medio-lateral and vertical directions, respectively
g	gravitational acceleration, $9.81 m/s^2$
GaM	gastrocnemius medialis muscle
GRF	ground reaction force
IPA	initial peak acceleration
(k)Hz	(kilo)hertz, unit of frequency (1 per second)
K-L	Kellgren-Lawrence ostroarthritis grading scale (0-4)
kPa	kilopascal, unit of pressure
LR	loading rate
M-L	medio-lateral
m/s	metre per second, unit of velocity
MRI	magnetic resonance imaging
MIVC	maximal isometric voluntary contraction
N/cm^2	unit of pressure, 10 kilopascal
Nm	Newton metre, unit of torque
OA	osteoarthritis
QFm	quadriceps femoris muscle
PP	peak-to-peak acceleration
RAND-36	RAND 36-Item Health Survey 1.0
RF	rectus femoris muscle of QFm
ROM	range of movement
SD	standard deviation
SF-36	Medical Outcome Study 36-Item Short-Form Health Survey
SMA	skin mounted accelerometer
TUG	timed up & go test
VAS	visual analogue scale for assessment of subjective pain (0-100).
VI, VM, VL	vastus intermedius, medialis, and lateralis muscle of QFm, respectively
WOMAC	the Western Ontario and McMaster Universities Osteorthritis Index
3-D	three dimensional

1 Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder. OA is characterised by degeneration of articular cartilage, joint space narrowing, pain, and disability (O'Reilly and Doherty 2003). The knee is one of the diarthrodial joints most commonly affected by OA. According to the Health 2000 examination survey, the age-adjusted prevalence of clinically diagnosed knee OA was 6.1% and 8.0% in men and women over 30 years, respectively. The prevalence of OA increases with age; over ten percents of Finnish men aged 55-74 years suffers from knee OA (Riihimäki et al. 2004). The annual costs of knee joint replacement operations in Finland in 2003 totalled nearly € 50 million solely (Remes et al. 2007). Today, 6% of all paid disability pensions can be attributed to OA in Finland. It is estimated that the direct and indirect costs of OA in Finland are nearly one billion euros per year (Heliövaara and Paavolainen 2008).

Knee OA is a multifactorial disease affecting the whole joint (O'Reilly and Doherty 2003, Arokoski et al. 2007). The symptoms of OA, such as pain and stiffness of the joint and muscle weakness are strong risk factors for mobility limitation and impaired quality of life (O'Reilly and Doherty 2003, Gorevic 2004). The main goals in the treatment of OA are to decrease pain and maintain or improve physical ability. Physical exercises combined with control of overweight, form the basis for the non-pharmaceutical treatment of OA disease. There are a number of factors such as comorbidities, psychological and social factors, which can influence physical function in this disorder. Thus, it is important to determine the individual causes of functional impairment of every OA patient in order to adopt the most appropriate rehabilitative methods in that particular case. However, there are no recommendations for which physical function test(s) would be optimal for evaluation of physical capacity of knee OA patients.

There is growing evidence that certain biomechanical properties, such as joint deformity and injury as well as obesity, are important in the etiopathogenesis of knee OA (Felson and Zhang 1998, Sharma 2001, Brandt et al. 2006). Strenuous impact stress, and even cyclic loading in the physiological range, may increase the risk of cartilage degeneration in joints with malalignment or instability (Buckwalter 1995, Nuki and Salter 2007). Though the role of the neuromuscular system is not fully understood, a weakness in the quadriceps femoris muscle (QFm) has been suggested to be fundamental in the etiopathogenesis of this disease (Slemenda et al. 1997, Slemenda et al. 1998). Therefore, gait analyses conducted to measure the mechanical loading of the knee joint during human locomotion have become more common recently as a research method in knee OA. However, due to some methodological limitations and different experimental designs used in some of the previous studies it is difficult to conclude whether the patients with knee OA load their lower extremities more forcefully than healthy subjects

during walking. At the same time, simpler methods are needed for clinical gait measurements, in order to investigate larger study populations under different circumstances.

The aim of the present series of studies was to examine the biomechanics of gait and physical function in knee OA patients with a special emphasis on the measurement of the properties of QFm and joint loading assessment. The results were compared to those obtained from the age- and sex-matched control subjects. The goal was also to develop simple methods for clinical gait analysis utilising skin mounted accelerometers (SMA) to measure impact loading.

2 Review of the Literature

2.1 PATHOGENESIS OF KNEE OSTEOARTHRITIS

2.1.1 Pathophysiology

OA is viewed as a metabolically active, dynamic process, including both cartilage destruction and repair. These processes may be iniated by several biochemical and mechanical insults (Brandt et al. 2003a, Goldring and Goldring 2007). The first OA changes occurring in articular cartilage include a decrease in the superficial proteoglycan content, deterioration of superficial collagen fibrils, and an increase in the water content. The loss of proteoglycans and collagen results in diminished cartilage stiffness (Buckwalter and Mankin 1998, Pritzker 2003). Subsequently, the chondrocytes increase the synthesis of cartilage matrix proteins, the destruction of components in the extracellular matrix accelerates, and the thickness of cartilage may even increase. At the same time, calcified cartilage and subchondral bone become thicker in a response to the increased formation and resorption of the subchondral bone (Buckwalter 1995, Arokoski et al. 2000).

Ultimately, the concentration of proteoglycans decreases and collagen fibrillation declines due to diminished repair capabilities of chondrocytes. This process leads to splits of the cartilage extending down to bone. The degenerated cartilage with the disrupted collagen network cannot regenerate, and this pushes the OA tissue to the point of no return (Buckwalter 1995, Arokoski et al. 2000). On the other hand, Radin et al. (1972, 1973) postulated that the repetitive impulsive loading may first induce trabecular microfractures in the subchondral bone. According to this theory, subsequent remodelling increases the stiffness and thickness of the subchondral bone in an attempt to dampen impact forces. As a consequence, the overlying cartilage may become overloaded and break down resulting in cartilage degeneration and loss.

Knee OA also affects the whole joint including the synovium and extra-articular muscles (Brandt et al. 2006) (Figure 1). The local inflammation reaction (i.e. synovitis) with increased production of cytokines is present in the osteoarthritic joint. However, the synovial fluid contains much fewer leukocytes and the entire inflammation process is more limited in OA than in rheumatoid arthritis. In OA, the cytokines i.e. the inflammatory mediators, are produced especially by chondrocytes, but also by synovial leukocytes, as well as by osteoblasts and osteoclasts of bone (Goldring and Goldring 2007).

The factors promoting the inflammatory reaction are not known in the osteoarthritic joint, but classical symptoms of inflammation, such as swelling, pain, heat, and stiffness associate with the progression of OA. The proteolytic catabolism of articular cartilage is increased in OA. The proteoglycans and collagen network of extracellular matrix are degraded by matrix metalloproteases (Smith 1999, Goldring and Goldring 2007). Nitric oxide has been shown to diminish the production of proteoglycans and to inhibit the synthesis of collagen. Nitric oxide seems to indirectly activate the apoptosis of chondrocytes (Vuolteenaho et al. 2007). Adipokines, produced by adipose tissue, regulate not only metabolism but also the inflammatory reaction (Tilg and Moschen 2006). Adipokines are known to facilitate the release of factors that increase catabolism and inflammation in the chondrocytes (Otero et al. 2003).

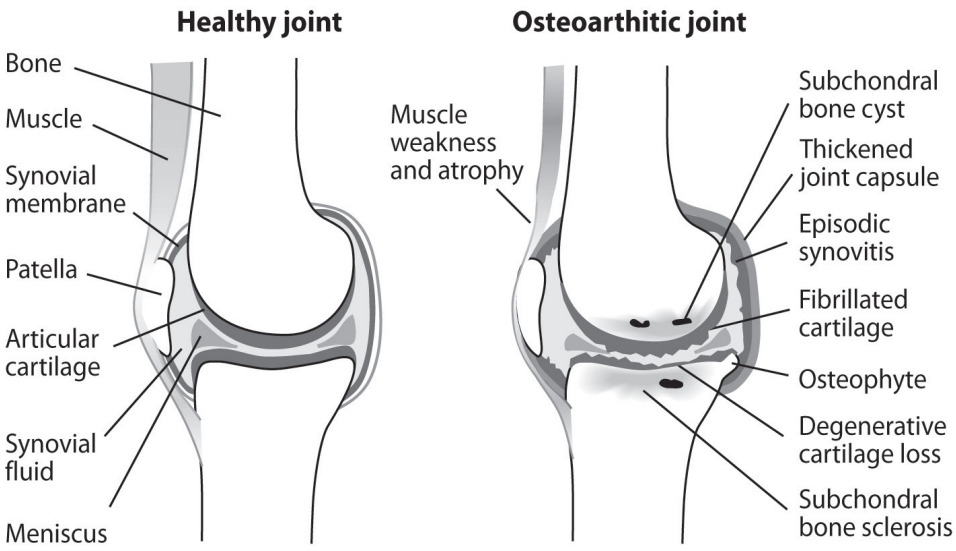

Figure 1. The pathophysiological processes involved in knee OA and their implications for disease progression and disability. The healthy (on the left) and affected knee joint (on the right). The role of muscle weakness is discussed more specifically in Paragraph 2.4 The Role of Periarticular Muscles in Knee Osteoarthritis.

2.1.2 Risk Factors

Knee OA is a multifactorial disease. The cause of OA remains unknown, though there is clear evidence for major risk factors, such as age, obesity, joint trauma, and heavy work load (Arokoski et al. 2007). The risk factors can be divided into systemic (for example age, gender, genetics, and overweight) and local biomechanical factors, such as joint injury and malalignment, overweight, and muscle weakness (Arokoski et al. 2001, Nuki and Salter 2007). Abnormal mechanical loading in various sport activities or during heavy work may activate the biochemical cascade that leads to joint degeneration and pain, but also even in normal mechanical loading if the cartilage is impaired (Nuki and Salter 2007) (Figure 2).

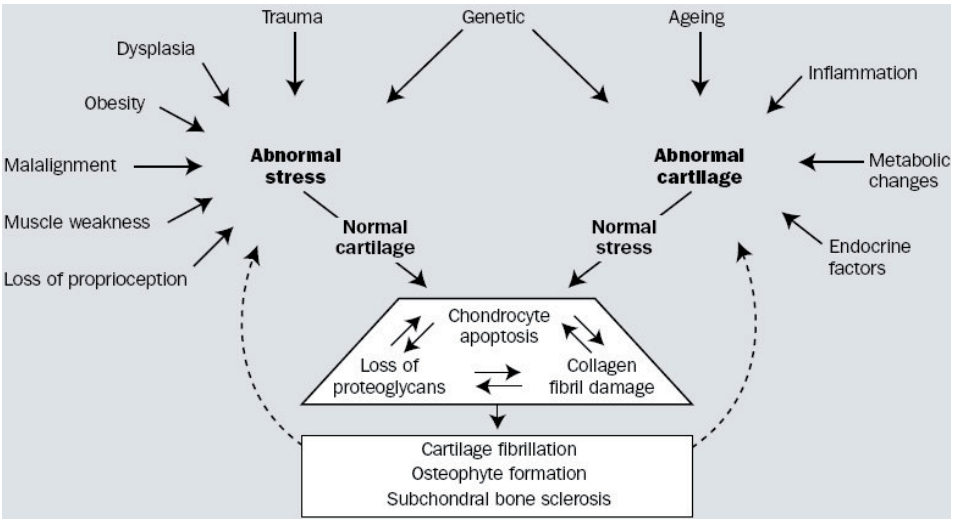

Figure 2. The known risk factors for OA. An abnormal, i.e. excess heavy, physical loading could cause degeneration of normal articular cartilage. The physical activity within a normal range, along with an impaired composition of the articular cartilage, could activate a cascade that leads to joint degeneration. Adapted with permission from Nuki and Salter (2005).

Aging is the most significant risk factor for knee OA (Felson 2004). In individuals under 45 years in Finland, the prevalence of clinically determined knee OA is 0.3% in men and 0.4% and women according to the Health 2000 examination survey. In men and women aged 75-84 years 15.6% and 32.1% suffer from knee OA, respectively. However, the prevalence of knee OA in Finnish women over 30 years has decreased by 50% in the past twenty years (Riihimäki et al. 2004).

Knee OA is more common in obese subjects than in subjects of normal weight (Cooper et al. 2000, Murphy et al. 2008). For example, obese women with body mass index (BMI) of 30-35 kg/m^2 had a four times higher risk for knee OA than non-obese women (Spector et al. 1994). The corresponding risk was 4.8 for men. Obesity is also a major risk factor for the incidence of bilateral knee OA, whereas local mechanical factors are more often associated with unilateral OA (Spector et al. 1994). The effect of obesity on OA has been thought to be mediated through the increased mechanical loading of the knee and hip. This would lead in cartilage damage in these weight-bearing joints. However, obesity is also associated with hand OA, which has given rise to the hypothesis that both mechanical and metabolic factors may mediate the effects of obesity on joints (Berenbaum and Sellam 2008).

Joint injury increases the risk for knee OA (Roos 2005). After knee injury, women had a three-fold and men a 5- to 6-fold risk for developing of knee OA, compared to healthy controls (Felson and Zhang 1998). Injuries to the anterior cruciate ligament associate most clearly with the incidence of knee OA (15-20%). As many as 50-70% of patients with

complete anterior cruciate ligament rupture, accompanied by concomitant injuries to the meniscus or other ligaments, exhibit radiographic knee OA changes after 15-20 years (Gillquist and Messner 1999). Furthermore, at 10 to 20 years after anterior cruciate ligament or menisci injury, on average, half of those patients have symptomatic knee OA (Lohmander et al. 2007). Total meniscectomy after an isolated meniscus tear has been a significant risk factor for knee OA, the relative risk being 14.0 after 21 years (Roos et al. 1998). Partial meniscectomy can also contribute to the development of knee OA (Burks et al. 1997, Andersson-Molina et al. 2002).

Heavy physical activity and occupational load are important risk factors for the incidence of knee OA (Vignon et al. 2006). Heavy physical activity may increase the risk of especially among obese individuals (Kujala et al. 1994, Spector et al. 1996b, McAlindon et al. 1999). On the other hand, regular and moderate physical exercise has been shown to be associated with a decrease in the development of knee OA (Manninen et al. 2001). However, most of the clinical or epidemiological studies have concluded that jogging exercise at moderate intensity or recreational physical activity do not increase the risk for knee or hip OA, provided that the weight-bearing joints have not been injured (Panush et al. 1986, Lane 1995). The increased risk for knee OA is also associated with those occupations that entail prolonged or repeated knee bending. The risk may be even higher in those activities containing both knee bending and mechanical loading (Cooper et al. 1994, Manninen et al. 2002).

With respect to the other mechanical risk factors, knee malalignment has been reported to be associated with the development and progression of knee OA (Sharma et al. 2001, Brouwer et al. 2007, Tanamas et al. 2009). Furthermore, the severity of the malalignment can predict the decline in physical function (Sharma et al. 2001). Genetic factors also seem to account for the existence of knee OA to a degree ranging from 39-65%, independently of the known environmental or demographic confounders (Spector et al. 1996a, Neame et al. 2004). This suggests that the articular cartilage of some individuals is congenitally vulnerable to mechanical wear and tear. Table 1 summarizes the factors that have been shown to increase the risk for knee OA. However, the prevention of OA is still a challenging task although there is a considerable body of evidence about the definite causal risk factors, such as obesity, joint injury, and occupational load.

Table 1. The Factors That Increase Risk for Knee OA

Risk Factor	Evidence	References
Age	+ + +	(Anderson and Felson 1988, Hart et al. 1999, Felson 2004, Riihimäki et al. 2004)
Obesity	+ + +	(Spector et al. 1994, Cooper et al. 2000, Berenbaum and Sellam 2008, Murphy et al. 2008)
Knee injury	+ + +	(Felson and Zhang 1998, Gillquist and Messner 1999, Roos 2005, Lohmander et al. 2007)
Heavy physical activity	+ +	(Kujala et al. 1994, Spector et al. 1996b, McAlindon et al. 1999, Vignon et al. 2006)
Heavy occupational load	+ +	(Cooper et al. 1994, Manninen et al. 2002, Vignon et al. 2006)
Meniscectomy	+ +	(Burks et al. 1997, Roos et al. 1998, Andersson-Molina et al. 2002)
Genetics	+ +	(Spector et al. 1996a, Neame et al. 2004)
Knee malalignment	+ +	(Sharma et al. 2001, Brouwer et al. 2007, Tanamas et al. 2009)

+ + + = strong evidence, + + = moderate evidence

2.2 DIAGNOSIS AND TREATMENT OF KNEE OSTEOARTHRITIS

2.2.1 Symptoms

Pain is the predominant symptom of knee OA with the pain being generally related to joint use and with relief at rest. As OA progresses, pain may become more persistent and can appear also at rest and during the night. For a patient with symptoms, the inability to have restorative sleep may reduce the pain threshold via associated fatigue and reduced well-being (O'Reilly and Doherty 2003). The extent of the pain is usually linked to the severity of radiographic OA changes, but not necessarily (Hochberg et al. 1989, Bagge et al. 1991). Subjective pain correlates strongly with the psychological status, such as depression and anxiety (Davis et al. 1992, O'Reilly et al. 1998). In clinical practice, the subjective pain can be estimated with a visual analogue scale (VAS) from 0 to 100 mm (Lequesne and Maheu 2003).

The mechanism of pain production in OA is not clear. The disease process may affect all intracapsular and periarticular tissues of the synovial joint leading to many possible sources of pain. The articular cartilage is aneural and avascular tissue. However, it has a rich sensory innervation exists in other joint tissues (O'Reilly and Doherty 2003). It has been suggested that several processes in bone or/and subchondral bone such as elevated intraosseus pressure, bone marrow oedema, structural changes, and periosteal stretching

may associate with the joint pain (Arnoldi et al. 1975, Felson et al. 2001). On the other hand, the capsular mechanoreceptors may be stimulated by intra-articular hypertension, and the ischemia caused by mild synovitis may activate nociceptors. One factor is muscle weakness, e.g. the weakness in the QFm has been shown to be a better determinant of pain and disability than any radiographic feature in knee OA (Lankhorst et al. 1985, Hurley and Newham 1993, Madsen et al. 1995). Thus, in OA of large joints the periarticular structures interfere often with the pain (O'Reilly and Doherty 2003).

Another typical feature in knee OA is short-lived morning stiffness, which is distinct from the more prolonged and often generalised joint stiffness characteristic of rheumatoid arthritis. The early morning stiffness, occasionally severe is believed to be related to inflammation. Patients with knee OA describe stiffness as a difficulty to rise from a chair, slowness of movements, or clumsiness later in the day (Altman et al. 1986).

Knee OA is the greatest contributor to impairment in functional ability of OA patients. The disability can be extensive containing mobility limitation, difficulty to cope with activities of daily living and social isolation. The principal contributors to disability are believed to include pain, reduced range of joint movement as well as muscle weakness (McAlindon et al. 1993, O'Reilly and Doherty 2003). Recently, Kauppila et al. (2009) suggested that in end-stage knee OA, the major attributes of self-reported disability was pain, obesity and antero-posterior (A-P) laxity of the knee joint. The effect of comorbidity on health-related quality of life was also considerable (Kauppila et al. 2009). Subjective physical functioning could be qualitatively estimated using the Western Ontario and McMaster Osteoarthritis Index (WOMAC) and Lequesne questionnaires (Bellamy et al. 1988, Lequesne and Samson 1991).

2.2.2 Clinical Findings

There are several signs in knee OA that can be identified during the clinical inspection. These include limping due to joint pain, decreased walking speed as well as reduced stride length and frequency (Perry 1992). Squatting may have become difficult for a patient suffering from knee OA. The deformity of the knee joint is usually a sign for advanced knee OA. Clinically detectable varus or valgus instability in the knee joint is regarded as a late sign of the disease. Coarse crepitus is considered to indicate the loss of congruency of the joint (O'Reilly and Doherty 2003).

Tenderness can be identified with palpation of the knee joint. Tenderness along the joint-line points to an intracapsular origin for pain and point-tenderness away from the joint-line is indicative of a periarticular lesion. Reduced range of movement (ROM), easily measured with a goniometer, is associated with physical impairment. The decreased ROM is mainly caused by osteophyte formation, remodelling, capsular thickening, and can be accentuated by soft tissue swallowing. Muscle wasting and weakness are difficult to examine but can be present in knee OA. The classical signs of inflammation, such as

heat, pain, and effusion indicate synovitis in knee OA. Laboratory tests do not play any role in the diagnosis of knee OA but they can help in the differential diagnosis (O'Reilly and Doherty 2003, Arokoski et al. 2007).

2.2.3 Radiological Findings

The plain radiograph serves as the primary investigation in the diagnosis of knee OA, as well as in assessing the severity of the disease. The advantages of radiography are evident: it is cost-effective and relatively safe, and its availability is excellent. However, the subjective pain and radiographic changes do not necessarily correlate with each other (Hochberg et al. 1989, Bagge et al. 1991). Furthermore, radiography is rather insensitive at detecting the early signs of knee OA (Watt and Doherty 2003). Magnetic resonance imaging (MRI) is more suited for detecting the early OA changes (Hayes et al. 2005). Furthermore, new physical and biochemical methods for early diagnosis of OA are under intensive development. These methods are mostly based on ultrasound, MRI, and biochemical tracers (Jurvelin et al. 2008).

Typical radiographic features in knee OA include joint space narrowing, osteophytes, subchondral bone sclerosis, cyst formation, osteochondral bodies, and bone deformity. Loss of cartilage is an early and a cardinal feature of OA leading to joint space narrowing in plain radiographs (Watt and Doherty 2003). The thickness of articular cartilage varies between individuals and joint surfaces (Adam et al. 1998). Therefore, no reference values for thickness of joint space exist. The osteophytes are a hallmark of OA, these being formed at joint margins by endochondral ossification. They can be regarded as a repair attempt and indicate redistribution of abnormal joint loading. Cysts are also typical radiographic findings in OA and occur mainly within the areas of bony sclerosis at sites of increased pressure transmission. Disintegration of the joint surface in OA results in the formation of osteochondral fragments. As these fragments are released into the joint space, they appear characteristically with the other established features of OA (Watt and Doherty 2003).

There are almost 30 classification systems for assessing the severity of knee OA. Some examples of classification systems are Ahlbäck (Ahlbäck 1968), Nagaosa (Nagaosa et al. 2000) and Kellgren-Lawrence (K-L) (Kellgren et al. 1963). The most widely used is the K-L scale, in which 0 refers to no OA and 4 indicates the most severe OA (Table 2). The reproducibility of K-L grading for knee OA seems to be either good or excellent (Günther and Sun 1999). The inter- and intra-rater reliability of Ahlbäck grading is only moderate or poor, respectively (Galli et al. 2003). K-L scale has been shown to correlate with MRI in cartilage defects, osteophytes, and joint effusion (Hayes et al. 2005).

