From the Department of Physiology and Pharmacology,
Karolinska Institutet, Stockholm, Sweden

Patellofemoral pain syndrome
Clinical and pathophysiological considerations

Jan Näslund

ABSTRACT

Patellofemoral pain syndrome (PFPS) is one of the most common musculoskeletal disorders and is reported to affect 15%–33% of the active adult population and 21%–45% of adolescents. Among adolescents, the incidence is reported to be higher for girls. PFPS affects athletes and nonathletes of both genders and is consistently reported in activities such as ascending or descending stairs and squatting or subsequent to long periods of sitting still (theatre or movie sign). Patients commonly report that the development of their pain is insidious and that the pain is either sharp and acute or diffuse and chronic. Since no consensus on the definition, classification, assessment, or management has been reached, no validation of clinical tests and signs is possible. PFPS is often a diagnosis of exclusion. The most widely accepted theory regarding the etiology behind PFPS suggests that the symptoms are the result of excessive patellofemoral joint stress (force per unit area) due to abnormal patellar tracking. Reports, however, have questioned a causal relationship between malalignment and knee discomfort in PFPS.

The overall purpose of this thesis was to explore possible pain mechanisms in PFPS. In the *first study*, we compared symptoms and clinical findings in a group of PFPS patients with a group of knee-healthy subjects. The main finding was that patients with a clinical diagnosis (made on two occasions and by different physicians) of PFPS may have additional diagnoses that are undetectable in the patient's history or in commonly used clinical tests.

In the *second study*, we treated PFPS patients using two modalities of sensory stimulation: electro-acupuncture and subcutaneous needling. Patients with PFPS reported alleviation of pain from both methods. The pain-relieving effect remained for at least half a year. None of the variables height, velocity, power, or force increased during observed physical function, the one-legged explosive jump. The activity score was unchanged in both treatment groups. The skin temperature at three locations on the leg did not change.

In the *third study*, we used bone scintigrams to examine patients suffering from PFPS. Diffuse uptake was found in 44% of the knees of patients with PFPS and in all three bony compartments of the knee: in 27 patellae, in 25 proximal tibiae, and in 19 distal femora. Uptake in the femur and the tibia occurred solely in the condyles.

Diffuse uptake on scintigraphy is regarded as a sign of accelerated bone remodeling. Apart from mechanical loading, hypoxia is a physiological factor that may be involved in triggering this remodeling. In the *fourth study* we evaluated a new photoplethysmographic (PPG) technique in healthy subjects to monitor local pulsatile blood flow in the patella. Different provocation procedures were applied to influence blood perfusion both superficially in the skin and in the patellar bone. Blocking blood flow in the skin significantly decreased the PPG signal from the skin but not from the patellar bone. During venous stasis, signals from both tissues decreased but the blood flow in the skin deteriorated more. Occlusion of arterial blood flow minimized both PPG signals. The application of liniment to the skin increased the PPG signal from the skin significantly more than from the patella. In a parallel study on a physical model with a rigid tube, we showed that the AC component of the PPG signal originates from pulsations of blood flow in a rigid structure and not necessarily from volume

pulsations. This study indicated that photoplethysmography can be used to measure local bone blood flow continuously and non-invasively.

Because these first studies supported the hypothesis that the supply of oxygen to the knee region in patients with PFPS is diminished we used the novel PPG method to compare the pulsatile blood flow in the patellar bone in patients and healthy controls in the *fifth study*. We found that pulsatile blood flow in PFPS patients was markedly reduced compared with knee-healthy patients during flexion of the knee to 90˚.

From this thesis it is concluded that:

- PFPS is a clinical diagnosis in which the patients can be divided into different subgroups according to radiological findings.
- The pain experienced by patients suffering from PFPS decreases after various types of sensory stimulations.
- Diffuse uptake on scintigraphy will be present in approximately half of the PFPS patients and may occur in any bony compartment of the knee.
- Pulsatile blood flow in the patellar bone can be studied continuously and non-invasively with photoplethysmography.
- Patients diagnosed with PFPS exhibit reduced levels of patellar pulsatile blood flow compared with healthy controls when the knee is flexed.

THESIS SUMMARY IN SWEDISH
Svensk sammanfattning

Patellofemoral smärta (PFS), också kallad främre knäsmärta (FKS), är den mest vanligt förekommande diagnosen på idrottskademottagningar (Murray et al., 2005; Kannus et al., 1999) men tillståndet diagnostiseras också ofta inom primärvård och skolhälsovård (Arrol et al., 1997). Besvären har genom åren givits många olika benämningar. Begreppet *chondromalacia patellae* myntades redan på tidigt 1900-tal (Aleman, 1928) och var under många år den vanligaste bennämningen. Idag anses *chondromalacia patellae* vara en diagnos som endast skall ställas efter en artroskopisk inspektion av knäskålens ledbrosk.

PFS är en diagnos namngiven efter en anatomisk smärtlokalisation. Det enda symtomet som det finns konsensus för i litteraturen är oklara främre knäsmärtor. I övrigt saknas det konsensus för diagnoskriterier, symtom, behandling och utvärderingsmetoder (The International Patellofemoral Study Group, 1997).

PFS anses vanligen bero på icke optimala mekaniska förhållanden mellan knäskålen och lårbenet (Fulkerson, 2004). Operativa metoder för att korrigera mekanisk obalans används när konservativa behandlingar inte ger tillfredställande resultat. För närvarande rekommenderas återhållsamhet med operativa behandlingar då få långtidsuppföljningar har visa på bra behandlingsresultat (Fulkerson, 2004).

Nyligen uppmanade IASP (International Association for the Study of Pain) till forskning kring smärtmekanismer bakom vanliga smärtdiagnoser (Woolf et al., 1998). Den mekaniska förklaringsmodellen bakom PFS har ifrågasatts (Dye, 2005). Arnoldi (1991) pekade på att ett högt intraossöst tryck, beroende på venös stas, kunde ge upphov till patienternas besvär. Butler-Manuel (1992) ansåg att patienter med PFS led av sympatisk reflexdystrofi (RSD) och han använde med framgång sympatikusblockader som behandling. Sanchis-Alfonso och medarbetare (1998, 1999, 2000) fann neurom samt ett ökat antal substans P-innehållande smärtnerver i det laterala retinaklet hos patienter med PFS och menade att dessa nervförändringar uppstår när retinaklet utsätts för kraftig uttöjning. Selfe och medarbetare (2002, 2003) argumenterade för att det föreligger en lokal ischemi och att denna skulle kunna förklara smärta hos patienterna.

Det övergripande syftet med min avhandling var att studera möjliga smärtmekanismer hos patienter med PFS.

I det första delarbetet undersökte vi om patienter som fått diagnosen PFS kunde indelas i undergrupper beroende på fynd vid kliniska och radiologiska undersökningar. Vi fann att röntgenundersökning av skelettet samt skelettskintigrafi visade på flera olika mönster indikerande att olika smärtmekanismer kan förekomma. De manuella kliniska testerna som vi använde i studie 1, hade inte sensitivitet eller specificitet nog för att särskilja dessa grupper. Konklusionen var att det bland patienter som erhållit diagnosen PFS kan finnas undergrupper med olika genes samt att vanligt använda kliniska undersökningsmetoder inte kan särskilja olikheter i bakomliggande patofysiologi.

I det andra delarbetet studerade vi om sensorisk stimulering (akupunktur) kunde påverka patienternas smärta, hoppförmåga och hudtemperatur. Tidigare har, i okontrollerade studier, akupunktur visat sig bidra till smärtreduktion hos patienter med PFS (Jansen, 1999). Vidare har hudtemperatur använts som variabel för att studera PFS (Ben-Eliyahu, 1992). Vi fann att elektroakupunktur men också ytlig nålstimulering

reducerade patienternas smärta signifikant jämfört med utgångsvärdena. Ingen skillnad mellan grupperna förelåg. Smärtreduktionen kvarstod i minst 6 månader. Hudtemperatur och hoppförmåga förändrades inte trots reduktion av smärtan.

I det tredje delarbetet studerades skintigrafiupptaget i knäleden. Våra resultat visade att diffust upptag var nästan lika vanligt i skenbenskondylerna som i knäskålen men oftare förekommande än upptag i lårbenskondylerna. Diffust skintigrafiupptag tyder på en ökad remodellering av benvävnad. Oavsett vilken faktor som stimulerar till ökad benomsättning så tyder våra fynd på att förändringen sker i knäledens alla tre benkomponenter.

En av de faktorer som kan tänkas ligga bakom en lokal ökning av benremodellering är hypoxi. Lårbenskondylerna, skenbenskondylerna och knäskålen har en gemensam arteriell försörjning utgående från a. poplitea. I det fjärde delarbetet beskriver vi en ny mätmetod för en icke invasiv och kontinuerlig mätning av pulsativt blodflöde i knäskålen. Med en ny typ av fotopletysmografi (PPG)-utrustning visade vi att selektiva provokationer av blodflödet i hud respektive i knäskål kunde studeras och att flödesregleringen signifikant skiljde sig åt i hud och benvävnad. I *in vitro* försök, på en modell av stela kärl, visade vi också att den pulsativa PPG-signalen härrör från pulsationer i blodflödet och inte från volymförändringar.

I det sista delarbetet studerades om patienter med PFS skiljde sig åt visavi knäfriska kontroller vad beträffar pulsativt blodflöde i knäskålen. Vi fann att, i samband med passiv knäflektion till 90º, så minskade det pulsativa flöde hos patienter med PFS.

Sammanfattande konklusion
Resultaten från detta avhandlingsarbete tyder på att:
- Patienter med den kliniska diagnosen PFS kan indelas i olika grupper relaterade fynd vid röntgenologiska undersökningar.
- Smärtan hos patienter med PFS kan lindras med hjälp av sensorisk stimulering.
- Ca hälften av PFS patienter uppvisar en ökad benomsättning i någon eller flera av knäets benkomponenter.
- Pulsativt blodflöde i knäskålen kan icke-invasivt och kontinuerligt studeras med att hjälp av fotopletysmografi.
- I samband med knäflektion har patienter med PFS lägre pulsativt blodflöde i knäskålen än friska kontroller.

Ett spekulativt samband mellan fynden i våra olika studier kan vara att hos patienter med PFS reagerar benvävnaden i knäskålen på intermittent ischemi genom att öka benremodelleringen samtidigt som ischemin ger upphov till smärta, en smärta som kan vara orsakad av sensitisering av nociceptorer (hyperalgesi) eller av aktivitet i beröringsfibrer (allodyni).

Books must follow science, and not science books.
- John Barlett (1820-1905)

LIST OF PUBLICATIONS

I. *Comparison of symptoms and clinical findings in subgroups of individuals with patellofemoral pain.* Jan Näslund, Ulla-Britt Näslund, Sten Odenbring, Thomas Lundeberg. Physiotherapy Theory and Practice June 2006 (accepted March 2005).

II. *Sensory stimulation (acupuncture) for the treatment of idiopathic anterior knee pain.* Jan Näslund, Ulla-Britt Näslund, Sten Odenbring, Thomas Lundeberg. Journal of Rehabilitation Medicine 2002;34:231-8.

III. *Diffusely increased bone scintigraphic uptake in patellofemoral pain syndrome.* Jan Näslund, Sten Odenbring, Ulla-Britt Näslund, Thomas Lundeberg. British Journal of Sports Medicine 2005;39:162-5.

IV. *Non-invasive continuous estimation of blood flow in human patellar bone.* Jan Näslund, Jonas Pettersson, Thomas Lundeberg, Dag Linnarsson, Lars-Göran Lindberg (submitted).

V. *Decreased pulsatile blood flow in the patella in patellofemoral pain syndrome: a controlled study.* Jan Näslund, Markus Waldén, Lars-Göran Lindberg (in manuscript).

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AKP	Anterior knee pain
BMD	Bone mineral density
BS	Bone scintigraphy
DXA	Dual-energy X-ray absorptiometry
IAKP	Idiopathic anterior knee pain
IASP	International Association for the Study of Pain
LDF	Laser Doppler flowmetry
MTSS	Medial tibial stress syndrome
MRI	Magnetic resonance imaging
NSAID	Non-steroid anti-inflammatory drug
OA	Osteoarthritis
OP	Osteoporosis
PFPS	Patellofemoral pain syndrome
PPG	Photoplethysmographic
RSD	Reflex sympathetic dystrophy (Complex regional pain syndrome I)
SP	Substance P
TCM	Traditional Chinese Medicine

1 INTRODUCTION

1.1 THE PATELLOFEMORAL PAIN SYNDROME

Patellofemoral pain syndrome (PFPS) is one of the most common musculoskeletal disorders (Murray et al., 2005; Kannus et al., 1999) and is reported to affect 15%–33% of an active adult population and 21%–45% of adolescents (Lindberg, 1986). Among adolescents, the incidence is reported to be higher for girls (Messier et al., 1991; Lindberg et al., 1986).

PFPS affects athletes and nonathletes of both genders (Messier et al., 1991) and is consistently reported in activities such as ascending or descending stairs and squatting or subsequent to long periods of sitting still (theatre or movie sign). This is regarded as the most important information in the patient's history (Galanty et al., 1994). Some authors have reported bilateral complaints in two-thirds of the patients (Vahasarja, 1995; Goldberg, 1991).

Patients commonly report that the development of their pain is insidious and that the pain is either sharp and acute or diffuse and chronic. A family history of similar symptoms may be present (Goldberg, 1991; Ficat, 1979). PFPS sometimes begins when loading of the patellofemoral joint suddenly increases. Military recruits of both genders are prone to develop PFPS (Milgrom, 1991). The true cause of PFPS is unknown, and the pain syndrome has been given various names (Study I, Table I).