Table 2. Grades for Severity of Knee OA According to the Kellgren-Lawrence Scale (Kellgren et al. 1963)

Grade 1 'doubtful'	Doubtful joint space narrowing, and possible osteophyte lipping
Grade 2 'minimal'	Definite osteophytes and possible joint space narrowing
Grade 3 'moderate'	Moderate multiple osteophytes, definite joint space narrowing, and some sclerosis, and possible deformity of bone ends
Grade 4 'severe'	Large osteophytes, marked joint space narrowing, severe sclerosis, and definite deformity of bone ends

2.2.4 Criteria for Diagnosis

The diagnosis of knee OA can be radiographic, clinical, or based on a combination of these two classification criteria (Arokoski et al. 2007). The radiographic knee OA is based solely on the radiographic changes. The cardinal features in knee OA are joint space narrowing, the formation of osteophytes, and possible indications of bone destruction. K-L grade 2 has been widely used as the inclusion criterion in knee OA studies (Flores and Hochberg 2003, Arokoski et al. 2007). Clinical knee OA relies on subjective symptoms, clinical findings, case records, and laboratory results. The agreement between clinical and radiographic methods for diagnosing knee OA is moderate (Toivanen et al. 2007). The combined radiographic and clinical criteria have been suggested for use when diagnosing knee OA (Altman et al. 1986, Flores and Hochberg 2003, Arokoski et al. 2007) (Table 3). If one combines the clinical, laboratory, and radiographic factors, the sensitivity and specificity of knee OA diagnosis are 94% and 88%, respectively (Altman et al. 1986).

Table 3. Combined Radiographic and Clinical Diagnosis Classification of Knee OA

Knee pain on most days of prior month
AND
At least one of the following:
Age over 50 years
Morning stiffness less than 30 min in duration
Crepitus on active joint motion
AND
Osteophytes at joint margins (X-ray spurs)

2.2.5 Treatment Guidelines

The goals in treatment of knee OA are to control and relieve pain, to maintain and improve physical function as well as to prevent the progression of the disease (Anonymous 2000, Jordan et al. 2003, Zhang et al. 2005, Arokoski et al. 2007, Zhang et al. 2008). The conservative non-pharmacological treatment, i.e. patient information, weight reduction, exercise, walking devices, braces and orthotic devices (Anonymous 2000, Jordan et al. 2003, Zhang et al. 2005), is the basis for the management of knee OA (Figure 3).

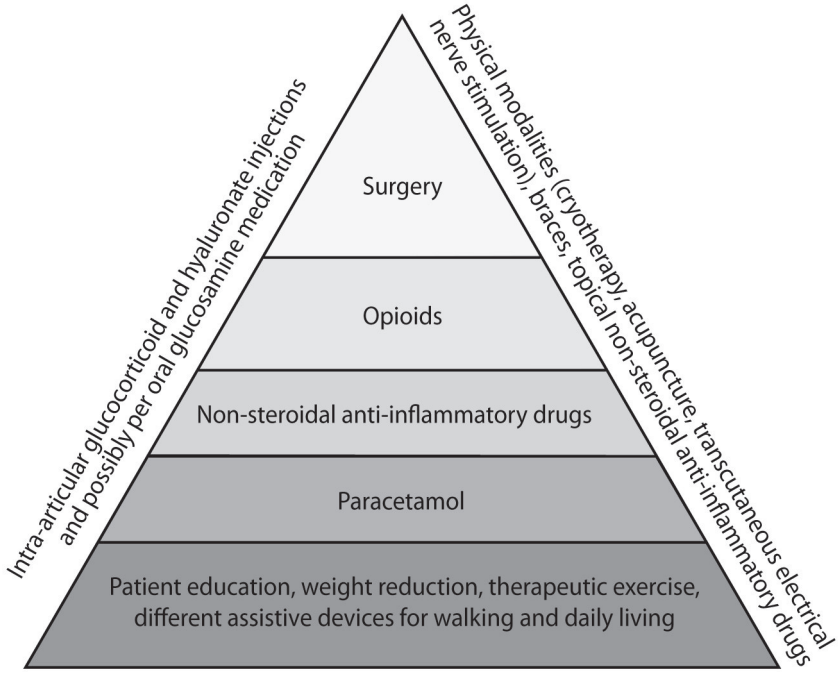

Figure 3. Treatment guidelines for knee OA. The conservative non- pharmacological interventions should be recommended for all patients. Redrawn with modifications from Arokoski et al. (2007).

The national and international knee OA guidelines recommend for a combination of pharmacological and non-pharmacological interventions for optimal management of mild to moderate knee OA (Anonymous 2000, Felson et al. 2000, Jordan et al. 2003). The principal medication for knee OA is paracetamol. If the efficacy of paracetamol is not adequate, non-steroidal anti-inflammatory drugs and mild opiates are recommended (Arokoski et al. 2007). Glucocorticoid or hyaluronate injections into the joint can also be used in treatment for knee OA (Lo et al. 2003, Arroll and Goodyear-Smith 2004). Surgical interventions are required in severe knee OA characterised by intolerable pain and serious functional impairment. Though even in those cases conservative treatment complements the surgery (Arokoski et al. 2007). However, only about 10% of all patients with OA knee pain will ever be considered for knee surgery (Peat et al. 2001).

2.3 PHYSICAL FUNCTION IN KNEE OSTEOARTHRITIS

2.3.1 Physical Function Measures

Physical function in knee OA can be evaluated by using many instruments. These include patient self-assessment techniques (e.g. WOMAC and Lequesne questionnaires) and objective methods (e.g. performance tests, physical examination of the joint and ROM measurement) (Bischoff et al. 2003). Self-reported measures of function are often primary outcomes in clinical studies but both types of techniques have methodological issues that must be taken into account (Bischoff et al. 2003). Several authors have concluded that self-reported techniques and performance tests exhibit good correlations in knee OA studies (Lin et al. 2001, Piva et al. 2004, Maly et al. 2006, Kauppila et al. 2009). However, the performance-based methods can identify limitations in physical function earlier and more frequently than the self-assessment techniques (Rozzini et al. 1997, Brach et al. 2002).

Several studies have been conducted to measure physical function of knee OA patients and to compare the performance tests results with those of the control subjects. Bremander et al. (2007) have recommended the use of the maximum number of knee bendings in 30 seconds and one-leg hop for distance as a measure of physical function for subjects with knee joint symptoms. According to Bremander et al. (2007) these tests are reliable and possess discriminative abilities. Namely, the subjects with knee joint symptoms after meniscectomy demonstrated significantly poorer performance in both tests, as compared to non-symptomatic meniscectomised controls. According to Piva et al. (2004) the get-up-and-go test is reliable with a minimum detectable change that is adequate for clinical use. The time needed to perform get-up-and-go test was longer for patients with knee OA than for controls. However, the authors recommended against using this test as a single measure of physical function (Piva et al. 2004).

2.3.2 Determinants of Physical Function

According to Jette et al. (2002) disability refers to a person's impaired performance for socially defined life tasks that are expected in a typical sociocultural and physical environment of the individual. Disability is a complex phenomenon influenced by pain, obesity, comorbidity, low-level of physical activity, social and psychological factors as well as local impairments in lower extremities (Sharma et al. 2003a). These will interfere with objective performance tests and physical function. However, in knee OA, the limitations in physical function or activities of daily living play a crucial role in the development of disability. Pain is obviously a central factor in the physical function impairments via its direct effects on the function (Sharma et al. 2003a), but psychological (Salaffi et al. 1991, van Baar et al. 1998a) and social (Bookwala et al. 2003, Ethgen et al. 2004) factors contribute to the development of pain. They can be considered as mediators of pain and functional limitations.

Patients suffering from knee OA have commonly different comorbidities, e.g. depression and cardiovascular diseases, which may contribute to disability in knee OA (Philbin et al. 1995, O'Reilly et al. 1998, van Dijk et al. 2008). There is emerging evidence that obesity is also associated with disability in knee OA (Creamer et al. 2000, Ling et al. 2003, Kauppila et al. 2009). The effect of radiographic severity of knee OA on disability has not been established (Creamer et al. 2000, Barker et al. 2004, Szebenyi et al. 2006). Several local factors of lower extremity function can influence the physical functional status of the individual. These include QFm weakness (O'Reilly et al. 1998, Steultjens et al. 2001, van der Esch et al. 2007), laxity of knee joint (Sharma et al. 1999, van der Esch et al. 2006) and proprioceptive inaccuracy (Sharma et al. 2003a, van der Esch et al. 2007) as well as restricted range of motion of the knee joint (Steultjens et al. 2000). On the other hand, greater muscle strength, improved mental health and self-efficacy, social support, and higher aerobic exercise activity can be seen as protective factors, decreasing the risk of deterioration of functional status (Sharma et al. 2003a).

2.4 THE ROLE OF PERIARTICULAR MUSCLES IN KNEE OSTEOARTHRITIS

2.4.1 Muscle Structure

The muscle composition of knee OA patients has been examined using MRI or ultrasound techniques. Recently, Petterson et al. (2008) attempted to identify determinants of QFm weakness in their patients with end-stage knee OA. They used MRI to measure the lean muscle and fat cross-sectional area from both limbs. The more affected limb exhibited a smaller lean muscle cross-sectional area. The authors concluded that both reduced voluntary muscle activation level and lean muscle cross sectional area contribute to muscle weakness in individuals with severe knee OA. Similarly to the situation in the healthy elderly, the best predictor of strength in the contralateral limb was the lean muscle cross-sectional area (Petterson et al. 2008).

Knee OA can also lead to histopathological changes in periarticular muscles. Fink et al. (2007) reported the atrophy of vastus medialis (VM) type 2 muscle fibers in all 78 subjects with end-stage knee OA while one third of the subjects exhibited atrophy of the type 1 fibers. Muscle samples also exhibited a grouping indicative of neurogenic muscular atrophy. The selective atrophy of type 2 fibers in 68% of the samples was hypothesised to result from pain-associated disuse. The soft tissue changes, i.e. calcification, fibrosis and lipomatosis, were commonly encountered in long-term disease (Fink et al. 2007).

2.4.2 Muscle Strength

Many authors have concluded that patients suffering from knee OA exhibit decreased strength of QFm (Tan et al. 1995, Fisher and Pendergast 1997, Slemenda et al. 1997, Hortobágyi et al. 2004, Lewek et al. 2004). Muscle weakness in knee OA, i.e. the disuse atrophy of the muscles, has been suggested to be elicited due to joint pain (O'Reilly et al.

1997, Hurley 1999), reflex inhibition of muscles that move the affected joint (O'Reilly et al. 1997, O'Reilly et al. 1998, Hurley 1999), and incapability to fully activate the QFm, resulting in the decreased force production (Fitzgerald et al. 2004, Lewek et al. 2004, Mizner et al. 2005b, Petterson et al. 2008). However, the ultimate mechanism behind the muscle weakness in knee OA is not fully understood. Importantly, decreased QFm strength may have crucial role in the development and progression of knee OA (Slemenda et al. 1998, Hurley 1999, Amin et al. 2009) (Figure 4).

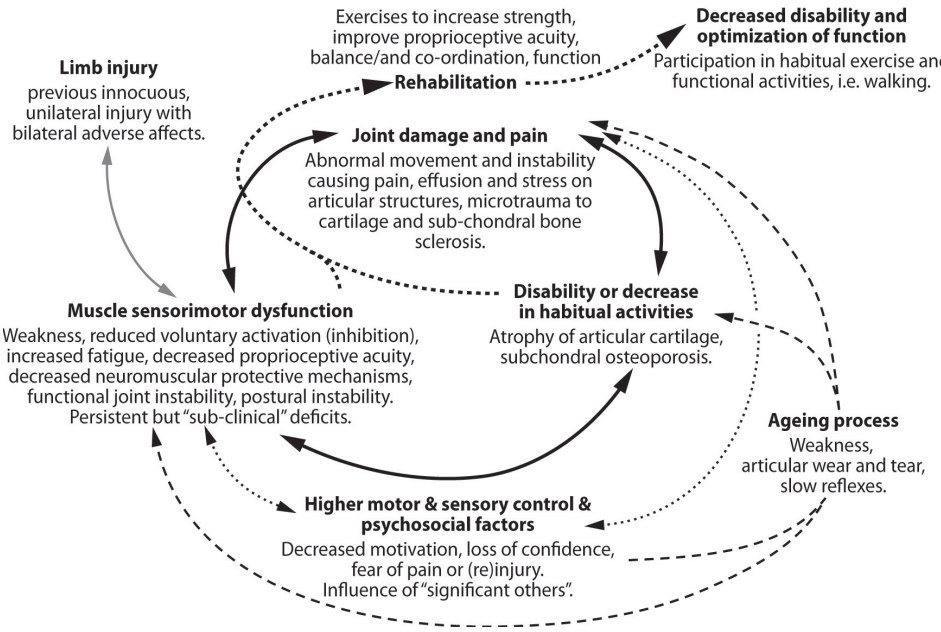

Figure 4. Complex interrelationships between the clinical aspects of OA, physiological, and psychosocial factors in the pathogenesis and progression of OA. Contrary to general belief, joint damage does not necessarily precede the disability and muscle weakness. The joint degeneration can also be a consequence of opposite processes (anticlockwise) in which age-related physiological changes cause muscle dysfunction and reduce the participation in physical activity. This can lead to joint damage. The directions of the arrows indicate the impact of each factor. Adapted with permission from Hurley (1999).

Exercise training especially at the lower-extremities may improve symptoms and protect against disability in persons with knee OA (van Baar et al. 1999). The effective types of exercise regimens for controlling pain and maintaining function include aerobic exercise (van Baar et al. 1998b, Minor et al. 1989, Kovar et al. 1992, Ettinger et al. 1997) and strength training (Hurley and Scott 1998, O'Reilly et al. 1999, Petrella and Bartha 2000).

2.4.3 Muscle Function

The neuromuscular system allows finely controlled movements, provides functional joint stability, and gives sensory information about limb position and movements. These functions constitute the neuromuscular protective mechanisms that minimize adverse loading during locomotion and prevent joint damage. Due to impairment in neuromuscular system protective mechanism in conjunction with aging, sensorimotor dysfunctions may play a significant role in the pathogenesis and/or progression of knee OA. However, the general assumption has been proposed that joint damage precedes pain, disability and muscle weakness (Hurley 2003).

Muscle spindles, joint receptors and Golgi tendon organs are proprioceptors providing information about the position and movement of the joint. If the sensitivity of proprioceptors becomes diminished, their ability to detect and transfer information to central nervous system will decline and the precision of the proprioceptive system deteriorates (Hurley 1999, Sharma 2003). Muscle fatigue (Skinner et al. 1986, Lattanzio et al. 1997), aging (Skinner et al. 1984, Kaplan et al. 1985, Petrella et al. 1997, Hurley et al. 1998), knee joint hypermobility (Hall et al. 1995), and effusion (McNair et al. 1995) have all been reported to affect the correct functioning of the proprioceptive system. Furthermore, the function of the proprioceptive system may be impaired in patients with knee OA (Sharma et al. 1997, Garsden and Bullock-Saxton 1999).

The joint reposition sense may be diminished also in the asymptomatic limb (Garsden and Bullock-Saxton 1999). This could partially explain the fact that the patients with unilateral knee OA usually develop bilateral joint degeneration (Mont et al. 1995). However, more studies are needed before conclusions can be drawn about whether the impaired proprioceptive system is a cause or/and an effect of the pathogenesis of knee OA (Sharma 2003). The motor and sensory functions are not separate, but closely interlinked. For example, during the heel strike in gait the proprioceptive system signals information about lower limb movement, position and loading. Mediated through the voluntary contraction and reflexes the muscle function provides appropriate movements, joint stability and shock absorption (Radin et al. 1986, Jefferson et al. 1990). The proprioceptive system continuously monitors and feeds back to the central nervous system to fine-tune the planned motor strategy through an appropriate muscle activity. Ultimately, this protects the joints from harmful loading (Hurley 1999, Sharma 2003).

2.5 NORMAL GAIT CYCLE

Background

Walking is a planned and controlled, but highly autonomous motor activity. During walking, changes in the vertical position of the body's centre of mass control the gravitational potential energy of the body, and are accompanied by opposite changes in the kinetic energy needed to produce the motion. This results in a pendulum-like mode

of movement that saves mechanical energy. At the optimal walking speed, recovery of the energy of the body, by exchanging potential and kinetic energies, is maximal (Minetti 2001).

2.5.1 Gait Phases

The gait cycle is determined as a time period between two consecutive heel contacts of the same foot. This cycle is divided into stance and swing phases. The former can be further grouped into single and two double support phases. Mathematically, gait cycle can be defined by the formula, gait cycle = stance + swing, where stance = double support + single support + double support. In time, the gait cycle takes approximately one second. During that second, 60% and 40% of the time is devoted to stance and swing phases, respectively. Naturally, walking speed and gait pathologies affect these time periods (Larsson et al. 1980, Vaughan et al. 1999).

The ground contact begins with the heel contact, proceeding to foot-flat during the single limb support and forefoot contact (Figure 5). The double support phase ends up with a toe-off. The stance and swing phases can be further divided into eight functional phases. The first two of the five stance phases, initial contact and loading response, occur during the weight acceptance. Mid- and terminal stance take place at the single support phase. The final phase of the stance is a pre-swing, in which the limb starts the forward movement (Perry 1992, Perttunen 2002).

The forward movement continues through the three swing phases (Figure 5). During the initial swing, the leg is accelerated forward by knee and hip flexion; the ankle joint is dorsiflexed. At the midswing, the swinging leg is aligned with the stance limb, which is in the midstance. The foot is prepared for smooth ground contact in the terminal swing with the help of eccentric (i.e decelerating) activity of the hamstrings (Perry 1992, Perttunen 2002).

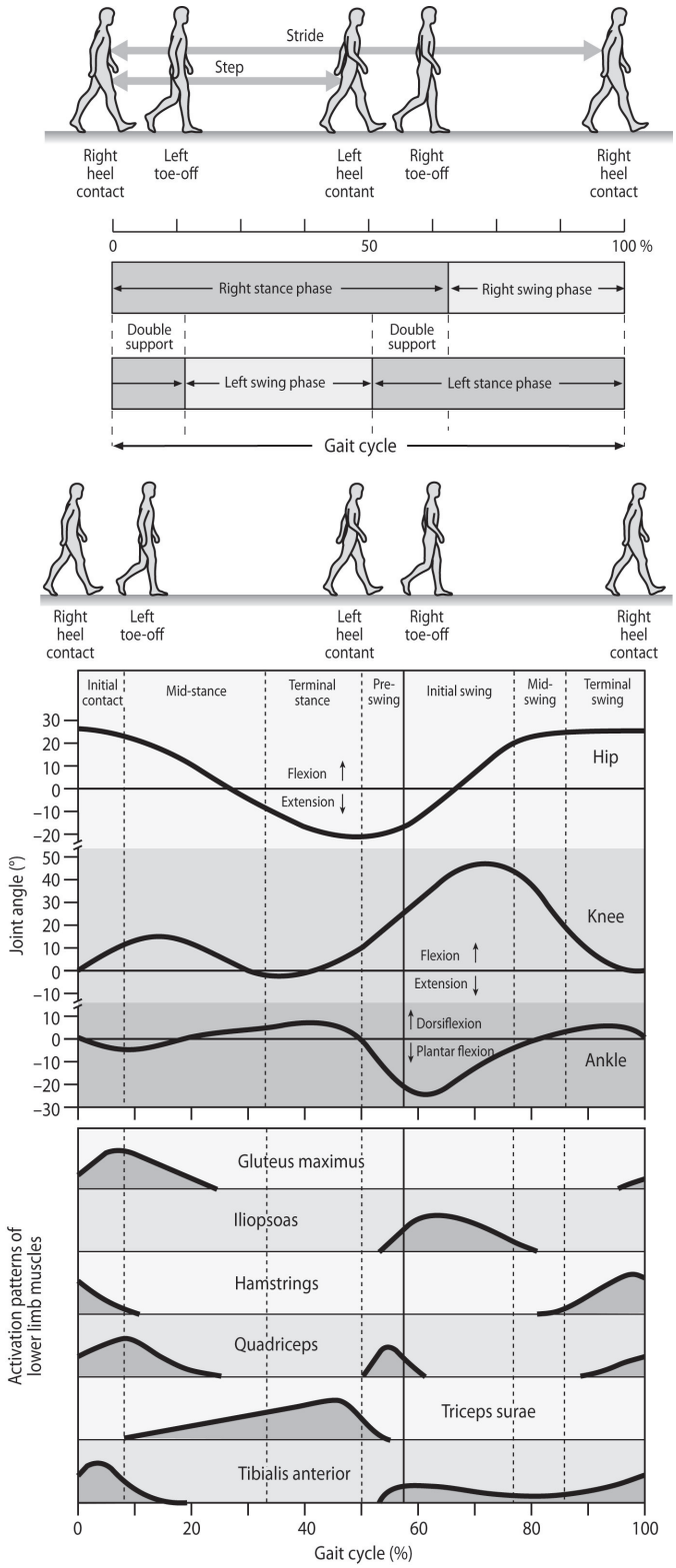
Stride
Step
Right heel contact
Left toe-off
Left heel contant
Right toe-off
Right heel contact
0
50
100 %
Right stance phase
Right swing phase
Double support
Double support
Left swing phase
Left stance phase
Gait cycle
Right heel contact
Left toe-off
Left heel contant
Right toe-off
Right heel contact
Initial contact
Mid-stance
Terminal stance
Pre-swing
Initial swing
Mid-swing
Terminal swing
Hip
Flexion
Extension
Knee
Flexion
Extension
Dorsiflexion
Plantar flexion
Ankle
Joint angle (°)
Gluteus maximus
Iliopsoas
Hamstrings
Quadriceps
Triceps surae
Tibialis anterior
Activation patterns of lower limb muscles
Gait cycle (%)

Figure 5. Upper panel: The normal gait cycle. The first double support phase consists 15% of the gait cycle. The stance and swing phases account for about 60% and 40% of the cycle period, respectively. Lower panel: The joint angles of hip, knee and ankle joints as well as muscle activity of selected muscles during normal gait cycle. The vertical line separates the stance and swing phases. Please, see the more detailed descriptions in the text. Adapted with permission from Whittle (2002).

2.5.2 Neural Control

Walking is governed by neural circuits that generate patterned motor activity. These neural networks are called central pattern generators which produce highly stereotyped rhythmic movements autonomously and are located in the brain stem and spinal cord. The function of central pattern generators has been investigated in animal models and the existence of central pattern generators has been proven also in humans with spinal cord injury (Eccels and Dimitrijevic 1985). Central pattern generators are able to coordinate locomotion in the absence of afferent feedback about movements. However, normally the information from the central and peripheral nervous system modifies the basic rhythm produced by central pattern generators. The appropriate peripheral afferent feed-back from skin, joint receptors, and from muscle spindles and Golgi tendon organs is essential for flexible human locomotion. The important role of the central nervous system, e.g. motor cortex, cerebellum and brain stem, cannot be overlooked when one is considering control of human walking and locomotion. Furthermore, the information from the vestibular system and vision are crucial in coordinating balance (Bear et al. 2001, Vilensky 2003) (Figure 6).

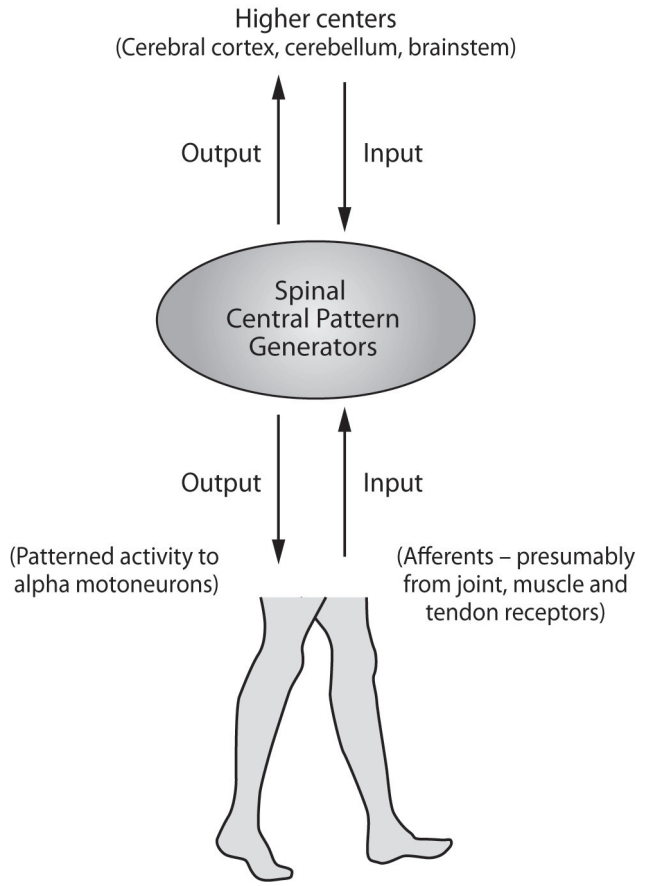

Figure 6. Schemantic drawing from the elements affecting (input, output) the neural control of human locomotion. An alpha motoneuron is an efferent neuron innervating the skeletal muscles. Adapted with permission from Vilensky (2003).

The supraspinal control contains the direct central pattern generators regulation, the peripheral sensory feed-back control, and systems that react to the visual information. The initiation of gait occurs in the brain stem, but the decision of initiation as well as fine tuning of walking is governed by the motor cortex. The cerebellum receives information about the prevailing state of central pattern generators and previous movement and the cerebellum is responsible for the continuous fine-tuning of walking (Barbeau et al. 1998, Popovic and Sinkjaer 2003).

2.5.3 Biomechanics of Stair Walking

Stair walking follows the same basic principles as level walking with stance and swing phases. However, the stance phase is prolonged and the body weight (BW) is accepted by fore- and midfoot in the contact phase (Riener et al. 2002). Stair ambulation also requires proper strength capacity (Protopapadaki et al. 2007, Larsen et al. 2009). The knee and hip

extensors act concentrically during the loading response in order to raise the centre of mass to the next step in stair ascent. Hip abductors and stance leg act powerfully to prevent pelvic tilt. At the end of stance phase when the knee is extended, QFm stabilises isometrically the knee joint as the centre of mass moves to the front of stance leg. Finally, the ankle plantar flexors push the body up- and forwards. The hip flexors are responsible for moving the swinging leg across the stance leg to the next step. Tibialis anterior muscle controls isometrically the movement of the foot during the swing phase and prevents the foot for hitting the upper steps (Andriacchi et al. 1980, McFadyen and Winter 1988).

In contrast to the situation in stair ascent, potential energy needs to be absorbed by the muscles during stair descent. The stance phase can be divided into two parts during stair descent: weight response and lowering of the centre of mass. The ankle plantar flexors act eccentrically until the ankle joint is extended to its normal position. The hip extensors and QFm also attenuate the downward movement of the body. During the midstance, the centre of mass descends to the lower step this being achieved by knee and hip joints flexion, ankle dorsiflexion, and QFm, hip extensors as well as ankle plantar flexors eccentric action (McFadyen and Winter 1988, Riener et al. 2002). The hip and knee flexors perform concentric work at the beginning of the swing phase. At the end of swing phase the hip flexors and tibialis anterior act eccentrically to prepare the foot for the next contact (McFadyen and Winter 1988).

The gait asymmetry increases especially during stair descending (Stacoff et al. 2005). The impulsive loading, which affects the musculoskeletal system and lower limb joint moments as well as ROM, are also higher during stair ambulation than during level walking (Andriacchi et al. 1980, Loy and Voloshin 1991, Protopapadaki et al. 2007). The inclination of the stairs can affect the biomechanics of stair ambulation (Riener et al. 2002, Stacoff et al. 2005).

2.5.4 Modern Gait Analysis

Background

Scientists have studied human walking for hundreds of years. However, recent progress in data processing and integration has made it possible to achieve a comprehensive perspective of gait during the last decade. Biomechanics is a scientific discipline that studies biological systems with the methods of mechanical engineering, and therefore human gait is an appropriate topic for examination with biomechanical tools. It has been postulated that gait analysis could be used as a clinical tool to evaluate different kinds of patient groups in order to obtain insight into the pathology of a specific disease, the effect of therapy or surgical intervention or utilised to plan appropriate rehabilitation programs (Perry 1992, Whittle 2002).

The purpose of modern gait analysis is to use different types of sensors to measure quantitatively appropriate analogy signals such as acceleration, muscle activation with

electromyography (EMG), plantar pressures, ground reaction forces (GRFs) with force plates, and joint angles. This data can be integrated with photogrammetry based on video recording of gait with high speed video cameras (Perry 1992, Whittle 2002). Finally, several spatio-temporal (e.g. walking speed, stride length, stride frequency, and contact times), kinematic (e.g. joint angles, angular velocities and accelerations), and kinetic (e.g. body accelerations, GRFs, joint moments) as well as other biomechanical variables (e.g. muscle activity, power, energy expenditure) can be analysed and reported.

Accelerations

Traditionally, accelerations of the body segments during gait have been estimated from video images. The accuracy of this kind of method is limited (Whittle 2002). SMAs are non-invasive, small and inexpensive devices which seem to be well suited for gait analysis. SMAs fixed on the lumbar spine have been widely used when investigating gait kinematics (Currie et al. 1992, Auvinet et al. 2002, Mayagoitia et al. 2002, Moe-Nilssen and Helbostad 2004). Furthermore, impulsive loading and shock absorption by the skeleton during human locomotion have been studied with SMA attached to the lower limb (Light et al. 1980, Wosk and Voloshin 1981, Folman et al. 1986, Loy and Voloshin 1991, Lafortune et al. 1995a, Gill and O'Connor 2003). The latter method has also been utilised in measuring heel pad (Kinoshita et al. 1993, Kinoshita et al. 1996) and footwear properties (Loy and Voloshin 1991, Lafortune and Hennig 1992) as well as soft-tissue resonance (Wakeling et al. 2003, Boyer and Nigg 2004). Several authors have concluded that SMAs, fixed on the lower limb, do provide a valid method for quantifying the magnitude of bone or joint acceleration (Saha and Lakes 1977, Ziegert and Lewis 1979, Nokes et al. 1984), provided that the sensor is properly pre-loaded (i.e. fixed) and its mass is low. Moe-Nilssen (1998), and Henriksen et al. (2004) have reported that the day-to-day reproducibility of the trunk accelerometer is good in the measurement of gait kinematics and mean accelerations during walking.

Ground Reaction Forces

The GRFs acting on the human musculoskeletal system during walking can be measured by force plates, commonly used in gait analysis. The GRF is of the same magnitude but opposite in direction as the net force of body segments mediated by the leg to the ground. The force plates allow the examination of three dimensional (3-D) GRFs in vertical, A-P, and medio-lateral (M-L) directions. The vertical GRF is the largest, about 120% of the BW during the loading response (Perry 1992). In walking, the classical vertical GRF curve is m-shaped (Figure 7), due to oscillation in the vertical direction as related to the movement of the centre of gravity of the subject (Ebenhart and Inman 1951). The first peak results from upward acceleration of the centre of gravity. The second peak occurs in the push-off phase or in the terminal stance when the body decelerates upward (Winter 1988). However, in some subjects during the initial contact phase, a sharp peak force can be registered due to an impulsive type of loading at heel contact, i.e. heel strike. This peak GRF can be 0.5-1.25 times BW and the duration of this transient peak is approximately 5-25 ms (Light et al. 1980, Simon et al. 1981, Folman et al. 1986).

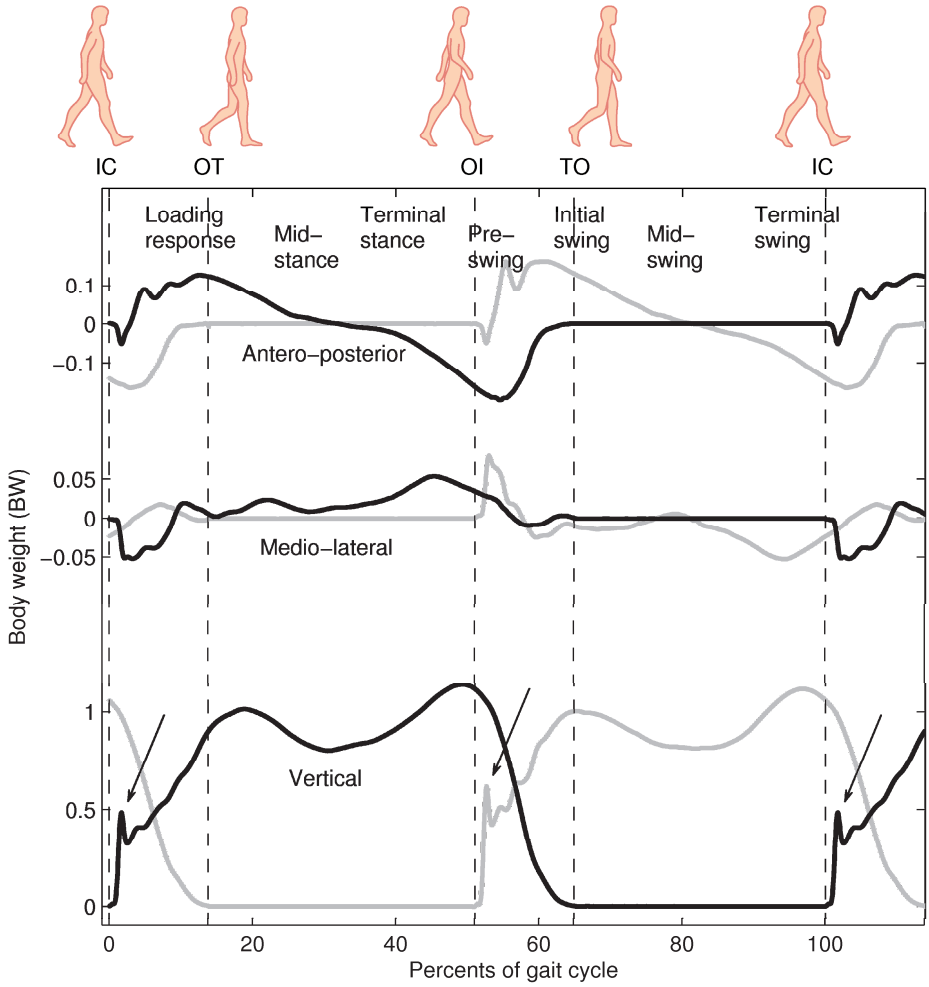

Figure 7. Three dimensional ground reaction forces (GRFs) during walking. The antero-posterior GRF (upper curves) is about 25% of the body weight (BW). The medio-lateral GRF (middle curves) is the lowest in the amplitude and is directed laterally during the nearly whole gait cycle. Some subjects may exhibit a vertical peak force at the very beginning of the contact phase. This is called heel strike transient (black arrows, lower curves). The black and grey lines represent ipsi- and contralateral limbs, respectively.

The amplitude of A-P GRF is about 25% of the BW. At the beginning of contact, the force is opposite to the direction of movement, because the centre of gravity is being decelerated. The A-P GRF is directed forward in the push-off phase. The M-L GRF is directed medially at the very beginning of the contact, but then laterally. The amplitude of M-L GRF is only 10% of the BW, and it contributes to maintaining balance during the contact phase (Perry 1992, Vaughan et al. 1999). When the gait speed, BW, step length or

frequency increases, the GRFs become higher (Soames and Richardson 1985, Perttunen and Komi 2001).

There is no consensus about the parameterisation of GRFs in gait studies, though usually the local maximum and minimum values from 3-D GRFs are reported. The abbreviations and indices for those parameters vary considerably. There is a lack of general agreement about sign conventions, though the positive direction of vertical GRF is usually upwards (Whittle 2002). Furthermore, there is no established method in the literature for calculating the loading rate (LR), which indicates the rate of vertical force development at the beginning of the contact phase (Radin et al. 1991, McCrory et al. 2001, Christina and Cavanagh 2002, Stacoff et al. 2005).

Knee Joint Moments

Joint moments in a given joint can be calculated by summing up muscle, ligament and friction torques that affect that joint. During normal walking, the net moment is almost fully caused by muscle torques, because friction forces are minimal. Again, there is no consensus statement on the reporting of the joint moments. Therefore, one needs to read carefully the gait literature, whether internal or external moments are being reported or whether the sign convention is based rather on clockwise – counter-clockwise than flexion-extension directions. The external moment regarding the joint axis is produced by the GRFs and inertial forces. It is equal and opposite to the net internal moment generated by the muscles. The internal extension moment is usually positive and, thus, corresponds to the external flexion moment (Winter 1988, Baliunas et al. 2002, Whittle 2002).

The knee joint is affected by an internal flexion moment at the initial contact. Then the QFm tries to extend the knee eccentrically at the loading response. The GM activates forcefully during terminal stance, and therefore a mild net flexion moment affects the knee joint at 30-50% of gait cycle. Between terminal stance and midswing, the knee joint exhibits an internal extension moment, as the knee joint bends up to 40 degrees. At that point, the QFm controls eccentrically the knee joint movement. During the terminal swing, knee flexors decelerate the limb to prepare for a smooth landing. Thus, knee joint is affected by a distinct flexion moment (Winter 1988, Whittle 2002).

The line of action of the net GRF, drawn in the centre of mass, in the frontal plane travels medially to the knee joint during stance (Noyes et al. 1992). During the whole stance, the knee joint is influenced by an external adduction moment, which is higher in magnitude than extension/flexion or rotation moments (Andriacchi and Mikosz 1991). The adduction moment is usually characterised by two peaks (i.e. w-shaped), occurring at the early and late stance, respectively (Hurwitz et al. 2002).

Plantar Pressure Distribution

Force plates are not able to distinguish pressures directed to different parts of the soles during the gait cycle. This kind of information would be useful in certain foot pathologies associated with diabetes and rheumatoid arthritis or post-operatively after corrective surgery (Lord et al. 1986). It is possible to examine plantar pressure distributions with an in-sole technique allowing measurement of many consecutive gait cycles (Cobb and Claremont 1995). Then subjects do not need to target their steps onto a pressure mat which enhances reliability of the gait analysis (Cavanagh et al. 1992).

The highest plantar pressures during walking can be measured beneath the heel, forefoot and hallux, whereas the lowest pressures exist beneath the midfoot and lateral toes. The loading of heel and forefoot are largest at the beginning and the end of stance phase, respectively (Soames 1985). The centre of pressure travels from the lateral heel along the midline of sole to the distal metatarsal bones, and finally beneath the 1st and 2nd toes (Katoh et al. 1983). It is known that the faster the gait speed, the higher are the plantar pressures (Rosenbaum et al. 1994, Perttunen and Komi 2001), as is the case concerning GRF (Soames and Richardson 1985) and also joint moments (Landry et al. 2007).

Electromyography

EMG has been extensively been utilised in the investigation of the function of the neuromuscular system during normal and pathological walking. The joint moment analysis is not able to reveal the active muscles that take part in the force production during gait cycle. Muscle activation patterns are well documented during normal walking on a level surface (Winter 1988, Perry 1992, Whittle 2002). In Figure 5, typical muscle activation patterns of different lower limb muscles are shown during the gait cycle. However, the same motor activity could be produced by various combinations of muscle activation patterns in normal gait, especially during the stance phase (Brandell 1977, Winter and Yack 1987, Whittle 2002). The variation of EMG-activity in proximal muscles that affects the hip and knee joints is greater than that in distal muscles affecting ankle joint. This is due to the fact that proximal muscles, in addition to providing weight support, are responsible for balance control (Brandell 1977, Winter and Yack 1987).

In general, the lower limb muscles are most active in expectation, i.e. prior to initial contact and during loading response. The main activity of weight supporting muscles, i.e. hamstrings and QFm, exist during the first 15% of a gait cycle. As QFm controls eccentrically the knee joint motion, the second peak in the EMG pattern of QFm is revealed at the time of the terminal stance up to the early swing phase (Murray et al. 1984). The peak activity of plantar flexors occurs in the middle of gait cycle. The hip extensor and knee flexors (gluteus maximus and hamstrings, respectively) function at the terminal swing, as they decelerate the forward movement of the swinging leg. The tibialis anterior activation pattern is biphasic. At first, it works during the load response and then during the early swing dorsiflexing of the foot (Winter and Yack 1987, Whittle 2002).

Photogrammetry

Photogrammetry can be defined as the measurement of three-dimensional objects (e.g. walking human) by two-dimensional images. Therefore, two or more cameras are needed to achieve 3-D measurements. In order to attain adequate accuracy, the 3-D system must be carefully calibrated. Almost all commercial systems use a 3-D calibration object, which is viewed by every camera. During the gait analysis with photogrammetry, the subject walks along a walkway in front of the cameras positioned to view the subject from different directions. The markers fixed onto the skin of subject at specific anatomical landmarks determine the appropriate body segments. As the markers are visible to at least two cameras simultaneously, the 3-D coordinates of the markers can be resolved (Nigg et al. 1999, Whittle 2002).

The accuracy of the photogrammetry mainly depends on the calibration error, the placement of skin markers and the amount of movement of skin markers in relation to the underlying bony landmarks. The measurement error in calibration is less than 1 mm, but the placement error and the movement of markers can be significant in some circumstances. The amount of error that the skin markers cause in the final results depends on which gait parameter is being assessed (joint angles, rotation or moments etc.) (Holden et al. 1997, Reinschmidt et al. 1997, Whittle 2002). Nowadays, the digital high-speed cameras can easily take 250 frames/s (frame interval 4 ms) increasing the measurement accuracy.

After gait measurements, the synchronically captured video files are processed using a computer. The kinematic data (linear and angular velocities and accelerations as well as joint angles and trajectories) can be calculated after tracking the skin markers with the relevant software. The 3-D position data of the markers can be combined into an appropriate template, i.e a model that includes the masses of every segment and their centres of gravity. Finally, this segment model can be synchronised with the GRF and other measured biosignals to establish a true biomechanical model for human motion (Nigg 1999, Whittle 2002).

2.6 GAIT CHANGES IN KNEE OSTEOARTHRITIS

2.6.1 Spatio-temporal Variables and Knee Joint Kinematics

Walking speed

Several authors have concluded that patients with knee OA exhibit lower preferred walking speed than the healthy controls of the same age (Al-Zahrani and Bakheit 2002, Gök et al. 2002, Chen et al. 2003a, Thorp et al. 2006, Rudolph et al. 2007, Astephen et al. 2008, Tanaka et al. 2008, Zeni and Higginson 2009). Furthermore, the gait speed seems to decrease in conjunction with the severity of radiographic disease (Thorp et al. 2006, Astephen et al. 2008, Zeni and Higginson 2009). There are only a few studies in which the authors have not found any statistical difference in self-selected walking speeds between

the knee OA patients and healthy controls (McGibbon and Krebs 2002, Mündermann et al. 2005, Landry et al. 2007) or between patients with less and more severe radiographic knee OA (Mündermann et al. 2005).

Stride Length and Frequency

The knee OA patients may spend a slightly larger portion of the gait cycle in stance (Thorp et al. 2006, Landry et al. 2007, Astephen et al. 2008), despite practically the same gait speeds as healthy controls (Landry et al. 2007). The mid-stance phase can also be delayed (Al-Zahrani and Bakheit 2002). Stride length (Al-Zahrani and Bakheit 2002, Baliunas et al. 2002, Gök et al. 2002, Chen et al. 2003a, Astephen et al. 2008, Tanaka et al. 2008) and stride frequency (Gök et al. 2002, Chen et al. 2003a, Astephen et al. 2008) have been reported to decrease in knee OA. These changes would partially result from the reduced gait speed. At nearly constant walking speeds, neither stride lenght nor stride frequency parameters have differed between knee OA patients and healthy controls (McGibbon and Krebs 2002, Landry et al. 2007). Unfortunately, many authors have not reported basic gait variables such as stride length and frequency (Thorp et al. 2006, Rudolph et al. 2007, Zeni and Higginson 2009), making it difficult to draw any firm conclusions about this issue.

Knee Kinematics

Gait speed has not been standardised in most studies that address knee joint kinematics in knee OA (Schnitzer et al. 1993, Kaufman et al. 2001, Al-Zahrani and Bakheit 2002, Gök et al. 2002). One would predict that this would greatly influence the reported results (Perttunen 2002, Möckel et al. 2003, Bejek et al. 2006, Landry et al. 2007). However, knee joint ROM in sagittal plane could be reduced in patients with knee OA even with standardised gait speeds (Baliunas et al. 2002). The knee joint flexion angle at the moment of initial heel contact has been reported to be more extended (Mündermann et al. 2005), flexed (Baliunas et al. 2002, Childs et al. 2004), or similar (Rudolph et al. 2007) in patients with knee OA. Neither the maximum knee flexion angle (Baliunas et al. 2002, Landry et al. 2007) during the gait cycle nor the terminal stance minimum angle (Baliunas et al. 2002, Mündermann et al. 2005) appear to differ at constant speeds between the healthy controls and patients with knee OA. However, the knee joint excursion during loading response is decreased in the patient group (Childs et al. 2004, Rudolph et al. 2007, Zeni and Higginson 2009). The disease severity in knee OA was associated with the diminished knee joint ROM during the whole gait cycle but, unfortunately, the authors did not control walking speed (Astephen et al. 2008).

2.6.2 Kinetics

Impulsive Loading

Excessive impulsive forces in the knee joint have been claimed to serve as co-factors in the iniation and progression of knee OA (Simon et al. 1972, Radin et al. 1973, Gill and O'Connor 2003). This has been verified in animal studies (Radin et al. 1978, Radin et al.

1982). However, there are very few human studies confirming the relationship between OA and impact loading. In the paper of Radin et al. (Radin et al. 1991) the authors stated that so called pre-osteoarthrotic patients with intermittent activity-related knee pain demonstrated higher axial tibial accelerations, i.e. higher impacts at heel strike than their healthy controls. Later, Chen at al. (2003b) reported that Caucasian women load their lower extremity more forcefully than Chinese women. The authors concluded that this might explain the lower prevalence of knee OA in Chinese females. However, these studies were cross-sectional in nature and presented no clinical evidence of knee OA (Radin et al. 1991, Chen et al. 2003b).

Between one third (7 from 21 subjects) (Radin et al. 1986) to nearly 60% (7 from 12 subjects) (Gill and O'Connor 2003) of healthy young adults have been claimed to exhibit high impulsive load at a normal gait speed at heel strike. Futhermore, one fifth (39 from 204) of knee OA patients have reported to exhibit a heel strike transient at freely chosen walking speed (Hunt et al. 2010). According to Radin et al. (1986), the non-heel strikers decelerate the angular velocity of shank prior to contact by active QFm contraction. This diminishes the impact type of loading on initial contact. The authors concluded that the subjects unable to decelerate their limb before ground contact may be at risk of developing knee OA later (Radin et al. 1986). Controversially, in the more recent work of Henriksen et al. (2006b) the authors detected no difference in impulsive vertical GRF or peak accelerations at heel strike between elderly knee OA patients (n=10) and their healthy controls. After relief of pain, the impact loading increased in the patient group while still remaining within the normal range (Henriksen et al. 2006b).

Due to the low number of subjects, different age-groups, cross-sectional study designs as well as subtle differences in walking speeds in the previous studies (Radin et al. 1986, Gill and O'Connor 2003, Henriksen et al. 2006b), the influence of impulsive loading on the incidence of knee OA remains open. Furthermore, there is a need of longitudinal studies in which the pathological loading level for the musculoskeletal system could be evaluated. For example, footwear properties (Loy and Voloshin 1991, Lafortune and Hennig 1992) and proper function of neuromuscular system may protect the musculoskeletal system from potentially adverse impact loading during locomotion (Jones and Watt 1971, Komi et al. 1987, Radin et al. 1991, Arampatzis et al. 2003).