Anterior knee pain (AKP)—a symptom common in traumatic and over-use knee disorders—is often used synonymously with PFPS (Study I, Table I) (Van Tiggelen et al., 2004; Lorberboym et al., 2003). Most authors regard AKP as a symptom of PFPS (Holmes et al., 1998), but the term has also been used to denote a distinct syndrome (Lichota, 2003). If no causative explanation for the pain is found, despite a thorough investigation, the term idiopathic anterior knee pain (IAKP) has been suggested (Holmes et al., 1998; Stanitski, 1994).

No consensus on inclusion and exclusion criteria has emerged in PFPS studies, and several diagnostic symptoms and tests have been proposed (Study I, Table II). Although a wide spectrum of symptoms has been reported for PFPS, the patients chosen for participation in PFPS studies have exhibited a limited range of symptoms, and different clinical tests have been used in the selection process (Cutbill et al., 1997). Because no consensus on definition, classification, assessment, or management of PFPS has been reached, it has been impossible to validate clinical tests and signs (The International Patellofemoral Study Group, 1997). PFPS is often a diagnosis of exclusion.

Although the cause of PFPS is obscure, it has been generally accepted as being secondary either to chondromalacia or to patellar malalignment. The most widely accepted theory regarding the etiology behind PFPS suggests that the symptoms are the result of excessive patellofemoral joint stress (force per unit area) due to abnormal patellar tracking, resulting in inflammatory pain (Fulkerson, 2002; Merchant, 1988). Reports, however, have questioned a causal relationship between malalignment and knee discomfort in the majority of PFPS patients (Dye, 2005; Sanchis-Alfonso et al., 2005; Arrol et al., 1997; Cutbill et al., 1997) and the phenomenon of rest pain (theatre or movie sign) has never been satisfactorily explained (Post, 2001; Reid et al., 1990). A

different etiology that takes a pain mechanism into consideration has been proposed. This new paradigm proposes that the etiology of patellofemoral pain arises from a loss of homeostasis in patellofemoral tissues (Dye, 2005).

Ischemia, caused by high intraosseous pressure, has been proposed as a plausible pain mechanism (Hejgaard et al., 1987). Studies by Bjorkstrom et al. (1980) and Slater et al. (1991) on cadaveric patellae found articular cartilage degeneration concomitant with disrupted blood supply. Using intraosseous venography, Waisbrod et al. (1980) observed that articular cartilage degeneration was accompanied by decreased venous outflow. In these studies, it was unclear whether impaired blood supply preceded or succeeded degenerative changes to the articular cartilage.

Arnoldi et al. (1975) found higher intraosseous pressure—in both the femur and the tibia—in painful knees compared with healthy knees. No mechanical explanation for the pain was found in non-arthritic subjects. Further work by the same author (Arnoldi, 1991) found a link between knee pain and intraosseous patellar pressure. Using intraosseous phlebography, Arnoldi (1991) also demonstrated that painful knees often have limited venous outflow. Badalemento et al. (1989) found cartilage capillary in-growth at the osteochondral junction in patients with chondromalacia patellae and osteoarthritis (OA).

Tissue hypoxia may serve as a trigger for the release of neural growth factors and substance P (SP). With the release of neural growth factor, hyperinnervation begins and SP-containing nerves might generate pain. Recently, Sanchis-Alfonso et al. (2005) found morphological and ultrastructural changes associated with ischemia including hypervascularization and increased vascular endothelial growth factor release in the lateral retinacula in painful patellofemoral malalignment.

Notably, even though several authors have concluded that ischemia is the main trigger for the pain in PFPS, they propose different backgrounds. Selfe et al. (2002) reviewed the growing body of evidence for the ischemia theory and concluded that we need to consider the influence of vascular malfunctions in PFPS.

In conformity with the ischemia theory, Dye et al. (1999) proposed the tissue homeostasis theory. The authors pointed out that the patellofemoral components of the knee are exposed to loads that frequently approach and often exceed the threshold for biologic tissue load acceptance and transference capability.

Merchant (1988) theorized that one subgroup of AKP was reflex sympathetic dystrophy (RSD) of the patella, which suggested that the sympathetic nervous system could be involved. Butler-Manuel (1992) also reported involvement of the sympathetic nervous system in PFPS and successfully treated his patients with sympathetic blockades.

Treatment modalities proposed for PFPS are often conservative and based on the cornerstones of physiotherapy and pharmacotherapy (pain killers or non-steroidal anti-inflammatory drugs [NSAIDs]). The basis of physiotherapy for patellofemoral problems is mostly mechanical and comprises lower limb exercises (Powers, 1998), stretches (Witvrouw et al., 2002), taping/bracing (Powers et al., 2004; McConnel, 1986), and foot orthotics (D'hondt et al., 2003). A decrease in pain has been reported following acupuncture (Jensen et al., 1999), transcutaneous electrical nerve stimulation (TENS) (Werner et al., 1993), and a reduction in activity levels (Thomeé et al., 1995).

When physiotherapy is unhelpful, various surgical techniques have been proposed to correct joint alignment (Fulkerson, 2002). Also, decompressive drilling of the patella has been suggested in cases of patellar hypertension syndrome (Miltner et al., 2003; Schneider et al., 2000; Hejgaard et al., 1984).

It is important to remember that pain in the anterior region of the knee is a frequent problem that is not always associated with a PFPS diagnosis. Posttraumatic articular injury is a common cause of anterior knee pain. Major blunt trauma to the patella may produce articular injury that results in a spectrum of anatomical manifestations from cartilage softening to osteochondral fracture. Other intra-articular problems such as loose bodies, meniscal tears, ligament ruptures, symptomatic plica semilunaris, neoplasm, and synovitis may also produce symptoms suggestive of patellofemoral pathology (Merchant, 1988).

In the peripatellar region, ligament injuries, tendinopathy, and bursitis must be excluded. Patellar tendinopathy has been reported in adolescent basketball players (Cook, 2001). Mild AKP is a common finding following anterior cruciate ligament reconstruction with a bone-patellar tendon-bone autograft (Jarvala, 2000). Among children and adolescents, apophysitis (Osgood-Schlatter disease and Sinding Larsen-Johansson disease) must be considered. Referred pain—particularly from hip pathology or lumbar radiculopathy—is another possibility (Ficat et al., 1979).

A thorough clinical examination involving the patient's history and physical and radiological examinations performed by experienced clinicians may reveal these diagnoses. Tumors, infections, or metabolic processes rarely accompany PFPS complaints but should not be disregarded (Percy et al., 1985).

This overlap among clinical syndromes combined with the present impreciseness of clinical criteria often confuses the interpretation and generalizability of clinical trials in PFPS. In the absence of any detectable pathology, anterior or retropatellar pain that is exacerbated during sustained sitting or while kneeling, ascending, or descending stairs or squatting is defined as PFPS. Dye et al. (1994) coined the term "Orthopedic Black Hole" to describe the challenging nature of patellofemoral problems.

A review of the treatment of chronic overuse sports injuries (Almekinders et al., 1994) concluded that the outcome of PFPS is significantly worse than of any other injury. Gillquist (1997) stated that basic knowledge concerning the etiology of PFPS is still sparse, and if we do not know what we are trying to treat, the outcome can only be accidentally effective. Also, the knee region is a common anatomical site of musculoskeletal pain. Self-reported knee pain has a prevalence between 7% and 19% in an adult general population of 15–75 years (Bergman et al., 2001; Urwin et al., 1998). Eleven percent of young children report incidents of everyday knee pain (Fearon et al., 1996). Even so, knee pain is reported to be the most predominant symptom in altitude decompression sickness (Ryles et al., 1996).

1.2   ANATOMICAL CONSIDERATIONS OF THE PATELLA

The patellar bone is situated anterior to the femur in the knee region. Superficially, it comprises a thin layer of cortical bone that surrounds a center composed of trabecular bone. The patella has no bone marrow cavity (Hughes et al., 1998). Anterior to the patella and deep below the skin is a trilaminar arrangement of fibrous soft tissue which

includes a transversely oriented fascia, an obliquely oriented aponeurosis, and the longitudinally oriented fibers of the rectus femoris tendon (Dye et al., 2003). All perfusion in the patella has been shown to occur via arteries descending from the popliteal artery proximal to the femoral condyles (Bonutti et al., 1998).

The patella has extraosseous (Study IV, Figure 1) and intraosseous arterial patterns (Study IV, Figure 2). The extraosseous pattern includes an anastomotic ring composed of the supreme genicular, medial superior genicular, medial inferior genicular, lateral superior genicular, and lateral inferior genicular arteries and the anterior tibial recurrent artery.

The intraosseous arteries are grouped into two main systems. The first comprises the midpatellar vessels, which enter through 10–12 vascular forminae located on the middle third of the anterior surface in an oblique direction. Bonutti et al. (1998) stated that this system supplies the dominant portion of arterial blood to the patella. The second system arises from the polar vessels through the deep inferior patellar surface upward and supplies the lowermost one-third of the patella. The arteries in this system communicate within the bone with branches of the midpatellar vessels (Gelfer et al., 2003).

Intraosseous phlebography of the patella indicates that the posterior surface of the apex patellae is the most important exit for veins that drain the patella (Arnoldi, 1991). Maralcan et al. (2005) studied the innervation pattern of patellae and found only two nerves: the medial patellar nerve and the lateral patellar nerve. The nerves accompanied the medial and lateral superior genicular arteries, respectively.

1.3   DEFINITION AND MECHANISMS OF PAIN

Pain is an important clinical issue that has a great impact on society and the well-being of individuals. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience with actual or potential tissue damage, or described in terms of such damage" (Mersky et al., 1994). Accordingly, pain is a complex, multi-dimensional phenomenon including sensory-discriminative, cognitive-evaluative, and affective-motivational components. Thus, pain is always subjective and for that reason a challenge to study.

It is important to remember that although acute pain (nociception) fulfills an important warning role, intermittent and chronic pain states are maladaptive. Inflammatory (homeostatic) pain may include specific symptoms such as *allodynia,* which is defined as pain due to a stimulus that does not normally provoke pain, and *hyperalgesia,* a heightened response to a stimulus that is normally painful (Table 1).

Table 1. Clinical classification of pain (Woolf, 2004).

Nociceptive pain	-	transient pain in response to noxious stimulus
Inflammatory (homeostatic) pain	-	spontaneous pain, allodynia, and hypersensitivity to stimulus in response to homeostatic reactions (inflammation)
Neuropathic pain	-	spontaneous pain and hypersensitivity to stimulus in association with damage or a lesion of the nervous system
Functional pain	-	hypersensitivity to pain resulting from abnormal central processing of normal input

In general, heightened sensitivity to any stimuli can be caused by several different mechanisms (Scott et al., 2004). Tissue trauma—and the ensuing inflammatory reaction—induces peripheral sensitivity to mechanical stimuli. This is a complicated process involving the vascular, the immune, and the sympathetic nervous systems, which will induce changes at several levels: the molecular, the cellular, and the physiological as well as the clinical (Figure I).

It has been suggested that the term *inflammation* should be re-defined to indicate the total cascade of events that participate in the re-establishment of homeostasis (Scott et al., 2004). Also, Woolf (2004) suggests that *inflammatory pain* be defined as pain that promotes the healing of injured tissue and thereby homeostasis. Likewise, Craig (2003) proposed that pain in humans is a homeostatic emotion reflecting an adverse condition in the body.
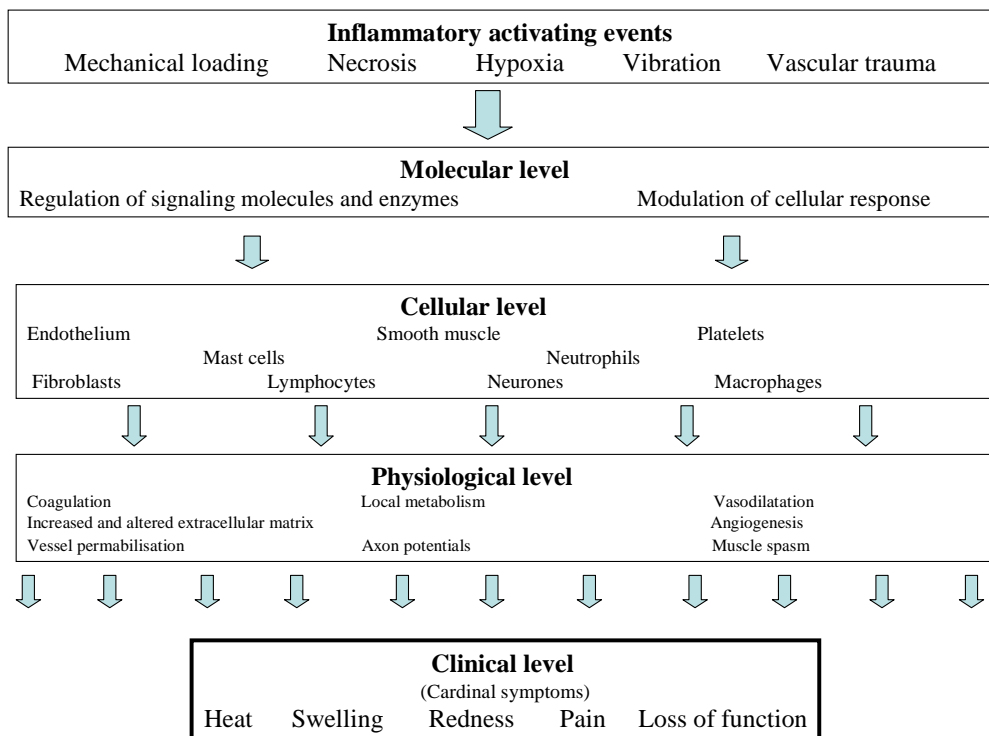

Figure 1. *Inflammation* is an umbrella term encompassing physical findings at four levels: molecular, cellular, physiological, and clinical (Scott et al., 2004).