Sagittal Plane Kinetics

GRFs are traditionally used to evaluate the gait of patients with knee OA. Messier et al. (1992) observed that patients with knee OA exhibited a higher vertical LR in the affected side compared to healthy controls, and the LR tended to be greater also in the unaffected side. This finding was confirmed in the recent paper by Mündermann et al. (2005). They reported an elevation of 50% in vertical LR in patients with knee OA. The authors also found an increased intersegmential axial LR in all joints of the lower extremity (Mündermann et al. 2005). However, Bejek et al. (2006) observed no difference in the vertical peak GRF variables during treadmill walking at relatively low speeds (0.27-1.11

m/s). On the other hand, Childs et al. (2004) reported lower LR, and vertical peak parameters in patients with knee OA.

The vertical LR may change in association with the disease severity. Zeni et al. (2009) reported that patients with moderate knee OA demonstrate higher LR than the patients suffering from severe knee OA. In general, patients with knee OA showed lower LR, peak vertical GRF as well as an axial joint reaction force at different gait speeds compared to their healthy controls. The differences were minimal at low speed (1.0 m/s). Interestingly, the differences in loading parameters decreased at fast, but not at self-selected, velocities provided that the gait speed had been taken into account during the analysis (Zeni and Higginson 2009).

The differences in A-P GRF variables at a constant speed between the knee OA patients and healthy controls are minimal (Messier et al. 1992, Zeni and Higginson 2009). When the gait speed was not taken into account, patients with moderate and severe knee OA exhibited lower peak GRFs in the A-P direction than the healthy controls. The disease severity had no effect on the measured A-P peak parameters (Zeni and Higginson 2009).

There are inconsistent previous findings about knee joint sagittal plane moments among patients with knee OA. However, the initial knee joint extension moment may not be different in patients with knee OA and in healthy age-matched controls (Baliunas et al. 2002, Rudolph et al. 2007). Astephen et al. (2008) reported that patients with moderate knee OA have a smaller knee flexion moment at early midstance (about 10-25% of gait cycle) compared to healthy controls. On the other hand, patients with severe knee OA demonstrate a greater overall magnitude knee flexion moment during mid-to-late stance (Astephen et al. 2008). According to Zeni et al. (2009), disease severity does not associate with the peak knee joint moments at different gait speeds when the walking velocity is taken into account in the analysis. On the contrary, Landry et al. (2007) observed that the lower knee flexion moment magnitude occurred at 25% of the gait cycle in patients with knee OA both at self-selected and fast walking speeds. Bailunas et al. (2002) have also reported a lower terminal stance knee extension moment in patients with knee OA, but not in any other phases of gait cycle. Female knee OA patients may have a lower knee flexion moment during walking than healthy females, OA males and healthy males. This emphasizes the importance of taking into account gender differences in joint loading assessment (Hunt et al. 2008).

Frontal Plane Kinetics

There are few reports dealing with the characteristics of M-L GRF in patients with knee OA during walking. The lateral GRF immediately after the initial contact might be higher in knee OA patients. In addition, the magnitude of the increase could be related to disease severity (Mündermann et al. 2005). However, Messier et al. (1992) found no differences in M-L GRF between the knee OA patients and healthy controls.

The forces acting onto a knee joint are not distributed equally between the medial and lateral tibiofemoral compartments during walking. The load transferred through the medial side is about 2.5 times higher than experienced by the lateral side. This produces an external adduction moment (Schipplein and Andriacchi 1991). Patients with knee OA are claimed to exhibit significantly higher (Baliunas et al. 2002, Hurwitz et al. 2002, Thorp et al. 2006, Landry et al. 2007, Rudolph et al. 2007, Astephen et al. 2008) or nearly similar (Mündermann et al. 2004, Zeni and Higginson 2009) first peak knee adduction moments during walking, when compared with their healthy controls. The first peak adduction moment increases (Mündermann et al. 2004, Mündermann et al. 2005) or is constant (Thorp et al. 2006, Zeni and Higginson 2009) in conjunction with the disease severity. Previous findings about the second peak adduction moment occurring at the late stance phase are inconclusive in knee OA studies (Hurwitz et al. 2002, Mündermann et al. 2005, Thorp et al. 2006, Astephen et al. 2008). It should be noted that there may be gender differences in knee M-L joint loading (McKean et al. 2007), and the lateral trunk lean as well as the toe-out angle could reduce the adduction moments and this could explain the variations in the results obtained in knee OA gait studies (Hunt et al. 2008).

The adduction moments correlated with the radiographic severity and the joint space narrowing of the medial compartment knee OA (Sharma et al. 1998). Later, Hurwitz et al. (2002) reported that the mechanical axis of knee joint was a better determinant of the adduction moment than the radiographic measures of disease severity. However, mechanical axis accounted for only 50% of the variation in the peak adduction moment and highlighted the need for dynamic evaluation of the loading environment, such as toe-out angle and lateral trunk lean (Hurwitz et al. 2002, Hunt et al. 2008). According to Miyazaki et al. (2002), the knee adduction moment during walking is a risk factor for the progression of the medial compartment knee OA. Mundemann et al. (2004) observed only a weak relationship between the maximum knee adduction moment at the preferred speed and self-selected walking speed. The authors concluded that the increased maximum knee adduction moment may not have been the initial cause of knee OA, but rather a consequence of morphological changes occurring in the pathological joint (Mündermann et al. 2004).

2.6.3 Muscle Activation Patterns

The correct functioning of the neuromuscular system is essential in diminishing impulsive loading, and in particular the importance of adequate QFm strength has been emphasised (Slemenda et al. 1997, Mikesky et al. 2000). More recently, Hunt et al. (2010) have questioned the effect of QFm strength on the impact loading in knee OA patients during walking. However, EMG measurements of muscle activity during the gait analysis have rarely been conducted among patients with knee OA. According to Childs et al. (2004) patients with knee OA exhibit prolonged activity of lower extremity muscles [tibialis anterior, vastus lateralis (VL), hamstrings and gastrocnemius]. A higher co-activation of the agonist-antagonist muscle pairs was observed in the OA patient group during the stance phase. The authors concluded that these findings on increased muscle

activation combined with decreased knee joint excursion represent an attempt to avoid pain and stabilise the knee joint during the loading response (Childs et al. 2004). Patients with severe knee OA may have greater activity of gastrocnemius medialis muscle (GaM) in early stance and swing but lower activity in late stance compared to patients with less severe knee OA This could indicate the need to increase stiffness in response to pain or laxity. The lateral hamstring exhibited higher activity in the stance of the knee OA patients, as compared to that of controls (Astephen et al. 2008).

Hubley-Kozey et al. (2006) investigated the neuromuscular function of patients with moderate knee OA changes. These patients demonstrated no decline in muscle strength but they were older, showed higher BW and had slightly lower walking speed. These patients exhibited reduced activity of the GaM during propulsion. It is possible that this could reduce the joint loading in the medial compartment of knee. During loading, the activity VL was higher whereas VM exhibited similar response in patients and controls. There was also a trend towards higher activity in the rectus femoris muscle (RF) during loading response and at late stance. The lateral hamstring showed prolonged activity during stance in patients with knee OA. The maximal activity, which occurred just prior to heel contact, was also greater in patients. The function of lateral and medial hamstrings was coordinated more effectively in the controls. The authors concluded that the principal neuromuscular patterns were similar in both groups, while the patients with knee OA tried to shift activation onto the lateral side. This reflected changes in the mechanical environment (Hubley-Kozey et al. 2006).

According to Hubley-Kozey et al. (2008), patients with severe knee OA activated all the measured lower extremity muscles over the majority of the stance phase and displayed high co-activation pattern throughout most of the gait cycle. These muscle responses are indicative of attempts to decrease medial joint loading and peak loading during push-off as well as to increase stiffness during the stance phase as a way to improve joint stability (Hubley-Kozey et al. 2008).

2.6.4 Stair Walking

Patients with knee OA frequently demonstrate difficulties in stair climbing (Stratford et al. 2006), evaluated by the time required to ascend or descend a given number of stairs. Stair ambulation performance is often used as a measure of function in OA patients (Rejeski et al. 1995, Gür and Cakin 2003, Shrader et al. 2004, Mizner et al. 2005a, Stratford et al. 2006). Unfortunately, there are rather few papers available about stair ambulation during the gait analysis among patients with knee OA. Recently, Asay et al. (2009) investigated patients with moderate or severe knee OA and compared the results with healthy controls during stair climbing task. Patients with more severe OA (KL ≥3) demonstrated a greater peak trunk flexion angle, lower peak flexion moment and higher peak flexion moment than the controls. There was no difference in the knee flexion angle at the initial contact. Patients with one knee more severely affected than the other exhibited a decreased peak flexion moment on their more affected side compared to the

contralateral side. The authors concluded that the patients with severe knee OA tried to reduce QFm demand by leaning their trunk forward during stair climbing (Asay et al. 2009).

Kaufman et al. (2001) found no differences in the maximum knee flexion during stair ascent and descent between the control subjects and patients with knee OA. The patients demonstrated lower maximum knee internal extension moments both during stair ascent and descent. Female OA subjects exhibited a greater peak knee extension moment as well as more knee flexion (Kaufman et al. 2001), again emphasizing the influence of gender. These results should be interpreted with caution, as the patients with knee OA were on average 27 years older, walked at significantly slower speed and possessed different anthropometries compared to the controls. Hinman et al. (2002) reported that the patients with knee OA did not exhibit delayed temporal onset of VM muscle relatively to VL, in contrast to healthy controls, during stair climbing. Bennell et al. (2004) observed that the joint-position sense and QFm onset associated with the knee flexion angle at initial contact during stair descent, and furthermore, the QFm strength correlated with the peak knee flexion angle occurring during the loading response. The authors concluded that the impaired sensorimotor function was not strongly associated with the altered joint kinematics in the knee OA patients during locomotion (Bennell et al. 2004).

3 Aims of the Study

The main purpose for these studies was to examine the gait biomechanics in patients suffering from knee OA. A second aim was to study the objective and subjective physical function in knees of OA patients by conducting measurements of strength and analysing the composition of quadriceps femoris muscle (QFm). The detailed goals of the present series of studies can be outlined as follows:

1.) It has been suggested that the proper function of neuromuscular system, especially the effective activation of QFm prior to heel contact, may protect the musculoskeletal system from adverse impulsive loads (Jefferson et al. 1990, Slemenda et al. 1997, Mikesky et al. 2000). The aims of the first study (Paper I) were to examine the impulsive loading of the musculoskeletal system under different conditions, the prevalence of the heel strike transient and the function of the QFm prior to the contact phase during walking in clinically healthy elderly subjects.

2.) The reproducibilities of the load measurements with skin mounted accelerometers (SMAs) during walking have not been fully evaluated. Furthermore, there is no established manner for reporting the peak loads, transients, or rate of loading in the gait literature The aim of the second study (Paper II) was to investigate the intra- and inter-day repeatability of loading measurements with SMAs during walking, A second purpose was to test different methods for calculating impulsive loading from GRF and acceleration data.

3.) Few attempts have been made to gain insight into the mechanical loading during walking with pre-determined gait speeds in patients with knee OA and to assess the effect of the severity of knee OA disease on gait and joint loading (Mündermann et al. 2005). The main goal of the third study (Paper III) was to examine the gait biomechanics of knee OA patients on level ground and during climbing stairs. The analysis system included SMAs, force plates, and EMG. Measurements were conducted at different constant speeds and the results were compared with those of age- and sex-matched randomly selected control subjects. A secondary aim was to investigate the influence of knee OA severity on the measured gait parameters.

4.) There is no consensus on the significance of possible interfering factors, such as pain, comorbidity, physiopathological, sociodemographic, psychological and social factors, on the physical function of patients suffering from knee OA. Furthermore, there are no guidelines how the physical function should be tested clinically in patients with knee OA. The main aim of the last study (Paper IV) was to examine the objective and subjective physical function and the properties of the QFm in men with knee OA and to compare the results with those of age- and sex-matched, randomly selected healthy controls. Secondly, the purpose was to estimate the effect of possible interfering factors on the observed differences in physical function between the OA and control groups.

4 Materials and Methods

4.1 SUBJECTS AND SELECTION

Total of 144 volunteers (21 women and 123 men) participated in three different experiments (1-3). The detailed physical characteristics of the subjects are described in Table 5 in Paragraph 5.1 Characteristics of Subjects. The subjects were fully informed of the procedures and risks associated with the experiments and gave their written consent. Studies were conducted according to the Helsinki Declaration and approved by the Ethics Committee of the Central Hospital of Central Finland (Experiment 1) and Kuopio University Hospital (Experiments 2-3).

The subjects in Experiment 1 were sampled from the population register of the city of Jyväskylä, Finland. A subject was accepted to participate in the study if she/he passed the clinical examination, and had no exclusion criteria (Table 4), and experienced no pain or functional disability in the lower limbs. In Experiment 2, ten healthy young male students of physics were recruited. They had no history of musculoskeltal trauma, surgery, or pain in the lower limbs.

The subjects in Experiment 3 were recruited from the city of Kuopio and its neighbouring area by a local newspaper advertisement. The subjects (n=54 males) were selected according to the clinical criteria of the American College of Rheumatology (Altman et al. 1991) for uni- or bilateral knee OA. The knee OA subjects were further divided into four subgroups according to the radiographic severity of their OA using the K-L grading (Kellgren et al. 1963) (Table 2). There were no statistical differences in physical characteristics between the knee OA subgroups but the mean weight of the control group was 10 kg lower than that of the OA group. Age- and sex matched control subjects (n=53) were randomly sampled from the population register of the city of Kuopio. They exhibited no hip or knee OA according to the clinical criteria of American College of Rheumatology (Altman et al. 1991). The exclusion criteria used in Experiments 1 and 3 are presented in Table 4.

Table 4. Exclusion Criteria of Experiments 1 and 3

- A history of previous hip or knee fracture
- Surgery of lower extremities (knee arthroscopy was allowed)
- Spine surgery
- A history of other trauma to the hip joint or in the pelvic region
- Clinical or radiological hip OA
- A knee or hip joint infection
- Congenital or developmental disease of lower limbs
- Paralysis of lower extremities

Any disease or medication that might have worsened physical function and interfered with the evaluation of knee pain, such as:

- Cancer
- Severe mental disorder
- Rheumatoid arthritis or spondyloarthritis
- Symptomatic cerebrovascular disease
- Endocrine disease
- Epilepsy
- Parkinson's disease
- Polyneuropathia, neuromuscular disorder
- Debilitating cardiovascular disease in spite of medication
- Atherosclerosis of lower extremities
- Concurrent low back pain or acute sciatic syndrome
- Corticosteroid medication
- Symptomatic spinal stenosis

4.2 EXPERIMENTAL DESIGN

4.2.1 Experiment 1

Experiment 1 was carried out in the Neuromuscular Research Center, University of Jyväskylä. The subjects performed level walking trials with self-selected normal and maximal speeds so they could become familiar with the experimental procedure. They wore similar gym-shoes as they walked along a 15-m-long walkway. A 10-m-long force platform, covered with a tartan-mat, was mounted in the middle of the walkway. The gait speed was measured using the photo-cells (Newtest, Oulu, Finland) placed in the middle of the walkway, 5 m apart from each other.

The subjects walked two times at their preferred normal speed and then two times at their maximal speed. After the level walking trials, stairs were placed at the end of the force platforms. The stairs consisted of four steps (height 20 cm, depth 30 cm, and inclination angle 33.7°), divided into two rows to permit measurements of both limbs separately. Stair walking trials were repeated twice at the preferred speed of the subjects. All signals were averaged during the contact phases from the second level walking trial and from both trials of stair walking.

4.2.2 Experiment 2

The gait analysis of Experiment 2, conducted in the Department of Physics, University of Kuopio, consisted of two parts: laboratory and corridor. There were two force platforms (see details in Paragraph 4.3.1) mounted in the middle of the walkway to allow the measurement of the 3-D GRFs. Gait speed was measured using a pair of photo-cells (Omron E3S-AR36, Japan) placed 2.5 m apart on either side of the force platforms. The method in use allowed collection of GRFs and accelerometer data simultaneously during the consecutive steps. The 10-m long laboratory walkway was covered with a thin rubber mat allowing measurement of one gait cycle with two consecutive steps on the force platforms. In that way, the subjects were able to take three acceleration and braking steps. The measurement area was covered on a long corridor with the same rubber mat as in the laboratory. The photo-cells were positioned 6 m apart from each other in the middle of the walkway in the corridor. Two to three consecutive gait cycles were measured on the mat for every subject.

During the measurements, the subjects walked barefoot six times using both their self-selected speed and a pre-determined constant speed (1.3 m/s±5%) along the laboratory walkway. The walking trials were repeated four times at both speeds in the corridor. The subjects were instructed to walk naturally at a steady speed. Trials in which the subjects did not walk at the required speed or contacted the force platforms improperly were rejected. The trial order was randomised. The above mentioned test protocol was repeated two days later in order to calculate the repeatability of the SMA measurements.

4.2.3 Experiment 3

In Experiment 3, the subjects walked barefoot at pre-determined gait speeds along the walkway in the laboratory (1.2m/s±5%), corridor (1.2; 1.5 and 1.7m/s±5%), and stairs (0.5 and 0.8 m/s±5%), performing stair ascents and descents separately. Stair walking trials were performed in custom-built stairs (inclination 29°, step depth 29.0 cm) and five consecutive gait cycles were analysed from each trial. The subjects were not allowed to hold onto the handrails. In all walking environments, the measurement area was covered with a rubber mat and the trial order was randomised.

All subjects performed warm-up trials before the measurements at every test location in order to familiarize then with the experimental procedure. Ten acceptable trials were

collected for further analysis in the laboratory, while three valid trials were required at every speed in the corridor and stairs. The subjects were instructed to walk naturally at a steady speed. Trials in which the subjects did not walk at the required speed were rejected. The subjective knee pain was rated using a VAS [range 0 (no pain) to 100 mm (unbearable pain)] separately for both limbs before gait measurements.

In Experiment 3, the subjects performed physical function tests (Paper IV) on different days. Prior to physical function testing, the subjects were familiarised with the test procedure and purpose. Adequate pauses between the tests were used to avoid fatigue. The same investigator directed the testing sessions, providing similar verbal encouragement for every subject to maximize the performance. The physical function was measured using tests in a random order. However, the 5-min walk and muscle strength measurements were assessed at the end of the session. The detailed descriptions of specific tests and strength measurements are shown in Paragraph 4.3.8 Physical Function Measurements. The subjective knee pain was assessed with the VAS method before the muscle strength measurements.

4.3 DATA RECORDING AND ANALYSIS

4.3.1 Ground Reaction Force Measurements

In Experiment 1, the 10-m force platform (Raute Oy, Lahti, Finland) was divided into two rows allowing the measurement of 3-D GRFs from left and right limbs separately (Paper I). GRFs were collected and stored with Motus software (Peak Performance Technologies, Englewood, CA, USA) at 1 kHz. Maximal reaction forces and LRs were measured in vertical and A-P directions (Figure 8). Force parameters were normalised by the BW.

The method described by McCrory et al. (2001) was used for calculating the LR. The heel strike transient was defined according to Radin et al. (1986). Subjects were classified as heel-strikers if the measured value was >1.2. The GRF values of stair ambulation were filtered with a best-fit Butterworth filter. Contact times were determined manually on the basis of vertical GRF deviation from the baseline by an experienced analyst. The contact phase was divided into braking and push-off phases depending on the direction of the A-P GRF (Mero and Komi 1986). The M-L GRF was not analysed due to its high variability (Herzog et al. 1989, Giakas and Baltzopoulos 1997).

The following spatio-temporal parameters were calculated with the GRF data: Step length and frequency as well as the duration of double support and the braking phase (Paper I).

In Experiments 2 and 3, three dimensional GRFs were determined using two force platforms (length 508 cm; width 464 cm) (Model OR6-7MA, Advanced Management Technology Inc, MA, USA). The natural frequencies of the force plates used in the vertical

and horizontal directions were 480 Hz and 300 Hz, respectively; cross-talk <2%, hysteresis ±0.2%, and non-linearity ±0.2%. The precision of the force plates were 1.4 N and 0.38 N in the vertical and horizontal directions, respectively. GRFs were collected and stored with software (Advanced Management Technology Inc, MA, USA) at 2 kHz. Only the steps between the photo-cells were accepted for processing and the first and last steps were omitted from the analysis. All data were further analysed with software based on MatLab 7.0.4.

Force parameters were normalised to the weight of the subject. Contact times were determined using the vertical GRF with an adaptive threshold level 0.001 of BW. Local maximum and minimum forces and their timings were measured in both the vertical (F_z), A-P directions (F_x) and M-L directions (F_y) (Figure 8). Loading parameters were defined from the beginning of the contact phase. Peak forces (F_{z1} i.e. heel strike transient, F_{z2} and F_{z3}) as well as maximal and average loading rates (LR_{max}, LR_{ave}, respectively) (Equation 1 and Equation 2) were measured from the vertical GRF data. LR_{ave} was calculated according to Stacoff et al. (2005). The LR_{ave} was not calculated in Experiment 3.

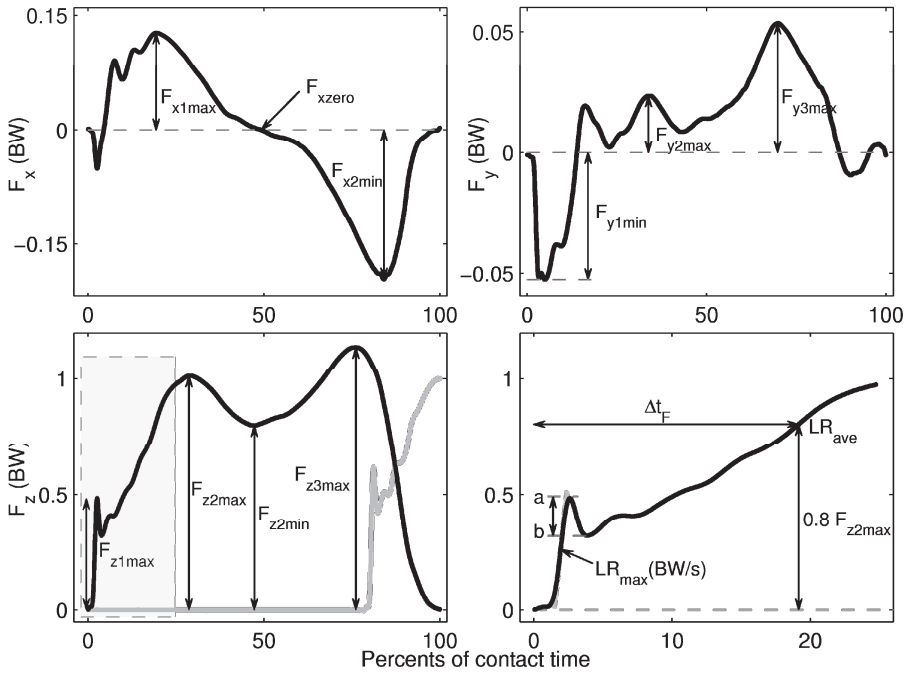

Figure 8. The gait parameters defined from the ground reaction force (GRF) data in antero-posterior (F_x), medio-lateral (F_y), and vertical (F_z) directions. $F_{x\ zero}$ indicates the border between the braking and the push-off phases. Loading rate (LR) was calculated with the formula LR = $F_{z2\ max}/F_{z2\ time}$ (McCrory et al. 2001) in Experiment 1. If the ratio a/b was >1.2, then the subject was categorised as a heel-striker. The initial part of the F_z is shown with an expanded scale (right lower corner) to clarify the definitions of maximal (LR_{max}) and average (LR_{ave}) loading rate parameters.