Joint pain is often caused by peripheral mechanisms, but that the central nervous system (CNS) may play a role should not be ruled out. Bilateral sensory changes have been reported in both knee and hip OA as well as in tennis elbows (Slater et al., 2005) and support the notion that joint pain has central components. The articular capsule, tendons, ligaments, synovium, and periosteum are richly innervated. The receptors respond to mechanical stimuli but also to chemical mediators.

The sensation of pain originating from bone tissue is poorly understood, although it is believed to mostly depend on the activation of nociceptors in the periosteum and in other tissues surrounding joint surfaces. It is unclear if a change in remodeling activity in bone tissue causes pain. Probably, the stress that is responsible for the remodeling—ischemia, axial loading, or high intraosseous pressure—induces the pain. This suggestion is supported by findings that pain in the subchondral bone can be caused by dynamic metabolic adaptations such as increases in bone turnover and remodeling (McCarty, 1997; Dye et al., 1986).

1.4 BONE BLOOD FLOW

The primary function of the cardiovascular system is to maintain a stable environment for tissue. In most tissues, capillary flow exclusively serves nutritional needs. In a few tissues, however, much of the capillary flow is non-nutritional and plays a key role in temperature regulation (Levick, 2000). Little knowledge of how microcirculation in bone tissue is regulated is available.

Bone remodeling is partly stimulated by the intraosseous fluid, which in turn depends on blood perfusion. Blood vessels are an important component in bone formation and maintenance, and bone tissue differentiation is related to the local presence of blood vessels (Kleinheinz et al., 2005). Bone is also a hematopoetic tissue and for that reason critically linked to blood perfusion.

Determinations of skeletal blood flow are not easily made in humans. Different methods measure different levels in the circulatory system, such as limb blood flow or local microcirculation. Blood flow in bone tissue has been indirectly measured using bone scintigraphy (BS) (Dye et al., 1993), single-photon emission computed tomography (SPECT) (Gelfer et al., 2003), Doppler ultrasonography (Lustig et al., 2003), the microsphere method (Anetzberger et al., 2004), and positron emission tomography (PET) (Iida et al., 1999). Direct measurements have been made using laser Doppler flowmetry (LDF) (Hughes et al.,1998; Notzli et al., 1989) and the intravital microscope television system in combination with confocal laser-scanning optics (Loaisa et al., 2002), but these techniques require surgical manipulation of the bone and may therefore produce artifacts attributable to local manipulation of the vessels.

Estimations of blood flow in the extremities have been made using an index of blood pressure measurements in the arm and leg (Weitz et al., 1996). Near-infrared spectroscopy has been used to determine a perfusion index in the tibia bone marrow (Binzoni et al., 2003). At present, however, no method is able to measure local blood flow in human bone tissue continuously and non-invasively.

1.5 HYPOXIA AND ISCHEMIA

Hypoxia is a pathological condition in which the body as a whole (generalized hypoxia) or in part (tissue hypoxia) is deprived of an adequate supply of oxygen. Hypoxia could be the result of a reduced supply of arterial blood or venous stasis (ischemic hypoxia), insufficient oxygen saturation (hypoxic hypoxia), or low hemoglobin (anemic hypoxia). The condition can have profound influences on circulation, but hypoxic vascular responses are not uniform across vascular beds.

Whether net vasoconstriction or vasodilation occurs in a vascular bed is dependent upon the balance between the local effects of hypoxia and changes in the neural and hormonal control of vascular tone. Considerable evidence demonstrates that this balance is dependent on species, vascular region, and the degree of hypoxia (Halliwill, 2003). In humans, during moderate hypoxia, the cerebral and coronary vascular beds undergo vasodilation. Hypoxia has the opposite effect in the lungs that it has in systemic circulation and is thus responsible for pulmonary vasoconstriction.

Ischemia is an absolute or relative shortage of blood supply caused by constriction or blockage of the blood vessels supplying or draining the tissue. An imbalance between oxygen demand and oxygen supply in the tissues is followed first by anaerobic metabolism and then by acidosis. Apart from effects on respiration and circulation, ischemia leads to sensitization of nociceptors, spontaneous pain, and mechanical allodynia (Birklein et al., 2000).

In bone, ischemia sometimes stimulates remodeling and neovascularization. It has been shown that exposure to intermittent normobaric hypoxia results in distinct tissue remodeling (Rakusan et al., 1999). Prolonged ischemia may cause cell death. Ischemia is reported to be responsible for osteonecrosis. Osteoporosis (OP) and OA are also reported to be linked to atheromatous vascular disease (Conacan et al., 2005).

2 OBJECTIVES

2.1 GENERAL GOALS

Underlying the diagnostic process is the assumption that a clinical diagnosis represents an accurate and concise summary of specific signs and symptoms. The diagnosis should reflect the etiology of the disorder or—when the etiology remains elusive—reflect the most meaningful clinical description of the state of the patient. Clinical diagnoses of pain syndromes are common and sometimes only based on anatomical location, as in lumbago or PFPS. The overall purpose of this thesis was to explore possible pain mechanisms in PFPS. A mechanism-based classification of pain could have profound implications for diagnosis and treatment.

2.2 HYPOTHESIS AND AIMS

Study I   We hypothesized that patients given the diagnosis of PFPS often have other differential diagnoses. Our aims were to compare symptoms and clinical findings in groups of individuals with PFPS and knee-healthy subjects.

Study II   We hypothesized that sensory stimulation will have a pain-relieving effect in PFPS. Our aim was to investigate whether acupuncture decreases pain, changes skin temperature, and improves physical function.

Study III   We hypothesized that the metabolic activity in the bone tissues of PFPS patients is disturbed. Our aims were to determine whether bone scintigrams show diffuse uptake and in what bony compartments of the knee region the uptake was localized.

Study IV   We hypothesized that photoplethysmography could be used to study pulsatile blood flow in bone tissue. Our aim was to evaluate a new PPG probe for measuring blood flow in the patellar bone.

Study V   We hypothesized that flexing the knee joint would interfere with the blood flow in the patellar bone of PFPS patients. Our aim was to compare pulsatile blood flow in the patella of patients with the same in the patella of knee-healthy controls.

3 SUBJECTS

Table II. Subjects in this thesis.

Study	Participants n (women/men)	Mean age years (SD)
I		
Group A (IAKP)	29 (19/10)	34 (9)
Group B (slow bone turn over)	29 (15/14)	34 (9)
Group C (diagnoses of pathology)	17 (12/5)	39 (10)
Group D (controls)	48 (30/18)	31 (8)
II		
PFPS (Group A and B in Study I)	58 (34/24)	34 (9)
III		
PFPS (Group A and B in Study I)	58 (34/24)	34 (9)
IV		
Knee-healthy controls	20 (8/12)	38 (9)
V		
PFPS	22 (13/9)	33 (11)
Knee-healthy controls	33 (15/18)	36 (10)

PFPS patients

Inclusion criteria:

1. *Age 20–50 years.* To avoid difficulties in differentiating between PFPS, late symptoms of apophysitis, and early symptoms of OA, patients between the ages of 20 and 50 years were chosen.

2. *Pain duration > 6 months.* Pain duration of more than 6 months has been proposed as a reasonable length in studies on PFPS (Cutbill et al., 1997).

3. *No functional (symptomatic) instability.* Instability may denote other pathology.

4. *Clinical examination finds no causative explanation for the pain.* PFPS is clinically a diagnosis of exclusion.

Exclusion criteria:

Patients were excluded if the clinical examination revealed any symptoms suggesting other pathology of the knee joint such as ligament or meniscus tears, synovial plica, tendinopathy, apophysitis, OA, neuroma, fat pad impingement, or patellar instability. Patients were also excluded if they had any previous injuries or operations in the leg or had received any treatment for the pain the last 12 months except for commonly used pain killers such as paracetamol or NSAIDs.

Controls

The healthy controls were selected from visitors to a health club. These subjects were age- and sex-matched as closely as possible with the patient groups. Potential control

subjects were excluded if they had had any experience of knee pain in the last 6 months or a history of previous knee trauma or surgery in the lower leg.

4 METHODS

4.1 STUDY DESIGN

Study I

Eighty patients who fulfilled the inclusion and exclusion criteria underwent a radiographic examination. Five patients dropped out before the radiographic examination due to the following: spontaneous pain relief (2), a rejection of further examinations (2), and a move out of the region (1). The radiographic examination of the 75 subjects revealed pathology in 15 of the patients. Scintigraphy was performed in the remaining 60 patients, and 2 patients had pathological focal uptake. Diffuse uptake on scintigraphy appeared in 29 patients, leaving 29 patients with IAKP.

Once the radiological examination was completed, the subjects were divided into three groups and a clinical examination comprising a patient history and a clinical test was performed. Crossley et al. (2001) and Cutbill et al. (1997) have summarized commonly used clinical symptoms and tests, and the ones proposed by Bizzini et al. (2003) were adopted (Study I, Figure 1). No radiological examinations were made in the control group.

Study II

Fifty-eight patients who fulfilled the inclusion and exclusion criteria were randomized into either an electro-acupuncture (EA, 30 subjects) or a minimal superficial acupuncture (28 subjects) group for 15 treatments taken twice a week. Skin temperature measurements were made before and after every treatment. All patients recorded their highest experienced pain on a visual analog scale (VAS) daily at bedtime, starting 2 weeks before the first treatment and continuing through the treatment period of 7–8 weeks. At 3 and 6 months, the patients were again asked to make VAS recordings for 2 weeks to follow up their progress. Before the first and the last treatment, patients were tested functionally on Ergo Power (Bosco, 1995) and asked to fill in Tegner's activity score (Tegner et al., 1985). They were told to continue with their normal life activities during the treatment and follow-up periods and to report any drugs taken.

Study III

Fifty-eight patients with PFPS underwent scintigraphy. Static anterior and lateral images of both knees were obtained using a gamma camera 3 hours after injection of 550 MBq of ^{99m}Tc-HMDP. The scans were visually evaluated blindly and separately by two experienced radiologists who then reached a consensus.

Study IV

Twenty healthy normotensive subjects with no history of knee pain were recruited to participate in this study. All PPG recordings were made on one single occasion. The subjects were supine in a quiet room with moderate light and a room temperature of 23ºC (±1º). The PPG probe (Study IV, Figure 4) was placed over the center of the patella and attached to the skin with adhesive tape (Study IV, Figure 5). After 15 min of rest, blood flow was recorded continuously from 60 s prior the interventions to 5 min after. Blood flow was measured with the knee fixed at 20º of flexion using a vacuum pillow (AB Germa, Sweden) during all interventions. All interventions and

measurements were made by one of the authors (JN). The PPG signal was analyzed by one of the authors (LGL) who was blind to the subjects and recording conditions.

To help elucidate the interaction of the PPG signal with blood in motion, an *in vitro* study of the PPG signal in a rigid tube was performed. The rigid flow-through model consisted of a hole (diameter 2 mm) drilled in a piece of acrylic glass (polymethylmethacrylate [PMMA]). The measurements were made using blood from 12 healthy blood donors with hemoglobin (Hb) concentrations ranging from 116 to 162 g/l. The blood circulated in a silicon tubing system described earlier (Lindberg et al., 1993). A waveform generator regulated a roller pump (Mekaneljo, Sweden) that simulated a pressure waveform which closely resembled human pulsatile blood pressure (Lindberg et al., 1993; Borgström, 1981). Blood flow in ml/min was determined by collecting the blood for 60 s at each pressure level. Measurements were made with both whole blood and hemolyzed blood.

Study V

Twenty-two PFPS patients and 33 controls were supine in a quiet room with moderate light and a room temperature of 23ºC (±1º). The PPG probe was placed over the center of the patellar bone and attached to the skin of the leg with double-sided adhesive tape. After the subject had rested for 15 minutes with the knees flexed 20°, blood flow was recorded continuously from 1 minute before until 5 minutes after a passive knee flexion to 90°. Blood flow was measured with the knee fixed at both 20º and 90º of flexion using a vacuum pillow.

An analyzing software (Daquhura 1.3, Linköpings Tekniska Högskola), measured the mean amplitude of the PPG signal before (baseline) and after passive knee flexion. All measurements were made by one of the authors (JN). The PPG signal was analyzed by a second author (LGL) who was blind to the origin of the recordings. One measurement was made on each knee.

4.2   CLINICAL EXAMINATION

(Studies I, II, III, and V)

The clinical examination comprised a patient history and clinical tests. Crossley et al. (2001) and Cutbill et al. (1997) have summarized commonly used clinical symptoms and tests, and we adopted the ones proposed by Bizzini et al. (2003) and Gerrard (1989).

Patient history:

Patients were asked about the onset and duration of their pain and about pain-provoking events—that is, activity-induced pain, pain on climbing the stairs, pain after sitting for a long time, and pain when squatting.

Clinical tests:

Compression test: With the subjects in a supine position, the examiner compressed the patella towards the femur while the patient held the quadriceps muscle relaxed and the knee was extended. The subjects were asked to report any experience of pain during the compression.

Medial and lateral tenderness: With the subjects in a supine position, the quadriceps relaxed, and the knee extended, the examiner palpated the medial and lateral borders

of the patella for local tenderness. The subjects were asked to report any experience of pain during the palpation.

Passive gliding of the patella: With the subjects in a supine position and the quadriceps relaxed, passive gliding of the patella medially and laterally was investigated. The subjects were asked to report any experience of pain during the gliding.

Quadriceps angle: With the subjects in a supine position, the quadriceps relaxed, and the knee extended, a long axis goniometer was used to measure the quadriceps (Q) angle from the spina iliaca anterior superior (SIAS) to the middle of the basis patella and from there to the tibial tuberosity.

4.3   RADIOGRAPHY

(Studies I, II, III, and V)

Standard anterior and lateral radiographic views together with an axial patellar view were taken of PFPS patients. For ethical reasons, the controls were not examined radiographically.

4.4   SCINTIGRAPHY

(Studies I, II, III, and V)

Bone metabolism and bone remodeling can be evaluated by specific bone-seeking radionuclides in a scintigraphic measurement (Study III, Figure 1). A positive BS indicates an increase in bone metabolism, but the method cannot determine whether the final result will be a net loss or a net gain in bone. A pathophysiologically elevated BS indicates an etiological relationship between the area with increased bone metabolism and the patient's symptoms. To manifest metabolic characteristics topographically, one must use a metabolically orientated modality such as Tc-99m scintigraphy or histologic examination of tissues.

BS can distinguish between localized skeletal conditions—such as stress fractures in the bone—and diffuse increased bone turnover. BS has been suggested as one method that can be used in the evaluation of patients with PFPS because it depicts physiological features whereas radiography presents biomechanical information (Dye, 1993; Hejgaard et al., 1987). Studies have reported tracer uptake to occur in the tibiofemoral compartment, the patellar compartment, or both (Boegard et al., 1999; Dye et al., 1986).

One dose of Tc-99m was given intravenously (550 MBq of ^{99m}Tc-hydroxymethylene diphosphonate [HMDP]) and allowed to concentrate in the bone. Anterior and lateral static images were made of both knees with a gamma camera 3 hours after the injection. The scans were visually evaluated blindly and separately by two experienced observers who then reached a consensus. They assessed the degree of localized uptake as one of the following: normal, diffusely increased, and focal. The controls were not examined scintigraphically for ethical reasons.

4.5   PHOTOPLETHYSMOGRAPHY

(Studies IV and V)

The PPG technique in reflection mode requires a light source and a photodetector (PD) placed adjacent to each other. The beam of light is directed toward the part of tissue in which blood flow is to be measured. The emitted light is reflected, absorbed, and scattered within the tissue, and only a small fraction of the emitted light is received by

the PD. The intensity of the reflected and scattered light is recorded by the PD and assumed to be related to blood flow changes occurring underneath the probe (Lindberg et al., 1991). The depth to which light penetrates a tissue is primarily a function of wavelength and the optical geometry of the probe but also of the optical qualities of the tissues of interest.

The electric signal detected by the photoplethysmograph consists of a steady component (DC)—which is related to the relative vascularization of the tissue—and a pulsatile component (AC)—which is synchronous with the pumping action of the heart. The amplitude of the heart-synchronous AC component is thought to be correlated with the blood flow under the probe (Kamal et al., 1989).

It has mostly been suggested that the AC component is related to pulsatile volume changes due to variations in the lumen size of the vessel (Challoner, 1979). However, recordings from rigid tissues have shown pulse-synchronous PPG signals (Sakamoto et al., 1979), and the pulsatile component of PPG recordings of the dental pulp has been used to detect blood flow and viability in teeth (Miwa et al., 2002). Moreover, it has been demonstrated in *in vitro* models that light transmission and reflection in blood can change with velocity, even if the volume of the illuminated blood is constant (Lindberg et al., 1993). Therefore, it has been postulated that both the AC and the DC components in PPG recordings depend on red blood cell (RBC) orientation and axial migration (Graaf, 1993; Lindberg et al., 1993). Such changes in RBC orientation are known to occur as a function of flow and shear ratio (for review see Fujii, et al.).

The technique used in Studies IV and V was based on assumptions outlined in Figure 3 (Study IV), which schematically illustrates the photon distribution in the patella. A two-channel PPG instrument (Department of Biomechanical Engineering, Linköping University, Linköping, Sweden) and a PPG probe were used to continuously record blood flow changes in the skin and the patellar bone. This newly designed probe for measurements of the patella (Study IV, Figures 4–5) contains one near-infrared light-emitting diode (LED) at 804 nm for deep tissue, two green light LEDs at 560 nm for monitoring blood flow at a depth of ~1 mm (skin) and one PD. All optical components were embedded in black-colored silicon.

The signals from each wavelength were processed in an amplifier and stored on a personal computer (PC). The pulse-by-pulse amplitude of the AC component of the PPG signal at each wavelength was subsequently extracted with a dedicated software (Daquhura 1.3, Linköpings Tekniska Högskola). Mean amplitudes were computed from a series of 20 consecutive pulsations before (baseline), during, and after the interventions.

4.6   PAIN ASSESSMENT

(Study II)

The VAS was used to assess pain intensity. Patients were asked to rate their maximum pain level on a 100-mm horizontal line between the anchor points 0 (no pain at all) and 100 (unbearable pain).

All patients recorded their highest experienced pain on a VAS daily at bedtime, starting 2 weeks before the first treatment and continuing through the acupuncture treatment

period of 7–8 weeks. At 3 and 6 months, the patients were again asked to make VAS recordings for 2 weeks to follow up their progress.

4.7 SKIN TEMPERATURE

(Study II)

Sympathetically mediated pain has been shown to be associated with temperature abnormalities (Jeracitano et al.,1992), and skin temperature has been used as an indirect indicator of autonomic activity after different types of sensory stimulation (acupuncture, TENS) (Dyrehag et al., 1997). In addition, skin temperature measurements have been used in the assessment of patellofemoral arthralgia (Devereaux et al., 1986) and PFPS (Ben-Eliyahu, 1992).

To study a possible involvement of the sympathetic nervous system, we decided to register skin temperature (Dyrehag et al., 1997). The PFPS patients—resting supine with the lower extremities bare—were acclimatized in a draft-free, temperature-controlled room (24ºC –25ºC) for at least 15 min before skin temperatures were recorded with a non-contact infrared thermometer (Raytek PM Plus, accuracy 0.1ºC). The distance between the sensor and the skin was fixed at 100 mm to give a spot area diameter of 24 mm.

Temperature was measured at three locations on each leg: the distal end of m. rectus femoris, the patella, and the midpoint on the anterior tibial muscle. Skin temperature measurements were made before and after every acupuncture treatment.

4.8 EXPLOSIVE MUSCLE PERFORMANCE TEST

(Study II)

The ability to jump vertically on one leg was measured on Ergo Power (Study II, Figure 1). The best attempt out of three was recorded. No warm-up exercises were allowed before the test, which was to resemble activities of daily living. Patients were tested before the first and last treatments.

Ergo Power precisely measures load displacements of any machine by using gravitational loads as external resistance (for example, the leg press and lattissimus dorsi machines). The platform displacements were monitored using simple mechanics and a sensor arrangement. The platform was mechanically linked to a shuttle, which glided on a track bar. The sensor consisted of two infrared photo interrupters locked on the shuttle and facing an optical code strip stuck to the track bar. The two outputs from the sensor were phase shifted by 90° to detect the direction of movement (up or down).

The sensor was interfaced to an electronic device, which included a microprocessor and software. The resolution of the microprocessor was 10 µs. When the shuttle was moved by the subjects, the signal from the optical transducer interrupted the microprocessor after each 3 mm of displacement. Thus, it was possible to calculate velocity, force, power, and work corresponding to the platform displacements.

The device has been validated (Bosco et al., 1995), and day-to-day reproducibility gave a correlation coefficient of $r = 0.88$, 0.97, and 0.95 for average push-off force (AF), average push-off velocity (AV), and average push-off power (AP), respectively. In any one case, the maximal error in the measurement system was calculated to be less than 0.3%, 0.9%, and 1.2% for AF, AV, and AP, respectively.

4.9 ACTIVITY LEVEL

(Study I, II)

Tegner´s activity score was used to assess levels of *work* and *sport* activity (Tegner et al., 1985).

4.10 ACUPUNCTURE

(Study II)

Acupuncture belongs to traditional Chinese medicine (TCM), an empirical system that has been used in the treatment of pain for centuries. That acupuncture is valuable in the relief of pain is supported by clinical trials, but studies that consider the etiology of the pain being investigated are sparse. The effects of acupuncture on pain must necessarily result from physiological or psychological mechanisms that have biological foundations. Acupuncture and some other forms of sensory stimulation elicit similar effects in man and other mammals, suggesting that sensory stimulation causes fundamental physiological changes.

Acupuncture excites receptors or nerve fibers in the stimulated tissue—which can also be physiologically activated by strong muscle contractions—and the effects are similar to those obtained by protracted exercise (Andersson et al., 1995). Both exercise and EA produce rhythmic discharges in nerve fibers; cause the release of endogenous neurotransmitters including opioids, monoamines, and oxytocin; and regulate the sympathetic nervous system (Andersson et al., 1995). Acupuncture also results in the peripheral release of sensory neuropeptides with vasodilatory properties (Blom et al., 1992). In an uncontrolled study, acupuncture had a significant and long-lasting effect in reducing pain and improving function for patients with PFPS (Jansen et al., 1999).

Patients were randomized into either the EA group (group A, 30 subjects) or the minimal superficial acupuncture group (group B, 28 subjects) for 15 treatments, 2 treatments each week. Group A received 2-Hz, constant biphasic square pulses with a pulse-width of 180 µs (Acus, Cefar Medical AB, Lund Sweden) at six acupuncture points in the knee region (Study II, Figure 2). The acupuncture points used were chosen according to a Western approach—that is, based on anatomic and neurophysiologic considerations (Thomas et al., 1996)—and are all points that are commonly used in the knee region. Before the cables were connected, the needles were twirled to evoke the sensation of "de Qi", which is often described as a sensation of tension, numbness, tingling, or tenderness. The stimulator delivered pulses at an intensity strong enough to evoke muscle twitching, just below the pain threshold.

Group B was treated with superficial minimal acupuncture, that is, six needles were inserted subcutaneously in the knee region 1 inch away from the traditional points but still in the same dermatome. No "de Qi" sensation was evoked in this group. The cables were connected to the handles of the needles, but the electrical stimulator was manipulated in such a way that no stimulation was given.

Disposable, sterile stainless acupuncture needles (Hegu Svenska AB), 0.3 mm in diameter and 30 mm long in group A and 0.15 mm in diameter and 15 mm long in group B were used. Treatment time in both groups was 30 min. All treatments were performed by two physiotherapists with 15 years of almost daily clinical experience in acupuncture treatment. Their training with Chinese teachers was western-orientated.

5 STATISTICS

Table III presents data levels and the statistics used in the different studies. The mean and standard deviation (SD) were calculated for quantitative variables (anthropometric data, pain duration, Q angle, and blood pressure) and the median approach was used for skewed distributions and for categorical data (PPG recordings, Tegner's activity score, VAS, and presence of pain). All tests used were two-sided and at the 5% level of significance. All data were analyzed with Statistica 6.0 (StatSoft, Inc, USA).

Study I

To determine the overall level of significance, the chi-square test was used to study differences for ordinal categorical data. This analysis was followed by pairwise post-hoc comparisons and the chi-square test. For quantitative values, the Kruskal-Wallis test was used to test between all four populations. In corresponding post-hoc comparisons, the Mann-Whitney U test was used to test between pairs. Sensitivity and specificity for the clinical tests were calculated in a 2 x 2 contingency table.

Study II

Sign test was used to test for systematic differences concerning change over time. Friedman's ANOVA was used to test for systematic differences between more than two repeated observations and Mann-Whitney to test for systematic differences between two independent groups at one time point. The Friedman's ANOVA for repeated measurement (time) was also used to analyze continuous data (temperature).

Study III

Data are presented as binomial: diffuse uptake or no diffuse uptake.

Study IV

Differences in blood flow between individual pairs, based on assessments before and after intervention, are expressed in percent of resting values. The Wilcoxon paired signed rank test was used to test differences between blood flow in the skin and bone tissue. In the physical model, the correlation coefficient (Matlab 7.0) was used to assess the association between the PPG signal and blood pressure.

Study V

For statistical analysis, the mean value of the individual bilateral measurements was used. Differences in blood flow between individual pairs of measurements—based on assessments before and after passive knee flexion to 90°—are expressed in percent of resting values, and the results are presented as medians and interquartile ranges. The Mann-Whitney U test was used to analyze differences in blood-flow signals between patients and controls. The joint distribution of paired measurements of PPG recordings is illustrated in a scatter plot (Study IV, Figure 1a-b).

To further calculate the systematic change between recordings, the method by Svensson (1998) was adapted. A distribution that differs between two recordings—so-called marginal heterogeneity—suggests systematic change. Systematic change can be quantified by measuring the relative position (RP). The possible values for RP range between -1 and +1. Values close to zero represent a negligible change from one session to another; a positive value for RP indicates a systematic change from a lower to a

higher value and a negative RP a change from a higher to a lower value. SYSRAN 1.0 for Matlab 6 was used to calculate RP and its corresponding 95% confidence interval.