Equation 1.

$$LR_{\max} = \max\left\{\frac{dF_z(t)}{dt}\right\}$$

Equation 2.

$$LR_{ave} = \frac{0.8F_{z2_{\max}}}{\Delta t_F},$$

where Δt_F is the time between the beginning of contact and $0.8F_{z2\,max}$.

4.3.2 Acceleration Measurements

Two lightweight triaxial (range ±10 g) Meac-x SMAs (Mega Electronics Ltd, Kuopio, Finland), fixed onto an aluminium plate, were attached tightly above and below the right knee joint by using an adhesive bandage (Acrylastic, BSN, Vibraye, Medical SAS, France) (Paper II). The SMAs were positioned on the more affected limb in patients with knee OA. The third SMA was attached on the contralateral limb below the knee in order to make enable a side-to-side comparison (Paper III). The SMAs were calibrated to produce comparable outputs. The positive z-axis (a_z or axial acceleration) of the sensor was aligned downward in parallel to the straight limb.

A portable bio-signal monitor (Biomonitor ME6000 T16 data-acquisition unit, Mega Electronics Ltd, Kuopio, Finland), fixed with a belt onto the subjects' back, was used to collect SMA and EMG data (see details about EMG measurements in paragraph 4.3.3 Measurement of Electromyographic Activity) (Papers II, III). For the measurements conducted in the corridor and stairs, the data were sampled at a frequency of 2 kHz and saved on an exchangeable memory card. All data were further transferred to Megawin 2.3 software (Mega Electronics Ltd, Kuopio, Finland). During the laboratory measurements, data were collected on-line at 1 kHz and transferred telemetrically (WLAN) to the Megawin 2.3 –software.

Contact times were also determined indirectly from the a_z data, as based on vertical GRF and signal shape analysis of the a_z data. Stride length and frequency were calculated from the a_z (Paper II). Initial peak and peak-to-peak accelerations (IPA and PP, respectively) as well as maximal and average acceleration transient rates (ATR_{max}, ATR_{ave}, respectively) (Equation 3 and Equation 4) were determined from the a_z and the resultant (a_r) directions (Figure 9). ATR_{ave} was calculated according to Lafortune et al (1992). The gravitational acceleration (g) was reduced from all measured acceleration values of the axial and

resultant directions. The IPA and PP were also measured in the resultant horizontal direction (a_{rxy}) Equation 5.

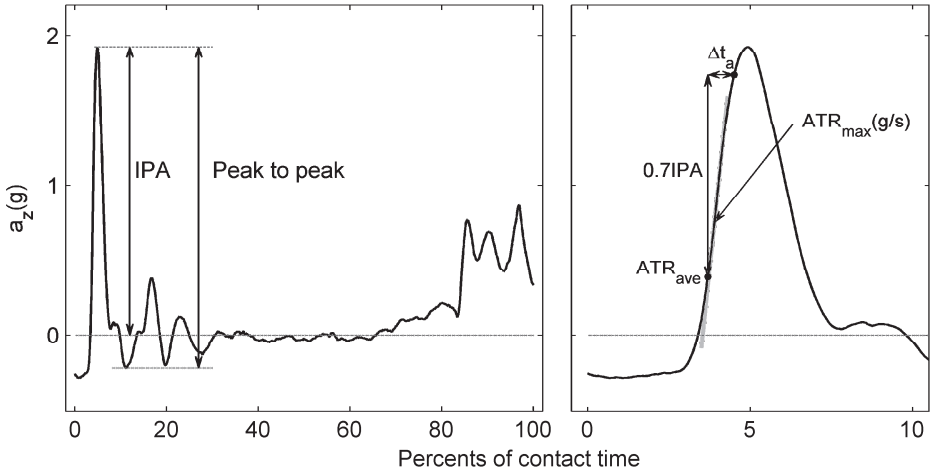

Figure 9. Gait loading parameters defined from the axial acceleration (a_z) signals. The initial part of the signal is expanded on the right to demonstrate the definitions of maximal and average acceleration transient rate (ATR_{max} and ATR_{ave}, respectively) parameters. IPA = initial peak acceleration.

Equation 3.

$$ATR_{\max} = \max\left\{\frac{da(t)}{dt}\right\}$$

Equation 4.

$$ATR_{ave} = \frac{0.7IPA}{\Delta t_a},$$

where Δt_a is the time between 0.2 and 0.9 IPA.

Equation 5.

$$a_{rxy} = \sqrt{a_y^2 + a_x^2}$$

4.3.3 Measurement of Electromyographic Activity

Muscle activity was measured bilaterally from the VM, VL, biceps femoris (BF) and GaM muscles at the sampling frequency of 800 Hz (Hermens et al. 1999). The data-acquisition system used to collect the EMG data (Paromed-System®, GmbH, Neubeuern, Germany) was the same as in the plantar pressure measurements (Paper I). Before the measurement, the skin area was well cleaned to keep the inter-electrode impedance low (<5 kΩ). The EMG was recorded with surface Ag-AgCl electrodes (M-00-S, Medicotest A/S, Olstykke, Denmark, inter-electrode distance of 20 mm) (Papers I, III). Cross-talk between the muscles was assumed to affect minimally the measured EMG signals because of the relatively small inter-electrode distance (Winter et al. 1994). In Experiment 1, the EMG data was high-pass filtered with a cut-off frequency of 10 Hz. Furthermore, the EMG data were full-wave rectified and averaged. The EMG activities of level walking and stair walking were calculated prior to the contact, i.e. from the pre-activation phase, using a 100 ms time frame. The averaged EMG values of VM and VL muscles were normalised according to the averaged EMG values during the maximal isometric force measurement (Paper I).

In Experiment 3, EMG data were collected using the 16-channel data logger (Biomonitor ME6000® T16, Mega Electronics Ltd, Kuopio, Finland). EMG signals were band-pass filtered with the cut-off frequencies of 7 Hz and 500 Hz and amplified by the ME6000 system (Paper III). All digitised EMG signals were fullwave rectified and averaged (Paper III). The EMG activity was normalised to the maximum EMG signal obtained during walking in the corridor at 1.5 m/s. The amount of muscle co-activation was determined according to the method of Rudolph et al. (2000) (Equation 6).

Equation 6.

$$(EMG_L + EMG_M) \times EMG_L/EMG_M,$$

where subscripts L and M denoted activity in the less and more active muscle, respectively.

The gait cycle was divided into five sections (see below) based on foot contact (Benoit et al. 2003). The mean EMG activity was calculated for every section separately.

I Foot contact (0%) to 10% loading response

II 11-30% early stance

III 31-60% late stance

IV 61-80% early swing

V 81-100% late swing

4.3.4 Measurement of Plantar Pressure Distribution

Plantar pressure distribution was measured with a commercial system (Paromed-System®, Medizintechnik GmbH, Neubeuern, Germany). The recording system fixed onto the subject's low back (total mass 570 g). Two insole pressure transducers were used to measure bilateral plantar pressure distribution (Paper I). Both insoles contain 24 piezoresistive sensors embedded in constrained hydrocells. The sampling frequency for each pressure sensor was 200 Hz. The sensors were positioned to record pressures from the most clinically relevant areas (Schumacher 1995) and covered over 50% of the insole. The pre-amplification factor was at 100 near to the electrodes and the input impedance was 10 GΩ. The EMG and plantar pressure data were saved on an exchangeable memory card and, subsequently after calibration, transferred to the Silicon Graphics workstation (Silicon Graphics, Inc, CA, USA) like the other biosignals (GRFs and EMG). Maximum pressures (kPa) were reported.

4.3.5 Gait Symmetry Calculation

The symmetry indices of the GRF and spatio-temporal (Papers I, II) as well as plantar pressure (Paper I) parameters were determined using the absolute symmetry index (ASI) (Giakas and Baltzopoulos 1997, White et al. 1999) The used equation is a modified version of the symmetry index equation used by Herzog et al. (1989). GRF data were broken down to its components allowing calculation symmetry in F_z, F_x, and F_y directions. The symmetry was consider acceptable if ASI <10%, perfect symmetry required an ASI of 0% (Equation 7).

Equation 7.

$$ASI(\%) = \left| \frac{(X_r - X_l)}{1/2(X_r + X_l)} \right| \cdot 100\%$$

4.3.6 Questionnaires

All subjects filled in questionnaires on comorbidities, leisure-time physical activity and questions concerning their work history in Experiment 3. The number of comorbidities was enquired with the following question: Do you have any other diseases (comorbidities)? Five disorder classes were listed: cardiovascular, respiratory, gastrointestinal, endocrinologic diseases and depression. The leisure-time physical activity was assessed from a 12-month history modified from the Minnesota leisure-time physical activity questionnaire (Lakka et al. 1994). The frequency of activities (sessions per year) was determined. A basic questionnaire was used to elicit information on the occupations [scale from 0 (no work) to 6 (in physical terms, the most demanding occupation)] (Mäkelä et al. 1993). Among the OA subjects, the use (yes/no) of prescribed pain relief medication [i.e. analgesics, non-steroidal anti-inflammatory drugs or other drugs] was determined for the previous six months as well as the occurrence of possible knee joint traumas (yes/no).

Knee symptoms were estimated in the patients by WOMAC (Bellamy et al. 1988, Soininen et al. 2008). The WOMAC is a tri-dimensional, disease-specific health status questionnaire, which consists of 24 questions in the areas of pain, stiffness and physical function relevant to patients with OA of the knee. The Visual Analogue (WOMAC VA 3.0) scaled format was used. The VA scaled version allows patients to estimate the symptoms by marking an X on a 100 mm long line (the beginning of the line = no symptoms, the end of the line = the worst possible symptoms). Scores were generated for the three dimensions of pain, stiffness and physical function by summing the coded responses and then dividing by the number of items. A composite score was generated by summing all of the responses and then dividing by 24 (total number of items).

Self-reported generic physical function was determined by using the physical function part of the RAND 36-Item Health Survey 1.0 (RAND-36) questionnaire. This instrument contains the same questions as the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36) (Hays et al. 1993, Hays and Morales 2001), but the scoring for the general health and bodily pain subscales differs slightly. The RAND-36 is composed of 8 multi-item dimensions: general health, physical functioning, mental health, social functioning, vitality, bodily pain and physical and emotional role functioning. There is a range from 0 to 100 in each subscale with higher scores indicative of a better health-related quality of life. The reliability and construct validity of the RAND-36, as a measurement of the health-related quality of life in the Finnish general population, have been established (Aalto et al. 1999). The RAND-36 is composed of 8 multi-item dimensions: general health, physical functioning, mental health, social functioning, vitality, bodily pain and physical and emotional role functioning. There is a range from 0 to 100 in each subscale with higher scores indicative of a better health-related quality of life.

4.3.7 Radiological Measurements

Evaluation of Plain Radiographs

Erect A-P and M-L radiographs were taken from both knees of the subjects accepted into the study (Paper I). The radiographs were evaluated blinded by a physician using the Nagaosa et al. (2000) grading scale in which a value 0 means no OA and 3 refers to severe OA.

In Experiment 3, standard A-P weight bearing and lateral radiographs as well as the weight bearing radiographs of both lower limbs were taken from both knees. The radiographs were evaluated blindly by an experienced radiologist using the K-L grading (Kellgren et al. 1963). The intra-rater reliability of K-L-grading is good (Sun et al. 1997). The knee varus or valgus alignment was measured using the method described by Moreland at al. (1987), and alignment was expressed as an absolute value (degrees) of the divergence from the straight line (zero degree).

Ultrasound measurements

The QFm were imaged with ultrasound (Aloka SSD 1000, Japan) from the midpoint of RF, VL and vastus intermedius (VI) compartments using a 5-cm wide probe at 5 MHz frequency (Paper IV). The measurement point was located midway between the lateral joint space and the trochanter major. During the measurement, the subject lay in the supine position. The monitor of the computer was used during scanning to ensure the best and sharpest bone echo. The probe was then assumed to be at right angles to the femur. The thickness of the subcutaneous fat and the thickness of the muscle group, including the RF, VL and VI, were assessed by means of a longitudinal real-time scan. The ultrasound images were further analysed with Scion Image for Windows software (Scion Corporation, Maryland, USA). The area (cm^2) beneath the probe and mean echogenicity of the three compartments (RF, VL and VI) were determined to evaluate the muscle mass and tissue composition.

The echogenicity is a measure for muscle composition and uses the 256 grey shades of the device. It was assumed that the increased echo intensity (i.e. higher mean grey shade value) of the muscle reflects increased heterogeneity in tissue composition, i.e. increased fat and connective tissue proportions. The method has been described in more detail elsewhere (Sipilä and Suominen 1991, Sipilä and Suominen 1996). Quantitative ultrasound measurements have been shown to correlate with the computed tomography measurements of muscle cross sectional area and muscle composition (Sipilä and Suominen 1993). The day-to-day reproducibility of ultrasound measurements has been determined previously. The coefficient of variation for echogenicity of VL has been shown to be less than 8% (Sipilä and Suominen 1996).

4.3.8 Physical Function Measurements

Lift Test

The lift test in use was modified from the test described by Strand et al. (2001). The subject was asked to repeat the lifting of the box (plastic box, 8.5 kg) from the floor onto a table (0.73 m high) and back for 1 minute. The technique used to perform the lifting was optional. The number of lifts was recorded. The reliability of counting lifts per minute has not been reported.

Pick-up Test

In the pick up test (Strand and Ljunggren 2001), the subject picked-up a piece of paper from the floor in the most comfortable way. The investigator assessed the performance with a scale 0 to 3, in which 0 = performance with flexibility and ease and 3 = inability to do the task or need for external support. The reliability of the pick-up test has been shown to be good (Strand and Ljunggren 2001).

Repeated Sit-to-stand Test

The subject was asked to fold the arms across the chest and to stand up from the sitting position and to sit down five times as quickly as possible (Seeman et al. 1994, Guralnik et al. 1995, Simmonds et al. 1998, Sharma et al. 1999). The mean value in seconds to complete the two trials was registered. Test-retest correlation has been shown to be good (r =0.73-0.76) for this test (Seeman et al. 1994, Suteerawattananon and Protas 2000).

Sock Test

The patient, wearing loose clothing, was asked to simulate putting on a sock in a standardised manner (Strand and Wie 1999). Before starting the test, the activity had first been demonstrated to the patient. The patient was asked to sit on a high bench, with both hands, one on each side, grabbing the toes with the fingertips of both hands. The foot was not allowed to touch the bench and had to be in the air at all times during the test. After testing each leg once, the patient was given a score on the most restricted performance. The test was performed for both sides. Scores are awarded in ordinal values from 0 to 3. Score of 0: patient could grab toes with fingertips and performed the action with ease. Score of 1: patient could grab toes with fingertips, but performed the action with effort. Score of 2: patient can reach beyond the malleoli, but cannot reach toes. Score of 3: patient could hardly, if at all, reach as far as the malleoli. The reliability of the sock-test has been shown to be acceptable (Strand and Wie 1999).

Stair Ascending and Descending Test

The subjects were asked to walk up and down twelve stairs as quickly as possible (Rejeski et al. 1995, Arokoski et al. 2004). The time needed to complete the task (separately ascending and descending stairs) was measured (rounded to the nearest tenth of a second) using a hand-held stopwatch. The task was performed three times and the mean velocity (m/s) of three trials was regarded as the result of the test. The stair climbing task has excellent test-retest reliability (Rejeski et al. 1995, Arokoski et al. 2004).

Straight Line Walking

The subject was asked to walk for 10 meters as straight as possible following a straight line on the floor (Cho and Kamen 1998). The time required to complete the 10 meter task was recorded and the mean of three trials was calculated. The time needed to complete the task was recorded (rounded to the nearest tenth of a second) using a hand-held stopwatch. The reliability of straight line walking has not been reported.

Timed up & go Test

Using a standard-high chair with arm rests, participants were asked to stand up from the chair, walk 3 m, turn, walk back and sit down quickly and safely (Podsiadlo and Richardson 1991, Freter and Fruchter 2000, Shumway-Cook et al. 2000). They were asked not to slow down before sitting back down in the chair. The time needed to complete the task was recorded to the nearest tenth of a second using a hand-held stopwatch. The

mean time of three performances was calculated in seconds. The timed up & go test (TUG) is clinically well established as a measurement of function for knee OA (Podsiadlo and Richardson 1991). The reliability of the test has been reported to be high (Morris et al. 2001).

20-m Speed Walk Test

The subjects were asked to walk 20 m as quickly as possible (Harding et al. 1994). The time needed to complete the task was recorded to the nearest tenth of a second using a hand-held stopwatch. The mean speed (m/s) from three trials was registered. The task was performed for three times and the mean speed (m/s) was regarded as the result of the test. The speed walk test has been successfully used to assess the walking ability of disabled and elderly patients (Grace et al. 1988, Reuben and Siu 1990). Harding et al. (1994) have reported excellent test-retest reliability (correlation coefficients of 0.987) for 20-m speed walk tests in patients suffering from chronic pain.

5-min Walk Test

Subjects walked a 20-m distance back and forth for 5 minutes (Harding et al. 1994, Simmonds et al. 1998). The participants were informed to "walk as quickly and safely as you can for 5 minutes". The 5-min walk test was chosen because it is considered as a useful measure of walking distance whereas the 20 m speed walk test assesses mainly gait speed. We also wanted to analyze which of these two tests would describe better the functional impairment or loss of functional activity in the knee OA. The score recorded was the total distance traveled (meters) during 5 minutes. Harding et al. (1994) and Simmonds et al. (1998) have reported good test-retest reliability for the 5-min walk test.

Muscle Strength Measurements

The maximal isometric voluntary knee extension and flexion torques (MIVC) were determined using a David 200 dynamometer (David Finland Oy, Outokumpu, Finland) in Experiment 1 and with a Lido dynamometer (Lido Active Isokinetic Rehabilitation System, Loredan Biomedical, West Sacramento, CA, USA) in Experiment 3. The measurements were made in the following order: left and right knee extension, right and left knee flexion (Paper I). The trial order was randomised in Experiment 3. The strength measurements were performed in the sitting position. The thigh was fixed on the seat by attaching the distal part of the femur. The ankle was attached to the moment arm just above the malleolus. The knee and hip angles were fixed at 70°. The arms were not allowed to take support during the tests to ensure that only the muscles of the limb being evaluated performed the action. The subjects exerted maximal unilateral force as rapidly as possible and maintained that force level for 3-4 s. The subjects performed as many maximal actions until the peak value no longer increased and the best result (Nm) was registered. Then, the results were expressed in proportion to subject's BW (Nm/kg). The isometric muscle force measurement has been established as a safe and useful way to examine knee OA patients (Nordesjö et al. 1983, Fransen et al. 2003). After checking the

force level with an oscilloscope, the force data was sampled and stored at 1 kHz with Motus -software (Peak Performance Technologies, Englewood, CA, USA) (Paper I).

Knee Joint Range of Movement

The ROM of the knee joint was measured with a standard goniometer method (American Academy of Orthopaedic Surgeons 1966). Briefly, in the knee flexion measurement, the axis of the goniometer was aligned with the center of the lateral epicondyle of the femur. The distal arm of the goniometer was aligned with the lateral malleolus, and the proximal arm was aligned with the greater trochanter of the femur. While the patient was lying supine, the knee flexion ROM was the value of active bending of the knee. Knee extension ROM was the angle of passive straightening of the knee while the patient was lying supine. The intraobserver reliability and criterion validity of the goniometers or active knee flexion and passive knee extension are good (Watkins et al. 1991, Brosseau et al. 1997).

4.3.9 Statistical Analysis

Mean values and standard deviations (SD) were calculated for the measured parameters, and the Kolmogorov-Smirnov and Levene tests were used to assess the normality of distribution and the equality of variances, respectively. The significance level was set at 0.05 (Papers I-IV). Pearson's and Spearman correlation coefficient was used to quantify the correlation between the normally distributed continuous (Papers I-IV) and the non-continuous variables (Papers IV), respectively. Two-tailed paired (Papers I-III) and unpaired (Papers I, III-IV) Student's *t*-tests were used to compare the two dependent and independent samples, respectively. An analysis of variance (one-way ANOVA) with Bonferroni adjustment for multiple comparisons was used to test for the statistical differences in the continuous parameters between the OA subgroups (K-L 1-4). The corresponding non-parametric tests (Kruskal-Wallis, Mann-Whitney and Wilcoxon) were used for ordinal scale parameters and for variables which were not normally distributed. For each patient, the knee with the highest radiographic OA score or clinical symptoms, provided that the scores were equal, was used for the analysis. The values were compared with those on the same side of an age-matched control subject (Papers III-IV).

The coefficient of variation (CV) was calculated with Equation 8 in order to measure inter-day variability for N = 10 subjects in Experiment 2. The intra-day variability (CV) was measured between the single trials performed during the first day. The repeatability was considered to be good if CV <15% (Moe-Nilssen 1998). All statistical analyses (I-IV) were performed with SPSS for Windows (SPSS Inc., IL, USA).

Equation 8.

$$CV = \frac{\sigma_{d_1 d_2}}{\frac{1}{2N}\sum_{i=1}^{N}\left(\bar{x}_{d_1}^{(i)} + \bar{x}_{d_2}^{(i)}\right)} 100\%,$$

where N = number of subjects and the standard deviation $\sigma_{d_1 d_2}$ between days 1 and 2 is

$$\sigma_{d_1 d_2} = \frac{1}{2N}\sqrt{\sum_{i=1}^{N}\left(\bar{x}_{d_1}^{(i)} - \bar{x}_{d_2}^{(i)}\right)^2},$$

where $\bar{x}_{d_k}^{(i)}$ is the mean of parameter x from all trials of i'th subject on day d_k.

5 Results

5.1 CHARACTERISTICS OF SUBJECTS

Over 80% of 27 subjects had no more than minor joint space narrowing (Paper I). All patients showed at least grade 1 knee OA in some joint compartment bilaterally. Joint space narrowing and osteophytes were more evident in the medial compartment of the tibiofemoral joint. Only one subject had severe radiographic OA in the right knee.

The patients with knee OA in Experiment 3 had 9.6% (P =0.001) higher BMI than the controls (Table 5). OA subjects demonstrated significantly poorer health-related quality of life in seven out of the eight separate scales as measured by the RAND-36 (Paper IV). There were no significant differences between the groups in terms of leisure-time physical activity (OA subjects 429±319 sessions/year vs. control subjects 350±208 sessions/year). The subjects with knee OA had been working in heavier occupations (P <.01) compared to the controls (occupational load rating 3.8±1.7 vs. 2.7±1.7, respectively). The OA patients were not suffering from more chronic diseases than the controls (Table 6).