Table III. Study designs and statistical methods

	Design	Variable	Assessment	Data level	Statistics
I	Observational Cross-sectional	Presence of pain	Yes/no	Dichotomous	Chi-square test
		Activity level	Tegner´s activity score	Ordinal, category	Kruskal-Wallis
		Alignment	Quadriceps angle	Continuous quantitative	Mann-Whitney
II	Randomized Controlled Trial	Pain intensity	VAS	Ordinal, category	Sign test Chi-square test
		Activity level	Tegner´s activity score	Ordinal, category	Friedman's ANOVA Mann-Whitney
		Vertical jump	Ergo power	Continuous quantitative	Sign test
		Skin temperature	Thermometer	Continuous quantitative	Friedman's ANOVA
III	Observational Cross-sectional	Osteoid mineralization	Bone scintigraphy	Dichotomous	Descriptive
IV	Methodological	Blood flow	Photoplethysmography	Continuous quantitative	Wilcoxon signed rank test
			Pulsatile pressure	Continuous quantitative	Pearson's correlation coefficient
V	Observational Cross-sectional	Blood flow	Photoplethysmography	Continuous quantitative	Mann-Whitney Relative position

VAS = visual analogue scale; ANOVA = analysis of variance

Ethics
All patients and controls participated voluntarily and gave their written, informed consent to participate in the studies, which were approved by the research ethics committee of the Faculty of Medicine at Lund's University

6 RESULTS

Study I

The main finding in our first study on PFPS was that patients who had been clinically diagnosed with the syndrome on two occasions and by different physicians may still have other diagnoses that are undetectable from the patient's history or from commonly used clinical tests. Radiography and a thorough clinical examination are adequate for a diagnosis of PFPS and will exclude serious pathology.

Patient history

Group D (the control group) experienced no pain in any of the pain-provoking activities and differed significantly from all patient groups in the symptoms reported. All differences in symptoms between groups A, B, and C were non-significant (Study I, Table IV).

Activity score

In Tegner's activity score, group D reported higher levels in *sport* activities than did groups A, B, or C (Study I, Table IV and Figure 2). There was no difference in *work* between groups. Differences between groups A, B, and C in *sport* and *work* activities were non-significant.

Clinical tests

Group D differed significantly from groups A, B, and C in all clinical tests: the compression test, medial and lateral tenderness, passive gliding of the patella, and the Q angle (Study I, Table IV). Group D had a mean Q angle of 10º, which differed from group A (14º), B (15º), and C (14º) (Study I, Table IV and Figure 3). Differences in clinical tests between groups A, B, and C were non-significant.

The sensitivity of the clinical tests to differentiate between groups B and C ranged from 0.29 to 0.83 and the specificity from 0.17 to 0.69 (Study I, Table V), indicating that these tests could not predict findings in radiographic examinations.

Study II

This study showed that patients with IAKP benefit from both EA treatment and subcutaneous needling. The pain-relieving effect remained for at least half a year (Study II, Figure 4).

The skin temperature at three locations in the leg was consistent with recordings in healthy subjects (Uematsu et al., 1988). The temperature was overall highest in the lower leg region, lowest in the knee region, and unchanging between the first and fifteenth treatments.

During each treatment session there was a small but non-significant increase in temperature. This increase in temperature was significantly less during the first and last treatments compared with all other treatments.

Functional testing on Ergo Power showed no increases in any of the parameters (height, velocity, power, or force) after acupuncture treatment, and there were no differences between the treatment groups (Study II, Figure 3). Initial testing revealed no differences

between the right and left leg. Tegner's activity score did not change in any of the treatment groups, neither for *work* (median 3, range 1–4) nor *sports activities* (median 3, range 2–5).

Study III

The study comprised 109 painful knees. Of the 58 patients who participated, 7 experienced unilateral pain and 51 bilateral pain.

Diffuse uptake on BS was found in 48 knees (48/109, 44%) in 30 patients (30/58, 52%). In 33 knees, uptake occurred in only one bone compartment; in 10 knees, diffuse uptake was found in two bone compartments; and in 6 knees, all three bone compartments (the distal femur, the patella, and the proximal tibia) exhibited diffuse uptake (Study III, Figure 2).

When diffuse uptake was found to occur in the bony compartments, the patella was the bone that was most affected. Of the 48 affected knees, uptake in the patella was found in 27, uptake in the proximal tibia in 25, and uptake in the distal femur in 19. Uptake in the femur and the tibia only occurred in the condyles.

None of the scintigrams of the seven patients who reported unilateral pain exhibited diffuse uptake at non-painful sites.

Study IV

1. *Vascular occlusion of skin tissue*

The PPG signal from the skin over the patella (560 nm) was blocked after local pressure (100 mm Hg) was applied to the area. The signal from the patellar bone (804 nm) showed some influences from the skin occlusion but was not significantly decreased ($P = 0.63$). There was a significant difference between the signals from the two tissues ($P < 0.001$) (Study IV, Figure 7a).

2. *Venous occlusion*

During venous occlusion, a significant decrease in both signals was found (bone, $P < 0.001$; skin, $P = 0.001$). The signal from the skin tended to decrease more than that from bone ($P = 0.052$) (Study IV, Figure 7b).

3. *Arterial occlusion*

The PPG signals from the skin and the patella were absent during arterial occlusion. After the pressure was released, a significant increase, compared with baseline, was seen in the signal from the patella ($P < 0.001$) but not from the skin ($P = 0.54$), and the difference between the signals from the two tissues was significant ($P = 0.02$) (Study IV, Figure 7c).

4. *Application of liniment.*

After liniment was applied, the PPG signal from the skin increased significantly ($P < 0.001$) while the increase in the signal from the bone was nonsignificant ($P = 0.07$). There was a significant difference between the signals from the two tissues ($P < 0.001$) (Study IV, Figure 7d).

5. *In vitro study of the PPG signal in a rigid tube*

Figure 8 in Study IV shows relative changes in the PPG AC signal when the pulsatile pressure was varied between 0 and 100 mm Hg, superimposed on a constant diastolic pressure of 70 mm Hg and at a constant frequency of 1 Hz (corresponding to 60 beats/min). The blood flow (ml/min) through the rigid tube varied linearly with the intra-tube pressure (Study IV, Figure 9). The experiments were performed using both whole and hemolyzed blood from the same donors. With whole blood, the PPG AC signal varied with the pressure pulse. When the values from PPG AC recordings were plotted against the pulsatile pressure, the correlation coefficient was 0.82. With hemolyzed blood, no pulsatile signals were recorded.

Study V

As the knee was flexed from 20° to 90°, blood flow was found to systematically decrease among the patients—RP = -0.32 (95% CI -0.48 to -0.17)—while no such systematic change was found in the control group—RP = 0.17 (95% CI -0.05 to 0.31). These changes in pulsatile blood flow during flexion differed significantly between the groups ($P < 0.0002$) (Study V, Figure 2).

7 DISCUSSION

From this thesis we conclude that patients with a clinical diagnosis of PFPS may also have other diagnoses that cannot be detected from the patient's history or from commonly used clinical tests. We also found that the patients could be divided into different subgroups according to radiological findings. The pain experienced by the patients decreased after acupuncture treatment, and the pain-relieving effect remained for at least half a year. The skin temperature, the ability to jump on one leg, and the activity level remained unchanged despite decreased pain levels. Further, we showed that diffuse uptake on scintigraphy is present in half of PFPS patients and can occur in all bony compartments of the knee. We have also shown that pulsatile blood flow in the patellar bone can be studied with a new PPG probe and that pulsatile blood flow in PFPS patients is markedly reduced when the knee is being flexed to 90º. Taken together, our results support the notion of an ischemic mechanism in PFPS.

7.1 CLINICAL SIGNS IN PFPS

To diagnose our PFPS patients, we used typical criteria which included experiences of pain when ascending or descending stairs, when squatting, or during or following a prolonged period of sitting. This agrees with many authors who used the same pain-provoking activities in their inclusion criteria for PFPS (Bizzini et al., 2003; Gerrard, 1989). Galanty et al. (1994) reported 95% sensitivity to pain from these activities. Crossley et al. (2001) found in a systematic review that, in general, PFPS was defined as the presence of pain around the patella in association with activities that load the patellofemoral joint.

Traditionally, validity is defined with reference to some *gold standard*. The challenge in many medical disorders is the absence of such a gold standard that unequivocally indicates the presence or absence of the disorder. Often no prototypic sign or symptom defines the presentation of a given disorder, and in PFPS there is no such set of signs and symptoms, because the term is merely an umbrella concept covering a multitude of conditions (Study I, Table II). AKP is, likewise, no more a diagnosis than "anterior shoulder pain". Accordingly, Grelsamer (2005) suggested that these terms should be abandoned in favor of diagnoses that more accurately explain a patient's pain.

Although AKP during or following prolonged periods of sitting with flexed knees is reported to be a typical symptom in PFPS (Arrol et al., 1997), Duri et al. (1999) reported that the most consistent symptom of another diagnosis, jumper's knee, was a feeling of deep-seated discomfort during prolonged sitting. All patients in their study on jumper's knee reported such symptoms, which suggest a low validity for the symptom *movie sign*. Pain from the knee region, while sitting with flexed knees, is also a common symptom in patients with Osgood-Schlatters disease (Shalaby et al., 1999).

For PFPS, no consensus on the definition, classification, assessment, or management has been reached (The International Patellofemoral Study Group, 1997) indicating that PFPS is to some degree a diagnosis of exclusion.

Most studies on PFPS are being performed on subjects between the ages of 20 and 50 years despite the fact that, in the clinical setting, most patients who complain of AKP are youth and adolescents. As a matter of fact, only a few PFPS studies in the literature include this age group. Among children and adolescents, apophysitis (Osgood-Schlatter

disease and Sinding-Larsen, Johansson disease) and enthesopathia must be considered. Chondrification is a physiologic process that sometimes and in certain areas of the human body (knee, hip, foot) will result in osteochondrosis. In this thesis, we have focused our research on subjects older than 20 years to avoid complications from growing bone tissues. Also, studies have reported that approximately 30% of adult PFPS patients do not benefit from commonly used conservative treatments (Kannus et al., 1999; Blond, 1998).

It is an inherent weakness of most observational studies that the sample is not representative of the population of interest. We studied patients who had been diagnosed with PFPS and referred for physiotherapy (Study I, II, and III) or referred to an orthopedic department because of unexplained knee pain and there had been given this diagnosis (Study V). In this respect, our population is representative, but they were not a random sample.

We found in our first study that none of the clinical tests used proved to be specific. Our finding questions the fact that many of the tests being used today are regarded as essential in the diagnosis of PFPS. Because clinical practice differs between clinicians, we wanted to study symptoms and clinical findings in patients with PFPS referred from different clinicians (Study I).

In a physical examination of students between 10 and 18 years, Galanty et al. (1994) reported that the only finding that was significantly related to AKP was pain during isometric contractions of the quadriceps. In their study, however, only 15 subjects were examined by two physicians. Reider et al. (1981) reported characteristic findings in different groups of patients complaining of patellar pain, but only one of the authors had examined the subjects. Harrison et al. (1996) used a questionnaire survey to study how three groups of clinicians rated the importance of 21 clinical tests related to PFPS, but no patients were examined. Nijs et al. (2005) studied five clinical tests used in the diagnosis of PFPS and concluded that only clinically irrelevant information was found and questioned the validity of the tests.

Apart from a typical patient history, the tests most commonly used to diagnose PFPS are inspections of malalignment, measurement of the Q angle, the compression test (Cutbill et al., 1997), and palpation for tenderness on the medial and lateral boarders of the patella (Crossley et al., 2002; Powers, 1998).

An exact definition of the terms patellar alignment, knee alignment, and lower extremity alignment does not exist but would be necessary as they are often used synonymously and contradictory results about malalignment have been presented (Arrol et al., 1997). When normal alignment has been examined in active, pain-free subjects, between 60% and 80% of the population falls into what is generally classed as "malalignment". This underscores an unacceptable use of this term (Post, 2001).

The Q angle was previously used not only as a sign of patellar maltracking but also—on radiographs—as an indicator of lower extremity malalignment (Post, 2001; Fulkerson et al., 1990). Messier et al. (1991) reported that a Q angle of over 20° should be regarded as maltracking of the patella. In our first study, only three persons would then have had a patellar malalignment syndrome. It must be remembered, however, that even radiographic measurements of knee alignment (Q angle) show great inter- and intraobserver variability (Ilahi et al., 2001).

Post (1993) infers that a positive compression test should be considered an indicator for malalignment of an extremity. Eighty-three percent of our patients in Study I would then suffer from extremity malalignment. Since no large population studies have been conducted to determine normal values for lower extremity alignment or patellar alignment, the presence and degree of malalignment is subjective, and what constitutes normal is under debate.

Fitzgerald et al. (1995) studied four different manual clinical tests for patellofemoral alignment where measurement reliability ranged from poor to fair. Their report indicated that such tests did not provide valid information, and they were unable to find a reliable clinical method for assessing alignment. Reid (1993) states that we have an unacceptable use of the terms that is misleading because they are applied to all variations of normal alignment in the lower limbs. As discussed above, the Q angle might no longer be regarded as reliable in diagnosing PFPS. In Study I we found a significant difference between the patient groups and the controls. The differences were, however, only a few degrees and are of limited clinical value.

The compression test is often positive and regarded as essential by some authors (Guzzanti el al., 1994; Goldberg, 1991). However, compression and apprehension tests have been reported to be positive in pain-free controls (Harrison et al., 1996). Our control group in Study I contained only one subject who had a positive compression test. This might be because our controls, who were highly active physically, were used to excessive mechanical loading.

The apprehension test is a test for patellar dislocation, and poor sensitivity has been reported (Malanga et al., 2003). Despite this, Leppala et al. (1998), Powers (1998), and Johnson et al. (1997) felt that patellar grinding and apprehension tests are characteristic clinical signs. However, the patellofemoral grinding test was intended to indicate pathological changes to retropatellar cartilage, and no studies have documented its sensitivity or specificity in the diagnosis of PFPS (Malanga et al., 2003).

Tenderness on palpation has been the method of choice for many years and in many diseases (Duri et al., 1995). In recent years, reports have been published on both poor and good inter- and intraobserver agreement for manual tests (Cook et al., 2001). This applies to palpation of pain areas in soft tissue as well as detection of joint movements and alignment (Ellenbecker et al., 2002; Johnson et al., 1997; Jacobs et al., 1995).

Holmes et al. (1998) reported that palpation for tenderness on the medial and lateral boarders of the patella together with measurements of passive gliding of the patella are highly subjective tests with no reliability. In Study I, no clinical test had both good sensitivity and good specificity. Positive findings of pain from palpation of different structures in the knee region as well as pain from provoking activities are not uncommon within other diagnoses. Taken together, these findings suggest that pain from palpation will only marginally help in diagnosing PFPS.

The only proposed diagnostic test designed to provoke ischemia is *the sustained flexion test* (Arnoldi, 1991) where the patient is asked to report pain from passively sustained knee flexion. We believe that this test deserves more attention.

7.2   IN SEARCH OF THE ETIOLOGY OF PFPS

Scintigraphy

Scintigraphy has been recommended in the evaluation of patients with PFPS and AKP because it depicts physiological features—such as bone remodeling or inflammation—while radiography yields biomechanical information such as fractures or osseous loose bodies (Dye, 1993; Hejgaard et al., 1987; Dye et al., 1986). The technique of BS allows one to define the metabolic and topographic characteristics of bone homeostasis with precision. BS has proved to be a more sensitive diagnostic modality than radiography in the evaluation of knee OA (Boegård et al., 1999).

It is not known whether the diffuse uptake observed on bone scintigrams of patients with PFPS is related to the cause or is a result of the syndrome (Matheson et al., 1987). Our patients in Studies I–III had a long history of pain (median 8 years) and low levels of activity. On the other hand, other studies have reported diffuse uptake on bone scintigraphy in 40%–55% of patients despite different inclusion criteria (Butler-Manuel, 1990; Hejgaard et al., 1987; Dye et al., 1986). This indicates that accelerated bone remodeling is present in at least half of the patients diagnosed with PFPS.

Butler-Manuel (1992) suggested that the patients suffered from RSD, a condition that sometimes exhibits metabolic changes in bone tissue, and he used sympathetic blockades in the treatment of the patients. Hejgaard et al. (1987) suggested that the diffuse uptake was secondary to high intra-medullar pressure and used decompression as the treatment.

We could speculate that the findings of diffuse uptake on bone scintigraphy may indicate regions of ischemic stress. This is in accordance with Dye et al. (1999) who suggested that the genesis of PFPS is a loss of homeostasis in the intraosseous environment of the patella and in the soft tissue of the peripatellar region in particular. The ischemia could be caused by higher intraosseous pressure (Miltner et al., 2003; Arnoldi, 1991), by redundant axial loading (Otter et al., 1999), or by decreased arterial blood flow (Kirschner et al., 1997). Interestingly, all of the bony parts that exhibited accelerated bone-remodeling in Study III have the same arterial supply.

PFPS (Dye et al., 1986), stress fractures (Murphy et al., 2002), and medial tibial stress syndrome (MTSS) (Magnusson et al., 2003) can be visualized on BS. The appearance of a mild increase in uptake on a scintigraph is an indication of the mildest form of bone stress and a sign of accelerated remodeling. Sites that are undergoing remodeling contain regions with a temporary loss of bone—as revealed by dual-energy X-ray absorptiometry (DXA)—and resemble osteopenia.

Magnusson et al. (2001) concluded that MTSS, with diffuse increases in scintigraphic uptake, is associated with low bone mineral density (BMD). Low BMD was found only in the region corresponding to the pain and to the diffuse uptake on BS, and BMD increased after recovery. Leppala et al. (1998) observed significantly lower BMD in the distal femur, the patella, and the proximal tibia of patients with PFPS. The differences were small and could have resulted from a remodeling process during the resorption phase. This is in accordance with our findings in Study III and supports our observation that the proximal tibia could be involved in PFPS.

Photoplethysmography, blood flow, and ischemia

In Study V, we found that patients diagnosed with PFPS had lower levels of pulsatile blood flow in the patellar bone when the knee was flexed, as measured with PPG. Our findings support the notion of an ischemic mechanism in PFPS. Since the PPG method is non-invasive, its advantage over invasive methods is that it can be easily used in studies on humans. To date, several angiographic studies of intraosseous blood supply in the human knee joint have been published (Iida 1999, Arnoldi 1991, Scapinelli 1967). However, these methods cannot be used to continuously study blood flow during a provocation. Iida (1999) found that ischemic bone marrow disorders such as osteonecrosis in the knee are likely to develop in areas with lower blood volume.

Disruption of the vessels supplying the patella has been shown to occur in some surgical techniques such as lateral release and during anterior cruciate ligament reconstruction with a bone-tendon-bone autograft (Bonutti et al., 1998). A higher incidence of avascular necrosis (Ritter et al., 1987) and a significant decrease in patellar radionuclide uptake on postoperative bone scans (Wetzner et al., 1985) have been reported in patients with lateral release. Use of the medial parapatellar approach means that the superior lateral genicular artery will be the only remaining vessel to provide a significant supply of blood to the patella (Brick et al., 1989). This surgical technique was found to predispose the patella to stress fractures owing to the compromised blood supply in the patellar region (Wetzner at al., 1985). Taken together, disturbances in arterial perfusion have an impact on bone metabolism in the knee joint.

Gelfer et al. (2003) used SPECT to show that postoperative transient patellar ischemia was related to clinical patellofemoral pain, and the findings support our results. The findings in our studies are also in agreement with the alternative, biologically orientated perspective of the genesis of PFPS (Dye, 2005). For the moment, we do not know whether the decrease in blood flow is causal or a consequence. Arnoldi (1991) suggested that PFPS is caused by higher intraosseous pressure due to venous stasis at the inferior pole of the patella. The venous stasis was suggested to arise during knee flexion, and the author proposed a diagnostic test, *the sustained flexion test*. The findings agree with our results where we have found evidence that patients with PFPS have a lower pulsatile blood flow when the knee is flexed to 90º.

Interestingly, Sanchis-Alfonso et al. (2000) found higher numbers of SP-containing nerve fibers in the lateral retinaculum of PFPS patients. Larger concentrations of sensory nerves containing SP are also found in newly formed vessels, and one of the most potent triggers for angiogenesis is ischemia.

Hypoxia is reported to be a major regulator of vascular endothelial growth factor in both normal tissue and tumors (Plate, 1996). Since Sanchez-Alfonso et al. (2005) reported similar findings in PFPS patients, this strengthens the suggested correlation between PFPS and ischemia. Recently, Alfredson et al. (2005) reported greater neovascularization in chronic Achilles tendinosis, another pain syndrome with unknown etiology and pathogenesis. The authors hypothesized that hypoxia might stimulate neovascularization. Sclerosis of the vessels immediately removed the pain.

Treatment effects

PFPS is generally considered to be a chronic pain condition that will respond in a positive way to different conservative treatment modalities based on the cornerstones of physiotherapy and pharmacotherapy (pain killers/NSAIDs). The focus of physiotherapy designed to treat patellofemoral problems is primarily mechanical (see *Introduction*); physiotherapy can also focus on lowering pain levels with sensory stimulation methods or by regulation of activity levels. Systematic reviews, however, have failed to find that any treatment modality has a significant positive effect (Heintjes, 2004; Heintjes, 2003).

Since no knowledge of the pain mechanism behind PFPS has emerged, all positive treatment effects must be considered non-specific. Previous studies on PFPS have most probably included patients with diagnoses that have different pathophysiologies. This clearly calls for further studies on the pain mechanism involved but also for stricter criteria in the definition of PFPS.

All treatment modalities that so far have been studied—including surgical—may decrease pain via several mechanisms. That all of the treatments proposed for PFPS can have either a short- or a long-term impact on blood perfusion must be remembered. Most conservative treatments of PFPS include sensory stimulation of the leg, even though the main purpose may be something else. There are several possible explanations for the pain-relieving effects experienced with sensory stimulation. In the periphery, nutritional blood flow has been found to increase after shallow penetration of the skin with an acupuncture needle (Sandberg et al., 2004; Haker et al., 2000). Segmentally, sensory stimulation can decrease pain levels via a gating mechanism (Melzack and Wall, 1965), and centrally, sensory stimulation might initiate endogenous opioid pain-relieving systems (Han, 1980).

Homeostatic reactions, and subsequent pain responses, are suggested to be regulated by afferent activity (Craig, 2003). The afferent stimulation resulting from the penetration of the skin by the acupuncture needle in both groups in Study II could have had an impact on local blood flow as well as on the regulation of pain and homeostasis since some afferent action potentials will also be transmitted in the control group. Our control group received a superficial and less aggressive type of acupuncture, meant to be of limited value concerning pain relief from opioids in the CNS or from gating effects in the dorsal horn. As there were no differences between true deep and minimal superficial acupuncture on pain intensity, the degree of afferent input cannot be a major factor in the pain relief that was obtained.

Proposed pain mechanisms in PFPS

Several authors have reported homeostasis in the knee region of PFPS patients to be disturbed (Sanchez-Alfonso et al., 2005; Leppela et al., 1998; Dye, 1993; Arnoldi, 1991; Butler-Manuel, 1990). The pathogenic paradigm proposed by Dye (2005) focuses on mechanical overload. Our results indicate that vascular problems also affect the homeostatic reactions found in PFPS.

The soft tissues of patients with PFPS often exhibit ischemia (Sanches-Alfonso et al., 2005). Patients can also have accelerated bone remodeling in any of the bony compartments of the knee joint, possibly due to intermittent ischemia (Näslund et al., 2005; Leppelä et al., 1998). The capillary in-growth into the cartilage at the

osteochondral junction that was found by Badalemente et al. (1989) might be secondary to ischemia. The phenomenon of rest pain in PFPS (theatre or movie sign) has never been satisfactorily explained but might be an example of allodynia. Allodynia is the term for pain arising from non-nociceptive afferent activity due to central sensitization, and can be induced by ischemia (Mitchell et al., 2002).

Recently, Craig (2003) proposed that pain in humans is a homeostatic emotion reflecting an adverse condition in the body that requires a behavioral response. Changes in the mechanical, thermal, and chemical status of the tissues of the body caused by stimuli that can induce pain are primarily important for the maintenance of homeostasis. We have presented evidence that PFPS can be linked to decreased blood flow in the patellar bone.

Our findings in Study V are in line with the homeostatic paradigm proposed by Dye et al. (1999), but we cannot be certain which stressor—that is, mechanical strain, venous occlusion, intraosseous pressure, or decreased arterial blood flow—is most responsible for the reduction in pulsatile patellar blood flow. Selfe et al. (2002) made similar arguments. They classified PFPS patients into three groups: hypoxic, inflammatory, and mechanical. Ischemia, however, may be the pain-provoking mechanism in all three categories since inflammatory changes can develop not only after ischemia but also after mechanical damage to the vascular system (Woolf, 2004; Craig, 2003).

8 CONCLUSIONS

From the studies in this thesis the following conclusions can be drawn:

- PFPS is a clinical diagnosis in which the patients can be divided into different subgroups according to radiological findings.
- The pain experienced by patients suffering from PFPS decreases after various types of sensory stimulations.
- Diffuse uptake on scintigraphy will be present in approximately half of the PFPS patients and may occur in any bony compartment of the knee.
- Pulsatile blood flow in the patellar bone can be studied continuously and non-invasively with photoplethysmography.
- Patients diagnosed with PFPS exhibit reduced levels of patellar pulsatile blood flow compared with healthy controls when the knee is flexed.

Perspectives and implications

The knowledge and experience we have gained in the course of these studies on PFPS have highlighted the pressing need for a consensus on definitions of commonly used terms, inclusion criteria, and pain mechanisms in musculoskeletal pain syndromes.

That the patients' pain may be secondary to a reduction in blood flow is well worth consideration. If this indeed is the case, patients complaining of patellofemoral pain should be taught to regularly exercise their thigh muscles to increase the flow of nutritional blood to the bone. Protecting the knee region from decreases in blood flow could also be of value. This might encompass both limitations in time spent with knees in flexion as well as protecting the knees from a cold environment or external stasis.

The lack of a reliable technique for estimating blood flow in bone tissue has been the main obstacle to an understanding of bone tissue homeostasis. Now that we have the ability to perform continuous and non-invasive blood flow measurements in bone tissue, the basic pathophysiology of disorders affecting bone tissue will be easier to investigate. Further development of the new PPG technique should focus on validating the probe so that measurements will be reliable and absolute in all areas of the human skeleton.

9 ACKNOWLEDGMENTS

I wish to express my sincere gratitude to each and every one who encouraged and supported me during my work with this thesis. I am honored to have had the opportunity to be a part of the Department of Physiology and Pharmacology, Karolinska Institutet.

Most importantly, I want to extend my gratitude to all patients and control subjects involved in my research.

My heart-felt gratitude goes to the following persons:

Thomas Lundeberg, my first tutor, for giving me the opportunity to enter the world of research and for believing in me and my paradigm-threatening ideas.

Dag Linnarsson, my second tutor, for supervising me in the second half, for showing me the light in the darkness of ignorance, and for guiding my final steps.

Lars-Göran Lindberg, my co-supervisor, for believing in me and my eager search for a new technique for blood measurements in bone tissue and for teaching me the secrets of photoplethysmography.

S*ten Odenbring,* my co-supervisor, for great encouragement, a supportive attitude, and clinical advice.