Table 5. Physical Characteristics of the Subjects (mean ± SD)

Experiment No	Age (years)	Height (m)	Weight (kg)	BMI (kg/m^2)	Original Paper
1 (n=27)	66.2±7.6	1.63±0.09	66.9±11.9	26.4±3.9	I
2 (n=10)	29.0±4.7	1.77±0.06	79.2±8.4	25.2±2.1	II
3 (n=107)					III, IV
Knee OA (n=54)	59.0±5.3	1.76±0.06	91.9±15.6	29.7±4.7	
K-L 1 (n=12)	57.7±5.8	1.77±0.06	92.5±20.5	29.5±6.1	
K-L 2 (n=15)	58.7±5.8	1.77±0.06	91.6±18.0	29.3±5.1	
K-L 3 (n=19)	59.1±5.1	1.75±0.05	90.7±11.2	29.6±3.7	
K-L 4 (n=8)	61.2±4.1	1.74±0.07	94.5±13.9	31.2±4.3	
Controls (n=53)	59.2±4.7	1.74±0.06	81.7±10.6	27.1±3.1	
P-value*	P =0.87	P =0.04	P <0.001	P =0.001	

**Comparison between knee OA and controls in Experiment 3; student t test for two independent samples. K-L = Kellgren-Lawrence knee OA grading, in which 0 refers to no OA and 4 indicates severe OA; BMI = body mass index.*

Table 6. Clinical Features of Knee OA Patients, Control Subjects and Knee OA Subgroups (Mean ± SD)

Variable	Controls	Knee OA	*P-value*[†]	Knee OA Subgroup				*P-value*[‡]
				K-L 1	K-L 2	K-L 3	K-L 4	
Knee pain VAS (mm)*	NA	6.6±10.3	*NA*	6.2±11.0	9.9±13.0	4.5±8.0	5.6±8.2	*ns*
Knee alignment (deg)	2.8±1.7	5.5±3.2	*<0.001*	4.3±2.1	4.6±2.4	5.1±2.8	10.1±3.5	*<0.01*
Knee flexion (deg)	145±6	131±13	*<0.001*	137±12	131±5	132±11	120±19	*<0.05*
Knee extension (deg)	-1.0±1.0	-4.0±4.0	*<0.001*	-3.0±4.0	-3.0±2.0	-4.0±4.0	-7.0±4.0	*<0.05*
Leisure-time physical activity (sessions/year)	350±208	429±319	*ns*	324±106	438±241	489±425	420±370	*ns*
Pain medication (yes/no), % of patients	NA	NA	*NA*	41.7	66.6	63.2	50.0	*ns*
Comorbidities (n)	0.5±0,7	0.6±0.7	*ns*	0.8±1.0	0.7±0.7	0.6±0.6	0.4±0.5	*ns*
Occupational loading history (0-6)	2.7±1.7	3.8±1.7	*<0.01*	3.2±1.8	3.9±1.8	3.9±1.4	4.1±2.0	*ns*
Knee trauma (yes/no), % of the patients	NA	NA	*NA*	16.7	40.0	57.9	62.5	*ns*

** Knee pain was separately inquired during functional tests. Student t-test for two independent samples, Mann-Whitney non-parametric test, one-way analysis of variance, Kruskal-Wallis test, and Chi-Square. †Comparison between groups Knee OA and Controls. ‡Comparison between Knee OA subgroups.*

There were no significant differences among the knee OA subgroups in terms of age, weight, height, or BMI (Table 5). The health-related quality of life assessed with RAND-36 did not differ between the knee OA subgroups (Paper IV). The absolute value of varus or valgus alignment in the knee was 42.6% lower (P <0.01) in the group with the lowest OA grade (K-L 1), as compared to the knees with the highest OA grade (K-L 4). In OA patients, the knee flexion and extension ROM values were 12.4% and 42.9% lower (P <0.05) in the knee with the highest OA grade (K-L 4) than in the knee with the lowest OA grade (K-L 1), respectively. There were no significant differences among the four subgroups in terms of BMI, VAS, leisure-time physical activity, the use of pain medication, the number of comorbities, or the occupational physical loading history.

5.2 WESTERN ONTARIO AND MCMASTER UNIVERSITIES OSTEOARTHRITIS INDEX

The WOMAC (Paper IV) detected the differences in subjectively assessed knee OA symptoms between the subgroups (Figure 10). The stiffness, function and composite scores, but not the pain score were associated with the severity of knee OA (P <0.05). The post-hoc analysis with Mann-Whitney test revealed that only the subgroup with the most severe knee OA (K-L 4) was different from the other subgroups in the WOMAC.

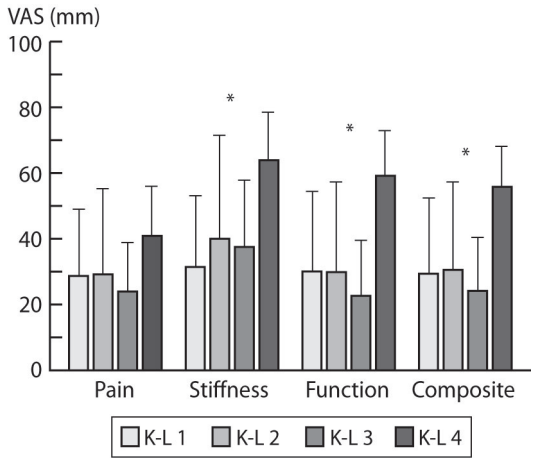

*Figure 10. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores (mean ± SD) in groups with different grades of knee osteoarthritis. The radiographic grading was made according to Kellgren-Lawrence (K-L) scale (Kellgren et al. 1963). *P <0.05 (Kruskal-Wallis test). VAS = visual analogue scale.*

The WOMAC scores correlated significantly with the results of physical function tests (see Table 11 in 5.5.1 Physical Function Tests). The highest associations with WOMAC were found in 20-m speed walk (r range = -0.51 to -0.61), 5-min walk (r range = -0.49 to -0.58), and repeated sit-to-stand tests (r range = 0.49 to 0.53). The knee extension and

flexion torques correlated inversely with all WOMAC scores. The passive knee joint extension exhibited a moderate association with stiffness, otherwise there was only a weak or no correlation between WOMAC and knee joint range of motion or knee alignment. BMI showed also a linear correlation with the results of physical function tests (P <0.05-.001), with the exception of the lift test (P =0.11) (Paper IV, data not shown).

5.3 REPRODUCIBILITY OF MEASUREMENTS WITH SKIN MOUNTED ACCELEROMETERS

5.3.1 Repeatability of Acceleration Measurements

IPA and PP parameters in a_z and a_r as well as a_{rxy} (a_{rxy} data not shown) exhibited good (CV <15%) inter-day repeatability. The ranges of CV of ATR_{max} below and above the knee in the direction of the lower limb were 13.9-16.0% and 13.9-19.8%, respectively, depending on the walking circumstance. The repeatability of ATR_{ave} in the a_z direction and ATR_{a1r} parameters showed generally poorer repeatability (Table 7).

The gait speed has only a minor effect on CV values, and repeatability was generally rather similar in the natural (corridor) and constructed environment (laboratory). ATR_{ave} in the a_z direction as well as ATR parameters in the resultant direction showed better inter-day repeatability in the corridor than in the laboratory with both gait speeds. However, the CV values of axial ATR_{ave} and ATR in the resultant direction were over 15% except for the resultant ATR_{max} in the corridor. The CV values seemed to be inferior in the corridor at constant speed (Paper II, data not shown).

Table 7. Range for Coefficients of Variation (CV%) within a Day (Intra-day) and between Days (Inter-day) of Selected Vertical Ground Reaction Force and Acceleration Parameters at Constant and Normal Walking Speeds in the Laboratory and Corridor.

Parameter	Range of CV (%)	
	Intra-day	**Inter-day**
Contact time from acceleration (CT_{acc})	2.2-2.7	0.9-2.9
Stride frequency	1.4-2.3	1.4-1.8
Stride length	1.2-2.3	1.0-2.2
First vertical peak force ($F_{z1\ max}$)	8.0-9.8	7.9-8.2
Second vertical peak force ($F_{z2\ max}$)	3.3-3.5	2.7-3.0
Local minimum after $F_{z2\ max}$ ($F_{z2\ min}$)	2.4-2.5	1.8-2.5
Third vertical peak force ($F_{z3\ max}$)	1.8-2.0	2.3-2.5
Maximum loading rate (LR_{max})	16.9-19.4	13.1-14.0
Average loading rate (LR_{ave})	11.2-11.7	7.1-8.4
Axial initial peak acceleration, measured below knee (IPA_{a1z})	8.4-10.8	8.6-14.0
Axial initial peak acceleration, measured above knee (IPA_{a2z})	13.8-19.3	6.9-10.8
Axial peak-to-peak acceleration, measured below knee (PP_{a1z})	9.2-11.3	8.6-11.2
Axial peak-to-peak acceleration, measured above knee (PP_{a2z})	12.7-17.8	8.0-13.9
Axial maximum acceleration transient rate, measured below knee ($ATR_{max\ a1z}$)	11.8-15.5	13.9-16.0
Axial maximum acceleration transient rate, measured above knee ($ATR_{max\ a2z}$)	17.0-19.2	13.9-19.8
Axial average acceleration transient rate, measured below knee ($ATR_{ave\ a1z}$)	15.4-19.7	21.0-29.2
Axial average acceleration transient rate, measured above knee ($ATR_{ave\ a2z}$)	21.3-24.6	16.7-22.8
Resultant initial peak acceleration, measured below knee (IPA_{a1r})	9.0-13.3	9.0-10.1
Resultant initial peak acceleration, measured above knee (IPA_{a2z})	14.2-17.0	6.3-13.3
Resultant peak-to-peak acceleration, measured below knee (PP_{a1r})	9.9-13.7	7.6-12.2
Resultant peak-to-peak acceleration, measured above knee (PP_{a2r})	13.8-17.2	8.7-12.4
Resultant maximum acceleration transient rate, measured below knee ($ATR_{max\ a1r}$)	17.2-22.5	12.3-27.9
Resultant maximum acceleration transient rate, measured above knee ($ATR_{max\ a2r}$)	17.0-20.0	9.5-16.5
Resultant average acceleration transient rate, measured below knee ($ATR_{ave\ a1r}$)	22.3-36.3	29.9-45.5
Resultant average acceleration transient rate, measured above knee ($ATR_{ave\ a2r}$)	27.9-34.0	12.6-18.7

5.3.2 Reliability of Acceleration Measurements

The linear correlation coefficients at normal speed between LR_{max} and axial ATR_{max} were 0.92 (P <0.01) and 0.66 (P <0.05), as measured with the SMAs installed below and above the knee, respectively. The corresponding values in the a_r direction were 0.88 (P <0.01) and 0.71 (P <0.05). At a constant walking speed, LR_{max} also exhibited a significant linear correlation with the axial and resultant ATR_{max} (r range = 0.80-0.92; P <0.01). LR_{ave} correlated neither with ATR_{ave} nor with LR_{max} under any circumstance, but LR_{max} was significantly related to ATR_{ave} (P <0.05-0.01), except for LR_{max} vs. $ATR_{ave\ a2r}$ at normal walking speed (r =0.594, P =0.07). $F_{z1\ max}$ showed a linear correlation with the axial and resultant IPA measured with the SMA below and above the knee (P <0.01) at both speeds. The highest linear correlation coefficients between F_{z1} and IPA were found with SMA below the knee in the a_r direction (r =0.909 and r =0.942 at constant and normal speeds, respectively). The LR_{max} vs. IPA in the resultant (a_r) direction, as measured in the setup with the transducer below the knee, demonstrated the highest correlation. The IPA_{1r} accounted for 89.9% (R^2) and 91.8% of the variation in LR_{max} at constant and normal speeds, respectively (both P <0.01). Table 8 shows selected examples which indicate that specific acceleration parameters (IPA, ATR) strongly explain the variation in GRF loading parameters except of LR_{ave}

Table 8. The Coefficients of Determination (R^2) between Selected Loading Parameters of Vertical Ground Reaction Force and Axial and Resultant Accelerations during Walking with Normal Speed. Accelerations Were Measured with the Skin Mounted Accelerometers Attached below the Knee. Values Are Percents (%).

	IPA_{a1z}	$ATR_{ave\ a1z}$	$ATR_{max\ a1z}$	IPA_{a1r}	$ATR_{ave\ a1r}$	$ATR_{max\ a1r}$
$F_{z1\ max}$	76.9†	43.2*	79.0†	88.7†	53.7*	80.3†
LR_{ave}	8.6	2.5	6.5	11.0	9.5	13.4
LR_{max}	82.8†	50.4*	84.4†	92.4†	57.3*	77.8†

* = P <0.05, and † = P <0.01. $F_{z1\ max}$ = first vertical peak force; LR_{max} = maximum loading rate; LR_{ave} = average loading rate; ATR_{max} = maximum acceleration transient rate; ATR_{ave} = average acceleration transient rate; a_{1z} = acceleration in the direction of the lower limb below the knee; a_{1r} = acceleration in resultant direction below the knee. Squared Pearson correlation coefficient.

5.4 GAIT ANALYSIS

5.4.1 Gait Characteristics

The gait velocity decreased significantly with age (P <0.01) (Paper I). Age accounted for 25.5% and 40.6% (R^2) of the variation of walking speed at normal and maximal velocities, respectively. The step length divided by subject height was the best single predictor of walking speed (R^2 =0.733 in self-selected and R^2 =0.755 at maximal speed). The SL/HT decreased with age (normal: r = -0.532; maximal: r = -0.655, P <0.01) but not the step

frequency (r = -0.087 and r = -0.010, P >0.05, at normal and maximal speed walking, respectively) (Paper I).

Table 9. Descriptive Gait Variables of Knee OA Patients and Controls with Different Walking Speeds at a Level Ground and Stairs (mean ± SD)

Experiment No 3	Subject Group	Contact Time, (ms)	Stride Frequency (Hz)	Stride Length (m)
Corridor, 1.2 m/s	Knee OA	726±44	0.91±0.05	1.34±0.07
	Control	736±56	0.91±0.05	1.32±0.07
Corridor, 1.5 m/s	Knee OA	659±50	1.00±0.05	1.50±0.08
	Control	673±58	1.01±0.05	1.50±0.07
Corridor, 1.7 m/s	Knee OA	632±57	1.06±0.06	1.60±0.10
	Control	641±56	1.07±0.53	1.59±0.08
Stairs up, 0.5 m/s	Knee OA	761±69	0.84±0.08	0.61±0.04
	Control	767±30	0.82±0.25	0.62±0.01
Stairs up, 0.8 m/s	Knee OA	478±35	1.29±0.06	0.62±0.03
	Control	477±33	1.31±0.06	0.61±0.02
Stairs down, 0.5 m/s	Knee OA	762±29	0.83±0.02	0.61±0.01
	Control	766±31	0.83±0.02	0.62±0.01
Stairs down, 0.8 m/s	Knee OA	505±31	1.31±0.06	0.62±0.02
	Control	510±28	1.30±0.05	0.62±0.01

The spatio-temporal gait parameters showed excellent intra- and inter-day repeatability in Experiment 2 (Table 7). The stride length and frequency, but not the contact time, were significantly different at the constant speed in the laboratory compared to the respective values in the corridor (Paper II). Stride frequency was lower in the laboratory during normal speed walking (P <0.05) (Paper II). The descriptive gait parameters of Experiment 3 are presented in Table 9. Walking speed had a significant effect on the spatio-temporal gait variables both in the level and stair walking.

5.4.2 Ground Reaction Forces

In the Experiment 1, the greatest vertical maximal force (F_{z2}) in the braking phase was seen during stair descent (1.52±0.21 BW). This value was 32.5% (P <0.001); 9.1% (P <0.05) and 48.2% (P <0.001) larger than those at the preferred speed of walking, maximal speed walking and stair ascent, respectively. The corresponding largest force in the A-P direction (F_{x1}) was detected during the level walking trials. However, the F_{x1}-force values even with the maximal speed were only 0.27±0.5 BW.

The largest LR was seen during maximal speed walking (14.27±4.63 BW/s), which was 68.4% (P <0.001); 31.3% (P <0.01) and 335% (P <0.001) larger than that found during normal speed walking, stair descent and stair ascent, respectively. The LR of stair descent (10.87±2.96 BW/s) was significantly (P <0.01) higher than that encountered during level walking at the self-selected speed (8.55±1.93 BW/s). The lowest LR occurred during the stair ascent (3.28±0.75 BW/s). Three subjects (11%) had a heel strike transient at normal walking speeds, whereas there were five (18.5%) heel-strikers when the maximal speed was required (Paper I).

LR_{ave} was 8.08±1.10 BW/s and 8.69±1.75 BW/s at constant and normal speeds, respectively (Paper II). The LR_{max} showed almost ten times higher values (77.5±33.0 BW/s and 85.1±37.2 BW/s with constant and normal speeds, respectively). The inter-day repeatability (Paper II) of the local maximum and minimum vertical GRF parameters was high (CV 1.8-8.2%). The CV of vertical LR_{max} and LR_{ave} were ≤14.0% and ≤8.4%, respectively indicating good inter-day repeatability. Intra-day repeatability between the single trials seemed to be in the same range as the inter-day repeatability between the averaged trials (Table 7).

Fifteen percents (n=8) of control subjects and 11% (n=6) of knee OA patients exhibited a distinct heel strike transient at the pre-determinend gait speed (1.2m/s±5%) in the laboratory. LR_{max} was 18.4% higher in the healthy control subjects than in the knee OA patients (61.5±22.7 BW/s vs. 51.9±18.6 BW/s, P <0.05) (Paper III). The same finding was even more evident in the contralateral side, i.e. in the less affected limb (26.1%, P <0.01). There were no statistical differences in any other vertical or A-P GRF parameters. The knee OA patients demonstrated bilaterally (more affected 17.5%; less affected 19.3%, P <0.05-0.01, respectively) greater first peak M-L GRF ($F_{y1\ min}$) than the healthy subjects. The last peak GRF in the push-off phase ($F_{y3\ max}$) in the more affected side was more forceful in the healthy controls (0.07±0.02 BW vs. 0.06±0.02 BW, P <0.05) than in the knee OA patients. The first vertical peak GRF ($F_{z1\ max}$) was significantly higher on both sides in patients with more severe knee OA (P <0.01). LR_{max} tended to decrease as a function of disease severity in the less affected side (P =0.08).

5.4.3 Acceleration

In Experiment 2, the measured acceleration variables in the a_z direction were significantly lower in the laboratory than in the corridor, even at constant gait speed. The same finding was evident also in the a_r direction (data not shown). IPA in the a_z direction were highest during normal speed walking along the corridor (1.83±0.59 g and 2.59±0.88 g above and below knee, respectively). These values were 25.1% and 21.1% higher than the corresponding values in the laboratory at normal speed.

The knee OA did not affect the IPA, PP acceleration measured with SMA below knee, or the acceleration attenuation (i.e. ratio of acceleration transmission = RAT) in level

walking (Paper III). The IPA and PP values increased as a function of gait speed in both groups up to 3.8g and 5.4g at 1.7 m/s, respectively. The a_z was accompanied by the resultant horizontal initial peak acceleration (IPA_{rxy}) of the same magnitude in both level- and stair walking (Table 10). The severity of knee OA had no effect on the acceleration parameters during level walking (data not shown).

During stair walking (Paper III), the patients with knee OA generally demonstrated significantly higher peak resultant horizontal acceleration measured below the knee (IPA_{1rxy}), as compared to the control subjects (P <0.05-0.01; stair ascending at 0.5 m/s, P =0.10). Patients exhibited also 14.4% decreased attenuation (RAT) across the knee joint in stair descent at 0.8 m/s (knee OA 1.43±0.61; controls 1.67±0.33, P <0.05). The IPA in resultant and the direction of lower limb were more pronounced (31.9% and 17.3%, respectively; P <0.05) in patients with knee OA in stair descent at higher speeds (Table 10). The resultant horizontal peak acceleration (IPA_{1rxy}) declined as a function of disease severity (P <0.05) in stair ascent at 0.8 m/s (data not shown).

Table 10. Acceleration Parameters (mean ± SD) from Level- and Stair Walking Trials in the Patients with Knee OA and the Healthy Controls

Experiment No 3	Subject Group	IPA_{1z} (g)	IPA_{1rxy} (g)	RAT (IPA_{1z}/IPA_{2z})	PP_{1z} (g)
Laboratory,	OA	1.96±0.86	2.05±0.59	1.40±0.40	2.65±1.14
1.2 m/s	Control	1.91±0.52	2.02±0.43	1.39±0.35	2.66±0.63
Corridor,	OA	2.17±0.89	2.25±0.64	1.39±0.39	2.87±1.19
1.2 m/s	Control	2.14±0.56	2.19±0.54	1.46±0.37	2.88±0.70
Corridor,	OA	3.08±1.23	3.09±0.79	1.39±0.43	4.17±1.60
1.5 m/s	Control	3.04±0.80	2.94±0.60	1.46±0.35	4.20±0.94
Corridor,	OA	3.83±1.45	3.62±0.97	1.43±0.50	5.18±1.89
1.7 m/s	Control	3.83±0.96	3.55±0.71	1.46±0.40	5.35±1.11
Stairs up,	OA	2.06±1.40	1.88±0.50	1.91±1.06	2.95±1.71
0.5 m/s	Control	2.02±1.04	1.76±0.62	2.12±0.92	3.05±1.33
Stairs up,	OA	4.23±2.09	3.22±0.92*	1.57±0.88	5.50±2.69
0.8 m/s	Control	4.42±2.26	3.00±1.34	1.84±0.68	5.82±2.78
Stairs down,	OA	0.71±0.20	1.70±0.84†	1.28±0.29	2.53±1.71
0.5 m/s	Control	0.69±0.26	1.40±0.56	1.30±0.20	2.56±1.10
Stairs down,	OA	1.29±0.35†	2.71±1.08*	1.43±0.61*	4.56±2.01
0.8 m/s	Control	1.10±0.32	2.38±1.24	1.67±0.33	4.91±2.11

*IPA_{1z} = initial peak acceleration in the direction of the lower limb below knee; IPA_{1rxy} = resultant horizontal direction acceleration below knee; RAT = ratio of acceleration transmission (IPA_{1z}/IPA_{2z}), in which IPA_{2z} = initial peak acceleration in the direction of the lower limb above knee; PP_{1z} = peak-to-peak acceleration in the direction of the lower limb below knee; g = gravitational acceleration. *P <0.05, †P <0.01. Student t-test for two independent samples and Mann-Whitney non-parametric test.*

5.4.4 Muscle Activation

The heel-strikers (n=5, 18.5%) exhibited 43.5% lower (P <0.05) pre-activity of VM muscle during maximal speed walking, but this was not present at their own preferred speed (Figure 11). Although there were some trends, no statistical differences in pre-activity of VL muscle were observed between the heel-strikers and the non-heel strikers (Paper I, data not shown). Examples of heel strike transients are presented in Figure 11, showing data from two subjects, one heel-striker and one non-heel-striker. The latter had a typical m-shaped vertical GRF. However, the heel-striker exhibited a distinct peak force at the very beginning of the contact phase, accompanied by little pre-activation of the VM.

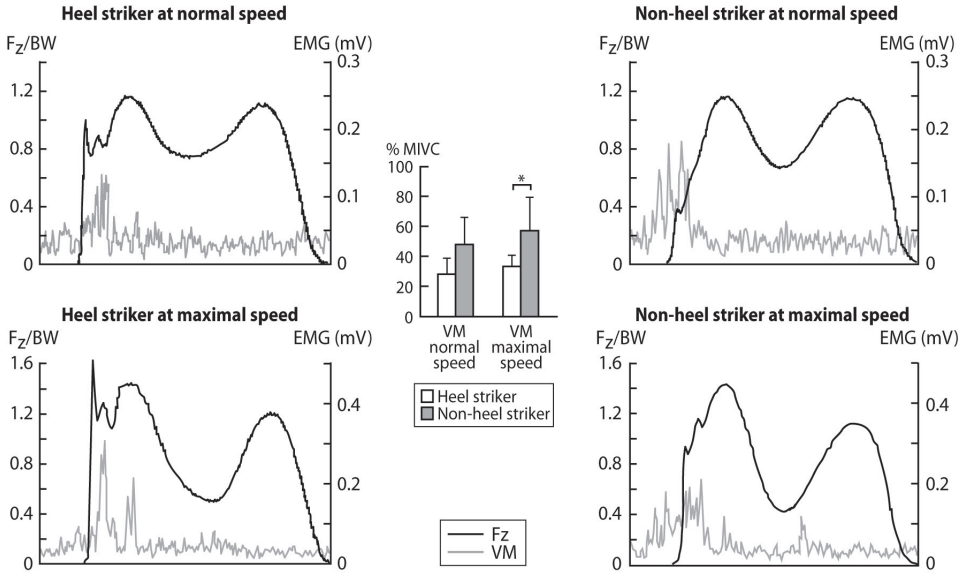

Figure 11. ***Bars:*** *The pre-activity (mean ± SD) of vastus medialis muscle (VM) at normal and maximal speeds in heel strikers and non-heel strikers. Electromyographic (EMG) activities have been normalised to averaged EMG values during maximal isometric voluntary contraction (MIVC).* ***Curves:*** *Typical examples [vertical ground reaction force (F_z) and full wave rectified EMG of VM] of level walking at normal and maximal speeds from two subjects one of whom was a heel striker. Both signals have been averaged and time-normalised from all contacts in each trial. *P <0.05 (Student t-test for two independent samples).*

Unfortunately, the activation of GaM was not measured during the MIVC condition (Paper I). Consequently, its EMG activity could not be used in comparison between the subjects. However, its pre-activation was most evident during the stair descent (all P <0.001). This value was 155% higher than that found during the level walking at the maximal speed. The pre-activity of the QFm, i.e. VM and VL muscles, was highest at maximal walking speeds. In VM muscle, its value was 24.1%, 37.1% and 22.9% greater than that found at the normal speed walking, stair ascent and descent, respectively. The corresponding percentages were 33.5%, 56.2% and 33.2% in VL muscle. The BF muscle

was strongly activated prior to floor contact during walking on the level, especially at maximal speed.

In Experiment 3, the activation of BF in the initial contact phase was significantly higher in the patients with knee OA (P <0.05-0.01) except at the fastest gait speed of 1.7 m/s (Figure 12, right upper figures). The VM activity in the late stance and early swing phases were significantly lower (P <0.05-0.01) in the healthy controls at all gait speeds (Figure 12, left upper figures). There were no differences in co-activation between the groups (data not shown). The pre-activity (i.e. activity in later swing) of VM and BF were not in assosiation with LR_{max} or F_{z1} during level walking in either controls or knee OA patients.

The controls showed significantly higher BF activity (P <0.05-0.01) prior to contact with the ground (late swing) during stair ascent at both speeds and lower activation of VM (P <0.05) at higher speed during stair descents (Figure 12). The BF activity during the late stance was 44.9% more forceful in controls during stair ascent at higher speeds. The controls exhibited 17.7% lower activation of VM during the foot contact phase in stair ascent at 0.8 m/s, as compared to OA patients. The same finding (P <0.05) was evident in BF at the lower speed of stair ascents and descents. The controls demonstrated lower activity of VM muscle in the early swing during the stair descent (P <0.05). The BF activity was higher at the lower speed in the healthy controls (P <0.05). The BF activity was lower (P <0.05) when the stairs were climbed at 0.8 m/s in the early swing in comparison with the controls.

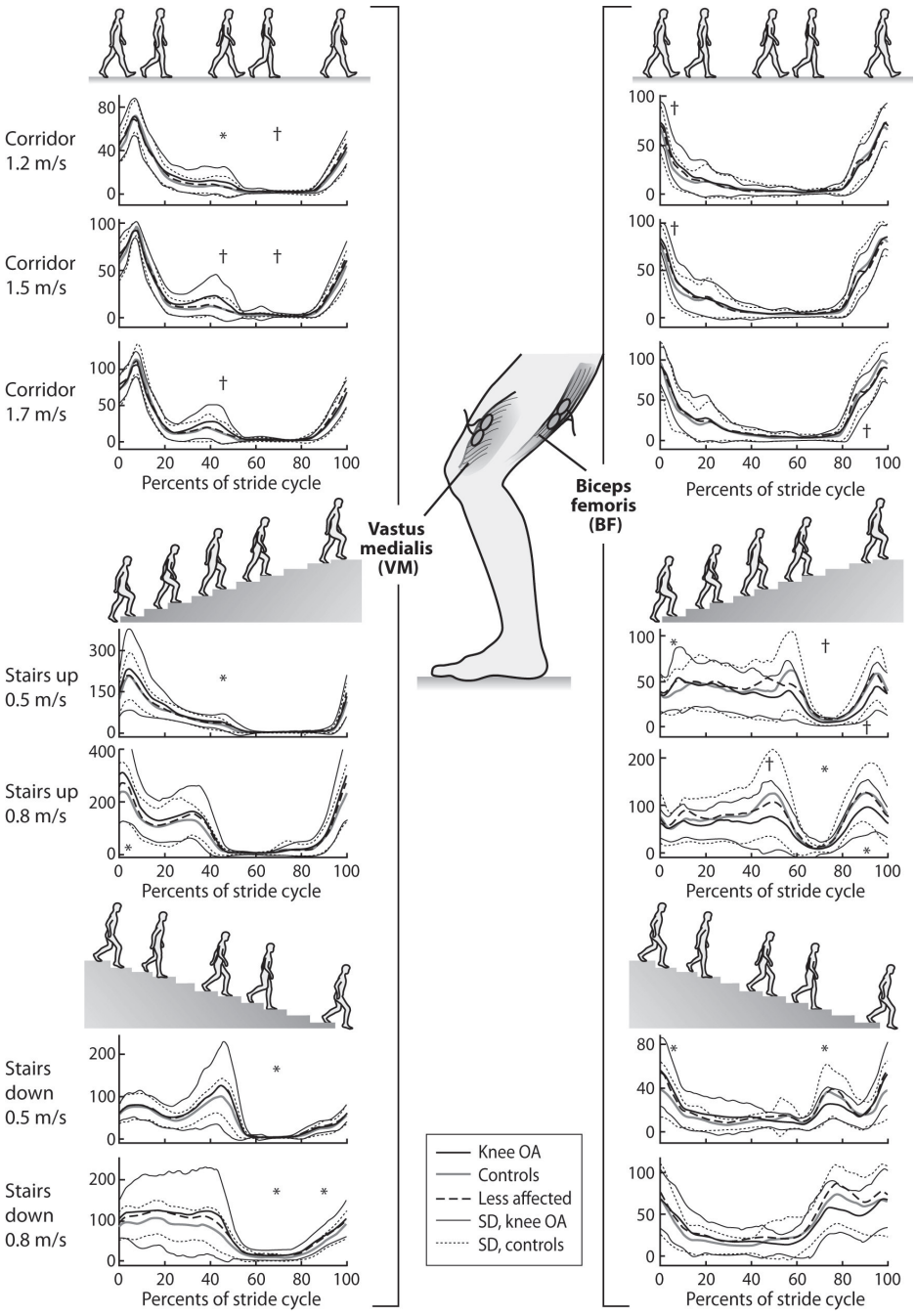

*Figure 12. Mean vastus medialis (VM) and biceps femofis (BF) muscle activation during level and stair walking with different gait speeds during the whole gait cycle in patients with knee OA and healthy controls. EMG is normalised to dynamic maximum measured at 1.5 m/s. *P <0.05; †P <0.01. (Student t-test for two independent samples and Mann-Whitney non-parametric test). Note: The statistical differences between more and less affected limbs are not shown.*

The VM activity of the more affected limb was stronger (P <0.05-0.01) than that of the less affected side at every gait speed during late stance (Figure 12). There were significant differences in the BF activity (P <0.01-0.001) in the swing phase, and VM activity in the stance (the first 10%, P =0.05) and late swing phases (P <0.01) in stair ascent with 0.5 m/s in the side-to-side comparison. The BF activation was significantly lower in the more affected limb during the whole stride while climbing stairs at higher speeds. The VM activation was higher in the more affected side (P <0.01) during the early contact (phases I and II) when the stairs were climbed at 0.8 m/s. There were also significant differences in the side-to-side comparison on stair descent with lower (BF phases III-V and VM II, V) and higher speeds (BF III, IV). The mean muscle co-activity was higher in stair ascent in the more affected side, though the difference was not significant at higher speeds (P =0.05). There were no correlations between the VM or BF muscle pre-activity and $F_{z1\ max}$ or LR_{max}.

5.4.5 Plantar Pressures

Peak plantar pressures beneath the heel (sensors 1-4) were largest (P <0.01-0.001) at the maximal walking speeds (Paper I). At that time, the peak pressures of sensors one and two, measuring heel strike, were 42.0% and 46.3% larger than the respective values at the preferred walking speeds, (sensor 1: 335±60 kPa vs. 236±39 kPa and sensor 2: 380±55 kPa vs. 260±32 kPa, respectively). These pressures were significantly lower (P <0.001) in stair walking. In the time normalised scale, the peak pressures beneath the heel occurred earlier at the maximal speed than at the normal speed walking (sensor 1: P <0.001 and sensor 2: P <0.01) in proportion to the duration of contact (sensor 1: 6.1±3.2% vs. 8.8±4.0% and sensor 2: 6.5±3.4% vs. 11.2±6.0%). The maximum pressures occurred significantly later (P <0.001) during stair walking (sensor 1: 32.2% and 23.3% in stair ascent and descent, respectively).

5.4.6 Gait Symmetry

Although there were some statistically significant differences in the kinetic parameters there was no asymmetry (ASI <10%) between the left and right limbs in spatio-temporal or kinetic parameters during level walking (Paper I). The ASI-values were higher in stair walking, but again no difference was observed between the stair ascent and descent. The asymmetry was most evident (14-45%) in the peak plantar pressures (sensors 1-24) but on the other hand, the strongest symmetry (1.7-7.2%) was found in the spatio-temporal parameters during level walking. The asymmetry did not associate with the radiological OA findings (Paper I).

In general, the vertical GRF parameters (contact time, $F_{z2\ max}$, $F_{z2\ min}$ and $F_{z3\ max}$) showed high symmetry (ASI <10%) at both gait velocities (ASI 0.2%-4.8%), but the ASI of the vertical loading parameters i.e. $F_{z1\ max}$, LR_{max} and LR_{ave} were 15.1%, 26.5% and 14.0% at constant speed walking, respectively (Paper II). The corresponding values during the normal speed were 15.1%, 27.8% and 12.7%, indicating poorer symmetry. The ASI values

were low in the AP-direction (0.7%-8.4%), except for the $F_{x1\ max}$ parameter at normal speed walking (10.8%). The asymmetry increased in the M-L direction. The ASI of $F_{y2\ max}$ and its timing were 14.3% and 15.6% at the constant walking speed, respectively. The corresponding values were 16.9% and 16.2% in the normal speed. The $F_{y1\ min}$ and $F_{y3\ max}$ and their timing parameters showed good symmetry (1.5%-8.8%), except for $F_{y3\ max}$ at constant speed (ASI 10.2%).

5.5 PHYSICAL FUNCTION

5.5.1 Physical Function Tests

The results of the physical function tests (Paper IV) of the OA and control groups are shown in Figure 13. One control subject did not perform the 20-m speed walk trial (data missing). One knee OA patient (K-L 3) was not able to complete the stair walking trials and one (K-L 2) was not able to perform a 5-min walk task. The repeated sit-to-stand test was too demanding for one patient with the most severe knee OA (K-L 4).

The patients with knee OA exhibited significantly poorer performance than the controls in all physical function tests (P <0.001, pick-up test: P =0.002) (Figure 13). The differences between the mean values of the groups varied from 16% to 20% % in 5-min walk, 20-m speed walk, stair ascent and descent and lift tests. The control subjects were 19-26% faster in TUG, straight line walking tests and repeated sit-to-stand than the patients suffering from the knee OA. The patients with knee OA demonstrated significantly poorer physical function than the control subjects also in the sock-test. There were no statistical differences in any physical function test between the knee OA subgroups, although the patients with the most severe knee OA (K-L 4) tended to exhibit the worst performance in every task (Figure 13).

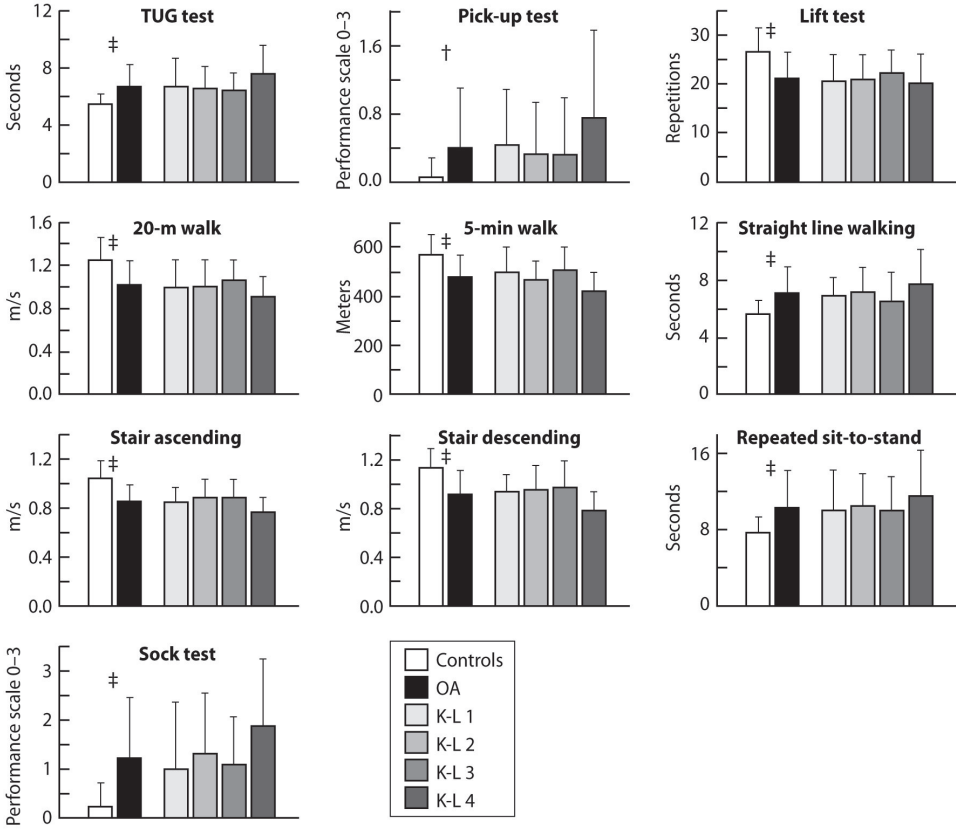

Figure 13. Physical function tests (mean± SD) in controls (n=52-53) and in men with knee OA (n=53-54). The knee OA patients were further divided, using Kellgren-Lawrence scale (Kellgren et al. 1963), into four subgroups according to the radiographic severity of their knee OA (K-L 1-4). The patients with knee OA exhibited significantly poorer performance than the controls in all physical function tests. There were no statistically significant differences between the knee OA subgroups in any of the tests. †P <0.01, ‡P <0.001. Student t-test for two independent samples, Mann-Whitney non-parametric test. TUG = timed up & go test.

5.5.2 Muscle Strength and Composition

In Experiment 3, the control subjects demonstrated significantly (P <0.05) higher knee extension (P <0.001) and flexion torques (Paper IV). The knee extension or flexion torques showed no differences between knee OA subgroups, but the knee extension torque exhibited a significant negative linear trend (P <0.05) as the severity of the knee OA increased. There were no significant differences between the groups in the absolute values of muscle thickness (cm) and area (cm^2) under the probe. The RF and VI, but not the VL muscle compartments of QFm exhibited significantly (P <0.05) higher heterogeneity in the knee OA group compared to the controls. There were no statistical differences in the thickness of the subcutaneous fat either between the OA and the control groups or between the OA subgroups. The QFm composition and size did not differ

between the knee OA subgroups. However, VL composition i.e. echogenicity and RF thickness both exhibited a significant ($P < 0.05$) negative linear trend with the severity of knee OA.

Table 11. Correlations between the Knee Strength Measurements, WOMAC, Functional Tests, Knee Alignment, and Knee Joint Range of Movement in the Patients with Knee OA (n=53-54).

	WOMAC				Knee Strength Measurements	
Functional Tests, Knee Alignment and Joint Motion	**Pain**	**Stiffness**	**Function**	**Composite**	**Knee extension Torque (Nm/kg)**	**Knee flexion Torque (Nm/kg)**
Lift test (number of rep.)	-0.41†	-0.42†	-0.39†	-0.40†	0.56‡	0.54‡
Pick-up test (0-3)	0.37†	0.36†	0.43†	0.43†	-0.52‡	-0.61‡
Repeated sit-to-stand (s)	0.52‡	0.49‡	0.53‡	0.53‡	-0.62‡	-0.64‡
Sock test (0-3)	0.29*	0.36†	0.38†	0.38†	-0.53‡	-0.56‡
Stair ascending (m/s)	-0.33*	-0.37†	-0.44†	-0.43†	0.56‡	0.56‡
Stair descending (m/s)	-0.43†	-0.42†	-0.55‡	-0.53‡	0.60‡	0.55‡
Straight line walking (s)	0.31*	0.45†	0.46†	0.44†	-0.55‡	-0.52‡
Timed up & go (s)	0.41†	0.40†	0.48‡	0.46‡	-0.69‡	-0.65‡
20-m speed walk (m/s)	-0.51‡	-0.57‡	-0.61‡	-0.60‡	0.62‡	0.68‡
5-min walk (m)	-0.49‡	-0.53‡	-0.58‡	-0.57‡	0.72‡	0.70‡
Knee alignment (degree)	ns	ns	ns	ns	-0.42†	-0.29*
Knee extension (deg)	ns	-0.31*	ns	ns	0.32*	0.28*
Knee flexion (deg)	ns	-0.28*	-0.27*	ns	ns	ns
Knee extension torque (Nm/kg)	-0.46‡	-0.42†	-0.50‡	-0.50‡	NA	NA
Knee flexion torque (Nm/kg)	-0.48‡	-0.50‡	-0.51‡	-0.52‡	NA	NA

**P <0.05; †P <0.01; ‡P <0.001. Pearson and Spearman correlation coefficient. WOMAC = the Western Ontario and McMaster UniverisitiesOsteoarthritis Index.*

Among the patients with knee OA, muscle strength was associated with the performance of physical function tests (all P <0.001) as well as with the knee alignment (Table 11). The strongest correlations were found in the 5-min walk (r range = 0.704 to 0.720), TUG (r range = -0.649 to -0.693), and 20-m speed walk (r range = 0.617 to 0.677). The isometric knee flexion torque had only a weak or moderate association with the lift test and repeated sit-to stand task (r =0.298 and -0.361, respectively) in the control subjects (data not shown). The knee extension torque demonstrated also a weaker correlation with the physical function in healthy controls, as compared to the knee OA subjects. The highest correlation coefficient values were found in the 20-m speed walk test (r= .485, P <0.001) in the control group. The absolute knee alignment degree had only a weak or moderate association with the functional tests (r range = 0.216 - $|-0.387|$; (P <0.05-0.001), in fact there was a non-significant correlation with the pick-up test (r =0.109, P >0.05). Muscle strength measurements were not associated with the muscle compositions. Subjective knee pain (VAS) did not correlate with the physical function, muscle strength measurements or knee joint range of motion (data not shown).

6 Discussion

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Study Populations

This thesis consists of three different study populations. One of the strengths of this study was the population used in original publications III and IV. The control subjects (n=53) were collected from the population register of over 10 000 candidates. The exclusion criteria were rather strict in order to limit possible effects of the confounding factors. However, the knee OA patients (n=54) demonstrated higher BMI than the controls. Obesity has been shown to be a causal risk factor for knee OA (Spector et al. 1994, Cooper et al. 2000, Berenbaum and Sellam 2008, Murphy et al. 2008). However, there were no statistical differences in the muscle thickness or thickness of the subcutaneous fat either between OA and control groups or between the OA subgroups. Therefore, the effect of subcutaneous fat or muscle thickness on the acceleration signal (Paper III) in the knee OA patients compared to the healthy controls is speculative. Furthermore, the results on muscle strength (Paper IV) and GRF (Paper III) measurements were normalised according to weight, thereby cancelling the effect of BMI.

Only men were recruited in the study, though the prevalence of knee OA is higher in females (Riihimäki et al. 2004). Women were excluded because of possible differences in hormonal activity in that age, which could have affected the muscle strength and composition measurements (Paper III). Women have in general more subcutaneous fat, challenging the surface-EMG and the ultrasound measurements. One must generalise these results to the female patients with knee OA cautiously, because there is some evidence for differences in gait patterns between male and female knee OA patients (Weidenhielm et al. 1994, McKean et al. 2007).

The number of subjects in the first study (Paper I) was relatively small (n=27). However, due to the strict exclusion criteria, the sample set could be considered to be representative for that population sample. The subjects of the first study had radiological, but not clinical OA. It is a well known fact that elderly subjects may have radiological OA changes even though they experience no pain or impaired functional capacity (i.e. clinical OA) (Brandt et al. 2003b). However, it is questionable, whether only minor radiological OA changes without any symptoms could significantly affect the EMG pattern during gait.

6.1.2 Gait Measurements

Reliability of the Measurements

There are many factors that could affect the reproducibility of a normal gait. These include the number of analysed gait cycles, targeting (i.e. a subject matches his/her step in a measurement area), different footwear, stair inclinations, walking speed variations and management of the acceleration and braking as well as transition steps in stair walking trials during data analysis (Yu et al. 1997, Perttunen 2002, Stacoff et al. 2005). Too low sampling frequency or an inadequate filtering may also distort the data (Collins and Whittle 1989, Hermens et al. 1999, Perttunen 2002).

In this thesis, the gait measurements were performed in two different gait laboratories. The first study (Paper I) was carried out in the Neuromuscular Research Center in the University of Jyväskylä. All subjects performed level walking trials along a 15-m-long walkway. A unique 10-m-long force platform, mounted in the middle of a walkway, was divided into two rows, allowing the measurement of 3-D GRFs from both limbs separately. The technical system enabled to measure many consecutive gait cycles during a single trial. The other gait analyses (Papers II, III) were executed in the University of Kuopio. A 10-m long walkway, covered with a thin rubber mat, permitted the measurement of one gait cycle with two consecutive steps on the force platforms. To achieve reproducible steady-state gait trials, six to ten steps were taken during walking on level ground (Perttunen 2002) and fifteen steps on stair ambulation (Stacoff et al. 2005) in the analysis. Thereby, the first and last three as well as transition steps were omitted from the data processing (Miller and Verstraete 1996, Yu et al. 1997). Furthermore, the walking speed was carefully standardised. As the speed is known to affect most of the gait parameters, speed variations would have made it difficult to interpret the results (Perttunen and Komi 2001, Möckel et al. 2003, Bejek et al. 2006).

Loading Rate Calculations

There is no established method in the literature for calculating the LR (Radin et al. 1991, McCrory et al. 2001, Christina and Cavanagh 2002, Stacoff et al. 2005). The method of McCrory et al. (2001) used in the first study (Paper I) may underestimate the true LR. However, in this case the values can be compared between the subjects and the different trials, even though some subjects had a distinct heel strike transient at the very beginning of the contact.