Stefan Eriksson, present head of the Department of Physiology and Pharmacology and *Bertil Fredholm*, former head of the department, for support when time was rough, for pragmatic solutions, and for a stimulating research environment.

Iréne Lund, research colleague, for logistical support, for endless statistical help, for skilful guidance in the making of the illustrations, for teaching me about every-day research problems, and for being a good listener.

Jonas Pettersson, for help with evaluation of the PPG technique in rigid tubes.

Henrik Lauge-Pedersen, Sörn Ehlers, Anna Sprinchorn, Dan Christensson, Markus Waldén, and *Mats Nylander* for help with recruiting the patients.

Elisabeth Svensson for creative discussions on statistical methods in biomedical research.

Audrey Singh, who edited the English text in study II.

Per Sveider, and *Bengt Ragnemalm,* for technical assistance with the PPG equipment.

Thomas Nixon and *Erik Lundeberg,* for preparing some of the illustrations.

All my other colleagues and staff at the Department of Physiology and Pharmacology who created a fantastic working atmosphere: *Bo Rydqvist, Mats Rundgren, Robert Frithof, Peter Wolf, Louise Bovin, Monica Thunberg-Eriksson, Maud Hoffstedt, Ann-Christine Johansson, Ulla Lindgren, Ulla Wester, Monica Pace Sjöberg, Christina Östlund,* and *Lena Öhman.*

Ulla-Britt, my co-author, life-companion and beloved wife, for endless discussions, infinite patience, and never-ending support.

Sofie and *Charlotte*, my lovely children and the most precious in my life.

10 REFERENCES

Aleman O. Chondromalacia post-traumatica patellae. *Acta Chir Scand* 1928;63:149-90.

Alfredson H. The chronic painful Achilles and patellar tendon: research on basic biology and treatment. *Scand J Med Sci Sports*. 2005;15:252-9.

Alietti P, Buzzi R, Pisaneschi A. Patella pain. *J Sports Trauma Relat Res* 1990;12:131-50.

Almekinders LC, Almekinders SV. Outcome in the treatment of chronic overuse sports injuries: a retrospective study. *J Orthop Sports Phys Ther* 1994;19:157-61.

Andersson S, Lundeberg T. Acupuncture – from empiricism to science: functional background to acupuncture effects in pain and disease. *Med Hypotheses* 1995;45:271-81.

Anetzberger H, Thein E, Becker M, Zwissler B, Messmer K. Microsphere accurately predict bone blood volume. *Clin Orthop Rel Research* 2004;424:253-65.

Arnoldi CC. Patellar Pain. *Acta Orthop Scan Suppl* 1991;244:1-29.

Arnoldi CC, Lemperg K, Linderholm H. Intraosseous hypertension and pain in the knee. *J Bone Joint Surg Br* 1975;57:360-3.

Arrol B, Ellis-Pegler E, Edwards A, Sutcliffe G. Patellofemoral pain syndrome. A critical review of the clinical trials on nonoperative therapy. *Am J Sports Med* 1997;25:207-12.

Badalamente MA, Cherney SB. Periosteal and vascular innervation of the human patella in degenerative joint disease. *Semin Arthritis Rheum*1989;18:61-6.

Ben-Eliyahu D. Infrared thermographic imaging in the detection of sympathetic dysfunction in patients with patellofemoral pain syndrome. *J Manipulative Physiol Ther* 1992;3:164-70.

Bergman S, Herrstrom P, Hogstrom K, Petersson IF, Svensson B, Jacobsson LT. Chronic musculoskeletal pain, prevalence rates, and sociodemographic associations in a Swedish population study. *J Rheumatol* 2001;28:1369-77.

Biedert RM, Warnke K. Correlation between the Q angle and the patella position: a clinical and axial computed tomography evaluation. *Arch Orthop Trauma Surg* 2001;121:346-9.

Biella G, Sotgiu ML, Pellegata G, Paulesu E, Castiglioni I, Fazio F. Acupuncture produces central activations in pain regions. *Neuroimage* 2001;14:60-66.

Binzoni T, Leung T, Hollis V, Bianchi S, Fasel JH, Bounameaux H, Hiltbrand E, Deply D. Human tibia bone marrow: defining a model for the study of haemodynamics as a function of age by near infrared spectroscopy. *J Physiol Anthropol Appl Human Sci* 2003;22:211-18.

Birklein F, Weber M, Ernst M, Riedl B, Neundörfer B, Handwerker HO. Experimental tissue acidosis leads to increased pain in complex regional pain syndrome (CRPS). *Pain* 2000;87:227-34.

Bizzini M, Childs JD, Piva SR, Delitto A. Systematic review of the quality of randomized controlled trials for patellofemoral pain syndrome. *J Orthop Sports Phys Ther* 2003;33: 4-20.

Bjorkstrom S, Goldie IF. A study of the arterial supply of the patella in the normal state, in chondromalacia patellae, and in osteoarthritis. *Acta Orthop Scand* 1980;51:63-70.

Blom D, Dawidson I, Angmar-Månsson B. The effect of acupuncture on salivary flow rates in patients with xerostomia. *Oral Surg Oral Med Oral Pathol* 1992;73:293-8 Blond L, Hansen L. Patellofemoral pain syndrome in athletes: a 5.7-year retrospective follow-up study of 250 athletes. *Acta Orthop Belg* 1998;64:393-400.

Boegård T, Rudling O, Dahlström J, Dirksen H, Petersson IF, Jönsson K. Bone scintigraphy in chronic knee pain: comparison with magnetic resonance imaging. *Ann Rheum Dis* 1999;58:20-6.

Bonutti PM, Miller BG, Cremen MJ. Intraosseous patellar blood supply after medial parapatellar arthrotomy. *Clin Orthop Relat Res* 1998;352:202-14.

Borgström P, Clementz LA, Grande PO. A servo-controlled roller pump for constant flow or constant pressure blood perfusion under normal pulsatile or non-pulsatile conditions. *Acta Physiol Scand* 1981;112:437-42.

Bosco C, Belli A, Astrua A, Tihanyi J, Pozzo R, Kellis S, Tsarpela O, Foti C, Manno R, Tranquilli C. A dynamometer for evaluation of dynamic muscle work. *Eur Appl Physiol* 1995;70:379-86.

Brick GW, Scott RD. Blood supply to the patella. Significanse in total knee arthroplasty. *J Arthroplasty* 19894 Suppl:S75-9.

Butler-Manuel PA. Sympathetically mediated anterior knee pain. *Acta Orthop Scand* 1992;63:90-93.

Butler-Manual PA. Scintigraphy in the assessment of anterior knee pain. *Acta Orthop Scand* 1990;61:438-42.

Challoner AVJ. Photoelectric plethysmography for estimating cutaneous blood flow. In: Rolfe P (ed) Non-invasive physiological measurements, 1979, Vol 1. Academic Press, London, pp125-151.

Conaghan PG, Vanharanta H, Dieppe PA. Is progressive osteoarthritis an atheromatous vascular disease? *Ann Rheum Dis* 2005;64:1539-41.

Cook JL, Khan KM, Kiss ZS, Purdam CR, Griffiths L. Reproducibility and clinical utility of tendon palpation to detect patellar tendinopathy in young basketball players. *Br J Sports Med* 2001;34:65-9.

Craig AD. A new view of pain as a homeostatic emotion. *Trends Neurosci* 2003;26:303-7.

Crossley K, Bennell K, Green S, Cowan S, McConnell J. Physical therapy for patellofemoral pain. *Am J Sports Med* 2002;30:857-65.

Crossley K, Bennell K, Green S, McConnell J. A systematic review of physical interventions for patellofemoral pain syndrome. *Clin J Sport Med* 2001;11:103-10.

Cutbill JW, Ladly KO, Bray RC, Thorne P, Verhoef M. Anterior Knee Pain: A Review. *Clin J Sport Med* 1997;7:40-5.

Davidson K. Patellofemoral pain syndrome. *Am Fam Physician* 1993;48:1254-62.

Devereaux MD, Parr GR, Lachmann SM, Thomas DP, Hazleman BL. Thermographic diagnosis in athletes with patellofemoral arthralgia. *J Bone Joint Surg Br* 1986;1:42-4.

D'hondt N, Struijs P, Kerkhoffs G, Verheul C, Lysens R, Aufdemkampe G, Van Dijk C. Orthotic devices for treating patellofemoral pain syndrome. (Cochrane report). Cochrane Library, Issue 3, 2003.

Doucette SA, Child DD. The effect of open and closed chain exercise and knee joint position on patellar tracking in lateral patellar compression syndrome. *J Orthop Sports Phys Ther* 1996;23:104-10.

Duri ZA, Aichroth PM, Wilkins R, Jones J. Patellar tendonitis and anterior knee pain. *Am J Sports Med* 1999;12:99-108.

Dye SF. The pathophysiology of patellofemoral pain. *Clin Orthop Rel Res* 2005;436:100-10.

Dye SF, Campanga-Pinto D, Dye C, Shifflett S, Eiman T. Soft-tissue anatomy anterior to the human patella. *J Bone Joint Surg Am* 2003;85:1012-17.

Dye SF. Patellofemoral pain current concepts: An overview. *Sports Med Arthrosc Rev* 2001;9:264-72.

Dye SF, Staubli HU, Biedert RM, Vaupel GL. The mosaic of pathophysiology causing patellofemoral pain: Therapeutic implications. *Operat Tech Sports Med* 1999;7:46-54.

Dye SF, Vaupel GL. The pathophysiology of patellofemoral pain. *Sports Med Arthrosopy Rev* 1994;2:203-10.

Dye SF, Chew MH. The use of scintigraphy to detect increased osseous metabolic activity about the knee. *J Bone Joint Surg* 1993;75:1388-406.

Dye SF 1993 Imaging of the knee. *Orthop Rev* 1993;22:901.

Dye SF, Boll DA. Radionuclide imaging of the patellofemoral joint in young adults with anterior knee pain. *Orthop Clin North Am* 1986;17:249-62.

Dyrehag LE, Widerstrom-Noga EG, Carlsson SG, Andersson SA. Effects of repeated sensory stimulation sessions (electro-acupuncture) on skin temperature in chronic pain patients. *Scand J Rehab Med* 1997;29:43-250.

Ellenbecker TS, Bailie DS, Mattalino AJ, Carfagno DG, Wolff MV, Braun SV, Kulikowitch JM. Intrarater and interrater reliability of a manual technique to assess anterior humeral head translation of the glenohumeral joint. *J Shoulder Elbow Surg* 2002;11:470-5.

Fairbank J, Pynsent P, van Poortvliet J, Phillips H. Mechanical factors in the incidence of knee pain in adolescents and young adults. *J Bone Joint Surg Br* 1984;66:685-93.

Fearon I, McGrath PJ, Achat H. 'Booboos': the study of everyday pain among young children. *Pain* 1996;68:55-62.

Ficat RP, Philippe J, Hungerford DS. Chondromalacia patellae: a system of classification. *Clin Orthop* 1979;144:55-62.

Filshie J, Cummings M. Western medical acupuncture. In Acupuncture. A scientific appraisal. Oxford: Butterworth-Heinemann; 1999. p. 31-59.

Finestone A, Radin EL, Lev B, Shlamkovitch N, Wiener M, Milgrom C. Treatment of overuse patellofemoral pain. Prospective randomized controlled trial in military setting. *Clin Orthop Rel Res* 1993;293:208-10.

Fitzgerald GK, McClure PW. Reliability of measurements obtained with four tests for patellofemoral alignment. *Phys Ther* 1995;75:84-92.

Fujii M, Nakajima K, Sakamoto K, Kanai H. Orientation and deformation of erythrocytes in flowing blood. *Ann N Y Acad Sci* 1999;873:245-61.

Fulkerson JP. Disorders of the patellofemoral joint. Fourth Edition. 2004 Philadelphia, Lippincott Williams & Wilkins.

Fulkerson JP. Diagnosis and treatment of patients with patellofemoral pain. *Am J Sports Med* 2002;30:447-56.

Fulkerson JP, Hungerford DS. Disorders of the patellofemoral joint. In: Grayson TH, (ed) Disorders of the Patellofemoral Joint (2nd ed.). 1990 Williams & Wilkins, Baltimore.

Galanty H, Matthews C, Hergenroeder A 1994 Anterior knee pain in adolescents. *Clin J Sport Med* 1994;4:176-81.

Garrick JG. Anterior knee pain (chondromalacia patella). *Phys Sportsmed* 1989;17:75-84.

Gelfer Y , Pinkas L, Horne T, Halperin N, Alk D, Robinson D. Symptomatic transient patellar ischemia following total knee replacement as detected by scintigraphy. A prospective, randomized, double-blind study comparing the mid-vastus to the medial para-patellar approach. *Knee* 2003;10:341-5.

Gerrard B. The patello-femoral pain syndrome: a clinical trial of the McConnell program. *Austr J Physiother* 1989;35:71-80.

Gillquist J. In "Konsensusrapport,. Del II. Nedre extremitetsskador". Ed. Rolf C. Rhône-Poulence Rorer AB 1997 Helsingborg.

Goldberg B. Patellofemoral malalignment. *Pediatr Ann* 1997;26:32-5.

Goldberg B. Chronic anterior knee pain in the adolescent. *Pediatr Ann* 1991;20:186-93.

Graaf R, Dassel A, Koeölink M, de Mul F, Aarnoudse J, Zilstra W. Optical properties of human dermis in vitro and in vivo. *Appl Opt* 1993;32:435-7.

Groothuis JT, van Vliet L, Kooijman M, Hopman MT. Venous cuff pressures from 30 mm Hg to diastolic pressure are recommended to measure arterial inflow by plethysmography. *J Appl Physiol* 2003;95:342-347.