One aim of study II was to test two different methods for calculating LR, namely average and maximal LR. The average LR did not correlate with the maximal LR or the average ATR measured with SMAs, but the maximal LR was associated with the average ATR. This result was interpreted to mean that the average LR is not a valid parameter for measuring impact loading. It does not take into account the possible heel strike transient and therefore it underestimates the true LR. Therefore, only the maximal LR was calculated in study III, even though the variability (CV 13.1-19.4%) and ASI (26.5-27.8%)

were quite high for this parameter (Paper II). The maximal LR calculation has been used in some other knee OA studies (Chen et al. 2003b, Mündermann et al. 2005). In order to achieve satisfactory reproducibility and stability for maximal LR parameter, the number of walking trials with constant gait speeds needs to be high enough.

Validity of Skin Mounted Accelerometer Measurements

The important finding of study II was that IPA and PP acceleration in the resultant axial direction as well as in the resultant horizontal direction exhibited good inter-day repeatability (CV <15%) in young healthy adults. More recently, Turcot et al. (2008a) using slightly different SMA devices reported that the values for tibial and femoral accelerations of knee OA patients during walking do not differ extensively when measured on separate days. However, there is no absolute limit for accepted CV in the clinical trials. The variation consists of random and/or systematic factors such as the properties of the device in use and selected parameter, study design, subject's biological variation and learning effect, i.e. the subjects usually improve their performance when repeating a task (Schmidt 1997). It was not possible to identify which of the above mentioned factors had the greatest effect on the reported CV values. However, the accelerometer measurements indicated that the variability between single trials within a day were in the same range as the variability of averaged trials between the days. This supports the concept that the inter-day variation in loading measurements of SMAs during walking is not caused primarily by the subtle differences in the attachment of sensors on different days. The variation is possibly primarily attributable to the sum effect of sensor placement, random and/or systematic changes in gait and the measured parameters.

The CVs of loading measurements with the SMA attached below the knee were better than those obtained above the knee. The soft tissue beneath the SMA above the knee on the lateral side is clearly thicker than that on the tibial plateau. High impact loading can produce a minor vibration of the sensor, resulting in poor repeatability in the evaluation of certain loading parameters. It should be noted that the results of the study (Paper II) cannot be directly generalised to the population suffering from the knee OA, because the knee joint motion could be slightly altered due to joint pain or laxity, especially on the more-affected side (Lewek et al. 2006).

It is difficult to measure the tibio-femoral contact forces in vivo during human ambulation. Some authors have used a force-measuring knee implant to reveal the real joint contact forces (Kim et al. 2009). Naturally, this method could not be utilised in larger populations, and non-invasive direct joint contact force measurements are currently not possible. Therefore, researchers have estimated the tibio-femoral contact forces by computational modelling (Taylor et al. 2004, Thambyah et al. 2005) or used indirect techniques to assess indirectly joint loading in the knee OA studies e.g. with accelerometer techniques (Radin et al. 1991, Henriksen et al. 2006b, Henriksen et al. 2008), measuring the GRFs (Chen et al. 2003b, Gill and O'Connor 2003, Mündermann et al. 2005,

Henriksen et al. 2006b) or taking advantage of joint moment analysis (Kaufman et al. 2001, Baliunas et al. 2002, Mündermann et al. 2005, Henriksen et al. 2006a). According to Kim et al. (2009) the calculated and measured joint contact forces are in a good agreement. This is encouraging for the development of non-invasive methods to be used in joint loading estimation.

The recent study (Paper II) demonstrated that the vertical GRFs and SMA variables, both in the axial and resultant directions, exhibited high linear correlations. This confirms the hypothesis that it is possible to predict certain vertical GRF parameters with SMA measurements. In particular, maximal ATR explained 43.4% to 85.3% and IPAs explained 49.1% to 91.8% of the variation of maximal loading rates. In addition, IPAs predicted 58.8% to 88.7% of the variation of F_{z1}. Previously, Lafortune et al. (1995b) have proposed a transfer function between the tibial a_z measured with the bone mounted sensors and GRF during running. However, if one considers the clinical gait analysis then it is clear that the SMAs are far more practical for use and therefore the recent finding (Paper II) is important for future development of mobile gait laboratory techniques. Although SMAs cannot measure the real forces on joint surfaces, they could be practical for use in clinical gait analysis because they provide reliable estimates of joint loading (i.e. IPA) in a non-invasive manner and can possibly distinguish normal from pathological walking (Turcot et al. 2008b).

6.1.3 Physical Function Assessment

The physical functioning was measured by utilising a battery of validated tests that could be practically applied in general practice (Paper IV). The tests used required the strength in the lower extremities, joint mobility and balance and were intended to mimic routine daily activities. However, it is possible that they do not properly measure aerobic capacity, which is also needed in daily life. One could argue that the differences would have been more significant, if the tasks had been prolonged to several minutes, as the knee OA patients may experience reduced aerobic capacity (Ettinger and Afable 1994). Therefore, the performance test results are unlikely to overestimate the true differences between the groups

It has been speculated that the patients with knee OA are not able to fully activate their QFm (Fitzgerald et al. 2004, Lewek et al. 2004, Mizner et al. 2005b). Unfortunately, the QFm activation level was not measured with a twitch interpolation technique during maximal voluntary force production. However, on average the subjective pain score described by the patients was quite low and the subjects were verbally encouraged to achieve their maximum torque. In addition, the subjects performed so many maximal actions that the peak value did not increase and the best result was registered. These factors would tend to decrease the possible deficit in the activation level during force measurements.

In order to obtain a better insight into complex interrelationships of muscle dysfunction in etiopathogenesis of knee OA, the composition of the QFm was measured with ultrasound (Paper IV). Previously, Sipilä and Suominen (1991) used ultrasonography to reveal that power-trained elderly men exhibit a more homogenous internal structure in their QFm than untrained men. The decreased homogeneity of muscles refers to increased fat and connective tissue content visualised by increased echogenicity in ultrasonography. The ultrasonography method has proven to be reproducible (Sipilä and Suominen 1991, Sipilä and Suominen 1996) and reliable when compared to computed tomography (Sipilä and Suominen 1993).

The different WOMAC dimensions correlated with the objective physical function tests, but only weakly or not at all to knee joint ROM. The association with the physical function was clearer than previously reported in hip and/or knee OA patients (Lin et al. 2001, Arokoski et al. 2004). Since previous authors had either smaller (Arokoski et al. 2004) or more heterogeneous (Lin et al. 2001) study groups, and they used slightly different test batteries, as compared to the present study (Paper IV), comparisons need to be made with caution. The comorbidities such as back pain, and depression could interfere with the WOMAC score of pain and physical functioning. This would limit its usefulness in clinical practise (Wolfe 1999). Interestingly, the mean WOMAC pain score of all knee OA patients was over 4 times higher (2.9±2.0 cm) than the mean subjective pain (0.7±1.0 cm), as assessed with VAS during the measurements. This also supports our idea that the results do not overestimate the true impairment in physical function of knee OA patients.

6.2 MAIN FINDINGS

6.2.1 Gait and Knee Osteoarthritis

Loading of the Lower Extremity

One of the main goals of the present thesis was to examine joint loading during walking, with special reference to potential changes in loading characteristics in OA patients. Nearly 20% of the asymptomatic subjects with mild knee OA features in radiographs exhibited a distinct heel strike transient in level walking at maximal speed. They showed decreased activity of VM muscle prior to contact with the ground (Paper I). Radin et al. (1986) have reported that one third of healthy adults load their lower extremities impulsively during normal walking. This has been hypothesised to lead to joint damage. The authors classified subjects as heel-strikers if the first vertical peak GRF >1.2. If peak a_z was >4.7g above lateral malleoli at the preferred walking speed, Gill and O'Connor (2003) later divided normal healthy subjects into either loaders or non-loaders. There are, however, several issues challenging the above mentioned assumptions on joint loading. First of all, one must consider if there is a definite limit between the physiological and pathological loading? Secondly, the subject walked barefoot in both studies. (Radin et al. 1986, Gill and O'Connor 2003). Nowadays, most people use outdoor shoes in western societies when they are walking. This could dampen the impact load (Loy and Voloshin

1991, Whittle 1999). Thirdly, longitudinal data confirming the hypothesis that impact loading during walking would lead in joint degeneration in humans is still lacking.

The ratio of acceleration transmission has been used to analyse the shock wave attenuation capacity of the musculoskeletal system (Voloshin and Wosk 1982). The authors reported that patients with painful or meniscectomised knee joints exhibited almost 20% reduced absorbing capacity compared to the situation in their healthy knee. There were no differences in the ratio of acceleration transmission during level walking between the patients with knee OA and their healthy age-matched controls. However, the knee OA patients displayed about 15% lower ratio during stair descent at faster speeds. It has been shown that the neuromuscular fatigue after stretch-shortening cycle exercise leads to reduced reflex sensitivity (Avela 1998). One could speculate that the musculoskeletal system is at greater risk to suffer potentially adverse effects of impulsive loading after prolonged exercise. Since knee OA patients seem have poorer physical capacity and muscle strength (Paper IV), the ability of their neuromuscular system to attenuate the shock wave propagation after fatigue is a topic warranting further investigation.

Neural Control Revealed by Electromyography

The human gait is a complex motor activity which is controlled by the central nervous system. In order to obtain a complete picture of joint loading during walking, gait measurements need to be integrated with the simultaneous observations on the neuromuscular system, for example by using the surface-EMG. One key mechanism that protects the lower limb and the whole body from injurious impulsive loading occurs via the activation of limb muscles prior to the landing of the limb (Jones and Watt 1971, Komi et al. 1987, Arampatzis et al. 2003). Furthermore, the muscle co-contraction is used to stabilize joint motion during human locomotion. The co-activation is believed to increase in knee OA as a counter-effect to joint pain and laxity (Benedetti et al. 1999, Childs et al. 2004, Lewek et al. 2006). There is some evidence that the activation pattern of the lower limb muscles is altered in patients with knee OA (Childs et al. 2004, Hubley-Kozey et al. 2006, Astephen et al. 2008). One of the most interesting results of this study (Paper III) was the finding the patients with knee OA exhibited differences in the activation pattern of VM and BF muscles. This served as a compensatory action both in the level and stair walking despite only subtle changes in the measured loading or spatio-temporal gait parameters at pre-determined walking speeds could be observed. Furthermore, the activation patterns of VM and BF muscles on the less affected side resembled the corresponding patterns of those obtained from the healthy controls. Earlier, Lewek et al. (2006) reported similar co-contraction indices in VL and lateral hamstrings as well as VM and medial hamstrings between the involved side of patients with knee OA and control subjects. On the other hand, co-contraction was higher in the involved side compared to the uninvolved one in the VL-lateral hamstrings –pair, supporting the recent results (Lewek et al. 2006).

Previous authors have hypothesised that some subjects are exposed to repetitive impulsive loading during heel strike because of inadequate function of QFm prior to contact (Radin et al. 1986, Radin et al. 1991). This hypothesis was supported by the results on the asymptomatic subjects with mild radiographic knee OA changes in the first study (Paper I). In the Experiment 3, 11% of knee OA patients exhibited a heel strike at walking speed of 1.2 m/s. The symptomatic knee OA patients might adopt a different gait strategy than asymptomatic patients with radiographic knee OA changes, as there was no correlation between the pre-activation of VM and GRF loading parameters in patients suffering from symptomatic knee OA (Paper III). Recently, Hunt et al. (2010) concluded that QFm strength is not related to gait impact loading in patients with knee OA. According to the authors, the rate of loading was primarily dictated by walking speed (Hunt et al. 2010). Henriksen et al. (2006b) have also questioned the hypothesis of whether the impulsive forces during heel strike contribute to the progression of knee OA. Unfortunately, they did not measure the muscle activation. However, as the etiopathogeneis of OA is multifactorial, there might be some subgroups that exhibit muscular dysfunction, and therefore may be exposed to joint deteriorating impact loading during locomotion (Hurley 1999, Henriksen et al. 2006b).

The Effect of Knee OA Disease Severity

Several reports have addressed the issue of knee OA disease severity on gait (Sharma et al. 1998, Hurwitz et al. 2002, Mündermann et al. 2005, Astephen et al. 2008, Asay et al. 2009, Zeni and Higginson 2009). According to a recent study (Paper III), the disease severity does not affect the SMA parameters, except that the resultant horizontal IPA was lower in patients with more severe knee OA when they were descending stairs at a higher speed. LR_{max} tended to decrease, and the first vertical peak GRF increased significantly as a function of disease severity. Previously, Mündermann et al. (2005) reported that the patients with more severe OA exhibited greater maximal knee adduction moments than the patients with less severe knee OA. This supports the earlier finding of Hurwitz et al. (2002), i.e. the radiographic disease severity predicts the peak knee adduction moment.

Later, Astephen et al. (2008) concluded that the gait differences that progressed with the knee OA severity included decreased stance phase knee flexion angles, decreased early stance knee extension moments, decreased peak stance phase hip internal rotation moments, and decreased peak ankle dorsiflexion moments. The effect of knee OA disease severity on stair climbing has been evaluated in only one study (Asay et al. 2009). Patients with more severe knee OA exhibited forward trunk lean in order to reduce the QFm demand (Asay et al. 2009). However, in the latter studies, the subjects with severe knee OA had significantly lower gait speeds than the patients with moderate knee OA (Astephen et al. 2008), or the self-selected gait speed was not reported (Asay et al. 2009). The knee OA subgroups in the third study (Paper III) were highly homogenous. This supports the hypothesis that the radiographic knee OA itself has no marked influence on gait when the walking speed is kept constant. Recently, Zeni et al. (2009) drew the same

conclusion as the differences between the knee OA subgroups disappeared when the walking speed was constant.

6.2.2 Quadriceps Femoris Muscle and Knee Osteoarthritis

Knee extension and flexion strength were reduced by 20% and 13%, respectively, in patients with knee OA. The values of knee extension and flexion strength were associated with the results of physical function tests in the patient group (Paper IV). This finding confirms the conclusion of many authors (McAlindon et al. 1993, van Baar et al. 1998a, Steultjens et al. 2001, Messier et al. 2002) that adequate muscle strength seems to be an important factor in the capability to perform daily activities. Amin et al. (2009) reported that the greater QFm strength could protect against cartilage loss at the lateral compartment of patellofemoral joint but not at the tibiofemoral joint. This finding was partially supported by the recent work in which the authors concluded that thigh muscle strength does not appear to predict an incident of tibiofemoral radiographic OA, but does predict incident symptomatic knee OA (Segal et al. 2009). Interestingly, the correlation between the muscle strength and the physical function was weaker in the control group (Paper IV). This would support the concept that there is a threshold in the force level that needs to be achieved in order to cope properly with the daily activities.

Mikesky et al. (2006) examined the effect of lower-extremity strength training on the incidence and progression of knee OA and compared the results to those of the flexibility exercise group. Strength training reduced the mean rate of joint space narrowing in OA knees by 26%. However, this change was not statistically significant. There tended also to be a decline in the frequency of knee OA progression in the strength training group. However, the joint space narrowing was more common in strength training group in knees that were radiographically normal at baseline. The joint space narrowing showed no association with strength, training compliance or observed changes in QFm or hamstring muscles strength. Furthermore, there was a trend towards improved function in strength training group, as evaluated with the WOMAC functional limitation score. Therefore, according to authors, it is difficult to accept that strength training would be harmful for adults without knee OA (Mikesky et al. 2006). Previously, Sharma et al. (2003b) had reported that the QFm strength was a significant risk factor for radiographic progression of knee OA in malaligned and lax knees, implying that strength training may lead to damage of at-risk OA knee joints. This highlights the importance of individually guided strength training in order to enhance joint protective muscle activity.

The VI and RF muscle composition, measured with ultrasound (Paper IV), exhibited significant differences in the patients with knee OA. The results supported the hypothesis that the knee OA patients exhibit muscle atrophy, which would be revealed as an increased echogenicity and decreased muscle thickness in the ultrasound assessment. The ultrasound method is valid (Sipilä and Suominen 1996) and it can provide information on the internal structure of muscle non-invasively and inexpensively. Sipilä and Suominen (1991) have earlier shown that the power-trained elderly men display a more

homogeneous internal structure of the QFm than the untrained men, indicating that long-term training can maintain the muscle composition and counteract the age-related replacement of contractile tissue by other tissues such as fat. The muscle thicknesses of the VL and VI compartments were higher in the controls after adjustment for BW (Paper IV). This is consistent with the higher force production seen in the control subjects. Previously, Arokoski et al. (2002) reported that the patients with hip OA do not demonstrate lower cross-sectional areas of the pelvic and thigh muscles compared to healthy age- and sex-matched controls. However, the cross-sectional areas of pelvic and thigh muscles were significantly lower on the more severely affected limb than in the better limb. The isometric hip adductor and abductor strength as well as the isometric and –kinetic hip flexor strength were lower in patients with hip OA. The hip extension and flexion strength are also reduced in the more affected limb, as compared to the less affected side (Arokoski et al. 2002).

6.2.3 Physical Function and Knee Osteoarthritis

The patients with knee OA exhibited significantly poorer physical function and lower knee extension and flexion muscle strength than the age- and sex-matched control subjects. In the patient group, the mean decline of performance ranged from 13% to 26%. Furthermore, the RAND-36 revealed that the patients with knee OA showed, in comparison with the control subjects, significantly impaired health-related quality of life in virtually all of the measured separate scales (Paper IV).

The grade of knee OA had a significant impact on ROM. This might indicate that the evaluation of the knee ROM is a sensitive clinical criterion in the radiographic determination of the severity of knee OA. Previously, the ROM has been shown to influence the functional ability in the knee OA. The patients with knee OA are known to exhibit decreased ROM and increased mediolateral laxity (Dekker et al. 1992, Pai et al. 1997). Steultjens et al. (2000) have also concluded that the restricted joint mobility is an important component contributing to disability in patients with knee OA. However, in the current study, the absolute changes were rather small between the groups, with K-L scores of 1 to 3. Second, because the WOMAC main dimensions were poorly correlated with the knee ROM, the use of knee ROM as the only functional test is questionable.

The grade of knee OA had no significant effect on the tested physical function, even though the patients with the highest grade of knee OA seemed to exhibit the worst performance in every task. Only the maximal voluntary isometric knee extension torque and knee joint ROM were related to the severity of knee OA. Similarly, there were no major differences between the self-reported function (WOMAC) in patients with K-L scores of 1 through 3. However, in the tertiary-stage (K-L score of 4), the extent of the self-reported functional disability was significantly higher. These findings are in agreement with the earlier studies (Jordan et al. 1997, Salaffi et al. 2005). In our study, the WOMAC function scale, but not the physical functioning in RAND-36, was associated with the severity of radiographic knee OA. Thus, the disease-specific WOMAC function index

seems to be a more sensitive indicator of radiographic severity of knee OA than most of the physical function tests and RAND-36. In our study, there were no statistical differences in age, anthropometry or subjective pain between the knee OA subgroups. Furthermore, the background information about leisure time physical activity, pain relieving medication, comorbidities, occupational loading history, and knee trauma revealed no divergences between the subgroups. Therefore, our initial hypothesis that the confounding factors would associate more closely with the impaired physical capacity than with the radiographic severity of the disease was not supported.

The degree of absolute knee alignment was associated with the functional tests, except for the non-significant correlations with the pick-up test. The knee alignment has shown to be an important factor in the development and progression of knee OA (Brouwer et al. 2007). Our results support the finding that the knee alignment could predict the decline of functional ability (Sharma et al. 2001). It can be concluded that the knee alignment may be a good indicator of disease severity and functional performance. We also recommend the use of repeated-sit-to-stand test and 20-m walk test in clinical practice. They are very reproducible tests (Harding et al. 1994, Seeman et al. 1994, Suteerawattananon and Protas 2000) and easy to perform. They also exhibited an excellent correlation with the WOMAC and muscle strength, both known to be important indicators of disability in knee OA (Lankhorst et al. 1985, Bellamy et al. 1988, Hurley and Newham 1993, Madsen et al. 1995).

6.3 CLINICAL IMPLICATIONS

Knee OA is a multifactorial disease that affects articular cartilage and also all the periarticular structures such as muscles, subchondral bone and joint capsule. Furthermore, severe knee OA may have adverse effects on the functional ability, mobility and mental health. Possibly, this could threaten seriously an individual's whole well-being. On the other hand, the patient with mild-to-severe knee OA may have quite normal physical function with negligible knee pain. When deciding treatment policy for an individual patient with knee OA, one needs to pay attention to the patient's physical functioning and quality of life irrespective of the obvious degenerative changes in the plain radiographs. A repeated sit-to-stand and 20-m walk test could be recommended in assessing the physical function in knee OA. These tests are reproducible and easy to perform.

The SMAs are practical and reproducible to estimate joint loading during walking. However, the knee OA patients demonstrate only slight changes in joint loading measurements compared to healthy subjects. Patients with knee OA may adopt different compensatory actions in gait. The accelerometer-based clinical gait analysis may be an advanced method for investigating the gait of patients with knee OA. However, on the basis of this study this method cannot be recommended for use in routine clinical practise.

7 Conclusions

The most important findings of the present studies (Papers I-IV) were:

1.) Almost every fifth of the asymptomatic subjects exhibited a distinct heel strike transient at maximal speed. This was associated with the lower pre-activity of vastus medialis muscle. The control of Quadriceps femoris muscle (QFm) prior to heel contact is possibly an important factor that reduces impulsive loads during walking in asymptomatic subjects with knee osteoarthritis (OA). There was no asymmetry in the kinematic or kinetic variables in level walking, while, the asymmetry increased during stair walking. Stair walking is a demanding motor task and the musculoskeletal system is loaded more forcefully during stair descent than in walking on the level ground at a preferred speed.

2.) Initial peak and peak-to-peak acceleration variables with skin mounted accelerometers exhibited good inter-day repeatability. Repeatability of the average and maximal acceleration transient rate parameters was generally not satisfactory. The loading variables obtained from the ground reaction forces and acceleration measurements during gait revealed high linear correlations, indicating that it is possible to estimate joint loads with the skin mounted acceleration measurements.

3.) The differences in measured accleration and ground reaction force parameters between the knee OA subjects and the controls were only minimal at constant gait speeds. However, OA subjects loaded their lower extremity more forcefully, especially during stair descent at a fast speed. The knee OA subjects used different muscle activation strategies to execute the same walking tasks. It seems that the faster speed in the stair descent activated maximal compensatory mechanisms among patients highlighting the differences between the knee OA and healthy subjects.

4.) The subjects with knee OA exhibited impaired physical function and inferior QFm composition and strength than the healthy controls. The Western Ontario and McMaster Universities OA Index (WOMAC) subscales and QFm strength were associated with the physical function tests in knee OA subjects. The radiographic knee OA grade had no linear correlation with the physical function, while passive knee motion, QFm strength, and WOMAC subscales were related to the radiographic severity of the disease. The results highlight the importance of QFm strength in physical function. In addition, the present results emphasise the importance of assessing a subject's subjective and objective physical capabilities before deciding on the optimal knee OA treatment strategy.

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Biomechanics of Gait and Physical Function in Patients with Knee Osteoarthritis

Thigh Muscle Properties and Joint Loading Assessment

The cause of osteoarthritis (OA) remains unknown but the mechanical aspects in the etiopathogenesis of knee OA seem to be important. This study was designed to examine the gait biomechanics and physical function of knee OA patients with a special emphasis on investigating the properties of the thigh muscles, and the usefulness of skin mounted accelerometers (SMAs) in assessing joint loading. The results reveal the effect of thigh muscle strength on physical function in patients with knee OA. The SMAs also proved to be practical and reproducible to estimate joint loading during walking.

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