Grana WA, Kriegshauser LA. Scientific basis of extensor mechanism disorder. *Clin J Sport Med* 1985;4:247-57.

Grelsamer RP. Patellar nomenclature. *Clin Orthop Rel Research* 2005;436:60-65.

Guzzanti V, Gigante A, Di Lazzaro A, Fabbriciani C. Patellofemoral malalignment in adolescents. Computerized tomographic assessment with or without quadriceps contraction. *Am J Sports Med* 1994;22:55-60.

Haker E, Egekvist H, Bjerring P. Effect of sensory stimulation (acupuncture) on sympathetic and parasympathetic activities in healthy subjects. *J Auton Nerv Syst* 2000;79:52-9.

Halliwill JR. Hypoxic regulation of blood flow in humans. In: Hypoxia: Through the lifecycle. Ed. Roach RC. 2003 Klüwer Academic/Plenum Publishers, New York.

Han JS, Tang J, Ren MF, Zhou ZF, Fan SG, Qiu XC. Central neurotransmitters and acupuncture analgesia. *Am J Chin Med* 1980;8:331-48.

Hansen P, Hansen J. Acupuncture treatment of chronic facial pain – a controlled crossover trial. *Headache* 1983;23:66-69.

Harrison E, Magee D, Quinney H. Development of a clinical tool and patient questionnaire for evaluation of patellofemoral pain syndrome patients. *Clin J Sports Med* 1996;6:163-70.

Heintjes E, Berger MY, Bierma-Zeinstra SM, Bernsen RM, Verhaar JA, Koes BW. Exercise therapy for patellofemoral pain syndrome. Cochrane Database Syst Rev. 2003 CD003472.

Heintjes E, Berger MY, Bierma-Zeinstra SM, Bernsen RM, Verhaar JA, Koes BW. Pharmacotherapy for patellofemoral pain syndrome. Cochrane Database Syst Rev. 2004 CD003470.

Hejgaard N, Arnoldi CC. Osteotomy of the patella in the patellofemoral pain syndrome. The significance of increased intraosseous pressure during sustained knee flexion. *Int Orthop* 1984;8:189-94.

Hejgaard N, Diemer H. Bone scan in the patellofemoral pain syndrome. *Int Orthop* 1987;11:29-33.

Holmes SV Jr, Clancy WG Jr. Clinical classification of patellofemoral pain and dysfunction. *J Orthop Sports Phys Ther* 1998; 28:299-306.

Hughes SS, Cammarata A, Steinmann SP, Pellegrini VD. Effect of standard total knee arthroplasty surgical dissection on human patellar blood flow in vivo: an investigation using laser doppler flowmetry. *J South Orthop Ass* 1998;7:198-204.

Iida S, Harada Y, Ikenoue S, Moriya H. Measurement of bone marrow blood volume in the knee by position emission tomography. *J Orthop Sci* 1999;4:216-22.

Ilahi OA, Kadakia NR, Huo MH. Inter- and intraobserver variability of radiographic measurements of knee alignment. *Am J Knee Surg* 2001;14:238-42.

Ireland ML, Wilson JD, Ballantyne B, McClay Davis I. Hip strength in females with and without patellofemoral pain. *J Orthop Sports Phys Ther* 2003;33:671-6.

Jacobs JW, Geenen R, van der Heide A, Rasker JJ, Bijlsma JW. Are tender point scores assessed by manual palpation in fibromyalgia reliable? An investigation into the variance of tender point scores. *Scand J Reumatol* 1995;24:243-7.

Jensen R, Gøthesen Ø, Liseth K, Baerheim A. Acupuncture treatment of patellofemoral pain syndrome. *J Alternative Compl Med* 1999;6:521–6.

Jeracitano D, Cooper R, Lyon L, Jayson M. Abnormal temperature control suggesting sympathetic dysfunction in the shoulder skin of patients with frozen shoulder. *Br J Rheumatol* 1992;31:539-42.

Johnson AG. Surgery as placebo. *Lancet* 1994;334:1140-2.

Johnson LL, van Dyk GE, Green JR 3rd, Pittsley AW, Bays B, Gully SM, Phillips JM. Clinical assessment of asymptomatic knees: a comparison of men and women. *Arthroscopy* 1998;14:347-59.

Jarvela T, Kannus P, Jarvinen M. Anterior knee pain 7 years after an anterior cruciate ligament reconstruction with a bone-patellar tendon-bone autograft. *Scand J Med Sci Sports* 2000;10:221-7.

Kamal A, Harness J, Irving G, Mearns A. Skin photoplethysmography – a review. *Comput Meth Prog Biomed* 1989;28.257-69.

Kannus P, Natri A, Paakkala T, Järvinen M. An outcome study of chronic patellofemoral pain syndrome. Seven-year follow-up of patients in a randomized, controlled trail. *J Bone Joint Surg Am* 1999;81:355-63.

Kannus P, Niittymäki S. Which factors predict outcome in nonoperative treatment of patellofemoral pain syndrome? A prospective follow-up study. *Med Sci Sports Exerc* 1994;26:289-96.

Kannus P, Aho K, Järvinen M, Niittymäki S. Computerized recording of visits to an outpatient sports clinic. *Am J Sports Med* 1987;15:79-85.

Kirschner MH, Menck J, Nerlich A, Walser R, Buhren V, Hofmann GO. The arterial blood supply of the human patella. Its clinical importance for the operating technique in vascularized knee joint transplantations. *Surg Radiol Anat* 1997;19:345-51.

Kleinheinz J, Stratmann U, Joos U, Wiesmann HP. VEGF-activated angiogenesis during bone regeneration. *J Orol Maxillofac Surg* 2005;63:1310-6.

Knardahl S, Elam M, Olausson B, Wallin G. Sympathetic nerve activity after acupuncture in humans. *Pain* 1998;75:19-25.

Laprade J, Culham E. Radiographic measures in subjects who are asymptomatic and subjects with patellofemoral pain syndrome. *Clin Orthop Relat Res* 2003;414:172-82.

Larsen PD, Hary M, Thiruchelvam M, Galletly DC. Spectral analysis of AC and DC components of the pulse photoplethysmograph at rest and during induction of anaesthesia. *Int J Clin Monit Comput* 1997;14:89-95.

Larsson RL, Cabaud HE, Slocum DB, James SL, Keenan T, Hutchinson T. The patella compression syndrome: surgical treatment by lateral retinacular release. *Clin Orthop Relat Res* 1979;134:156-67.

Levic JR. An introduction to cardiovascular physiology. Third edition. 2000 Oxford University Press Inc., New York, pp 301-28.

Levine J, Gordon N, Bornstein J, Fields H. Role of pain in placebo analgesia. *Proc Natl Acad Sci USA* 1979;76:3528-31.

Leppala J, Kannus P, Natri A, Sievanen H, Jarvinen M, Vuori I. Bone mineral density in the chronic patellofemoral pain syndrome. *Calcif Tissue Int* 1998;62:548-53.

Lichota DK. Anterior knee pain: symptom or syndrome? *Curr Womens Health Rep* 2003;3:81-6.

Lindberg LG, Öberg PÅ. Optical properties of blood in motion. *Opt Eng* 1993;32:253-7.

Lindberg LG, Öberg PÅ. Photoplethysmography. Part 2. Influence of light source wavelength. *Med Biol Eng Comput* 1991;29;48-54.

Lindberg U, Lysholm J, Gillquist J. The correlation between arthroscopic findings and the patellofemoral pain syndrome. *Arthroscopy* 1986;2:103-7.

Lindberg U. The patellofemoral pain syndrome. Thesis, Linköping University, Linköping Sweden, 1986.

Loaiza LA, Yamaguchi S, Ito M, Ohshima N. Electro-acupuncture stimulation to muscle afferents in anesthetized rats modulates the blood flow to the knee joint through autonomic reflexes and nitric oxide. *Auton Neurosci* 2002;97:103–9.

Lorberboym M, Ben Ami D, Zin D, Nikolov G, Adar E. Incremental diagnostic value of ^{99m}Tc methylene diphosphonate bone SPECT in patients with patellofemoral pain disorders. *Nucl Med Commun* 2003;24:403-10.

Lustig JP, London D, Dor BL, Yanko R. Ultrasound identification and quantitative measurement of blood supply to the anterior part of the mandible. *Oral Surg Oral Med Oral Pathol Radiol Endod* 2003;96:625-9.

Malanga GA, Andrus S, Nadler SF, McLean J. Physical examination of the knee: a review of the original test description and scientific validity of common orthopedic tests. *Arch Phys Med Rehab* 2003;84:592-603.

Magnusson HI, Ahlborg HG, Karlsson C, Nyquist F, Karlsson MK. Low regional bone density in athletes with medial tibial stress syndrome normalizes after recovery from symptoms. *Am J Sports Med* 2003;31:596-600.

Magnusson HI, Westlin NE, Nyquist F, Gardsell P, Seeman E, Karlsson MK. Abnormally decreased regional bone density in athletes with medial tibial stress syndrome. *Am J Sports Med* 2001;29:712-5.

Maralcan G, Kuru I, Issi S, Esmer AF, Tekdemir I, Evcik D. The innervation of the patella: anatomical and clinical study. *Surg Radiol Anat* 2005;27:331-5.

Matheson GO, Clement DB, McKenzie DC, Taunton JE, Lloyd-Smith DR, MacIntyre JG. Scintigraphic uptake of 99mTc at non-painful sites in athletes with stress fractures. The concept of bone strain. *Sports Med* 1987;4:65-75.

McCarthy E. The pathology of transient regional osteoporosis. The pathology of transient regional osteoporosis. *Iowa Orthop J* 1998;18:35-42.

McCarthy EF. Histopathologic correlates of a positive bone scan. *Sem Nucl Med* 1997;27:309-20.

McConnel J. The management of chondromalacia patellae. A long-term solution. *Aust J Physiother* 1986;32:215-23.

Merbitz C, Morris J, Grip J. Ordinal scales and foundations of misinference. *Arch Phys Med Rehab* 1989;70:308-12.

Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971-9.

Merchant AC. Classification of patellofemoral disorders. *Arthroscopy* 1988;4:235-40.

Mersky H, Mogduk N. Classification of chronic pain. International Association for the Study of Pain. IASP Press 1994, pp 210-3.

Messier SP, Davis SE, Curl WW, Lowery RB, Pack RJ. Etiologic factors associated with patellofemoral pain in runners. *Med Sci Sports Exerc* 1991;23: 1008-15.

Mitchell AC, Fallon MT. A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischaemia: results of a double blind randomised controlled trial. *Pain* 2002;97:275-81.

Milgrom C, Finestone A, Eldad A, Shlamkovitch N. Patellofemoral pain caused by overactivity. A prospective study of risk factors in infantry recruits. *J Bone Joint Surg Am* 1991;73:1041-3.

Millan MJ. The induction of pain: an integrative review. *Prog Neurobiol* 1999;57:1-164.

Miltner O, Siebert CH, Schneider U, Niethard FU, Graf J. Patellar hypertension syndrome in adolescence: a three-year follow up. *Arch Orthop Trauma Surg* 2003;103:455-9.

Minoves M. Bone and joint sports injuries: the role of bone scintigraphy. *Nucl Med Commun* 2003;24:3-10.

Miwa Z, Ikawa M, Iijima H, Saito M, Takagi Y (2002) Pulpal blood flow in vital and nonvital young permanent teeth measured by transmitted-light photoplethysmography: a pilot study. *Pedriatr Dent* 2002;24:594-8.

Mori Y, Fujimoto A, Okumo H, Kuroki Y. Lateral retinaculum release in adolescent patellofemoral disorders: its relationship to peripheral nerve injury in the lateral retinaculum. *Bull Hosp Jt Dis Orthop Inst* 1991;51: 218-29.

Murphy A, Wilson G. The ability of tests of muscular function to reflect training-induced changes in performances. *J Sports Sci* 1997;15:191-200.

Murphy E, FitzGerald O, Saxne T, Bresnihan B. Increased serum cartilage oligomeric matrix protein levels and decreased patellar bone mineral density in patients with chondromalacia patellae. *Ann Rheum Dis* 2002;61:981-5.

Murray IR, Murray AS, MacKenzie K, Coleman S. How evidence based is the management of two common sports injuries in a sports clinic? *Br J Sports Med* 2005;39:912-16.

Nijs J, Van Geel C, Van der Auwera C, Van de Velse B. Diagnostic value of five clinical tests in patellofemoral pain syndrome. *Man Ther* 2005 June [Epub ahead of print].

Nimon G, Murray D, Sandow M, Goodfellow J 1998 Natural history of anterior knee pain: a 14- to 20- year follow-up of nonoperative management. *J Pediatr Orthop* 1998;18:118-22.

Nitzan M, de Boer H, Turivnenko S, Babchenko A, Sapoznikov D. Power spectrum analysis of spontaneous fluctuations in the photoplethysmographic signal. *J Basic Clin Physiol Pharmacol* 1994;5:269-76.

Notzli HP, Swiontkowski MF, Thaxter ST, Carpenter GK, Wyatt R. Laser Doppler flowmetry for bone flow measurements: Helium-Neon laser light attenuation and depth of perfusion assessment. *J Orthop Res* 1989;7:413-24.

Näslund J, Odenbring S, Näslund UB, Lundeberg T. Diffusely increased bone scintigraphic uptake in patellofemoral pain syndrome. *Br J Sports Med* 2005;39:162-5.

Näslund J, Näslund U, Odenbring S, Lundeberg T. Sensory stimulation (acupuncture) for the treatment of idiopathic anterior knee pain. *J Rehab Med* 2002;34:231-8.

Otter MW, Qin YX, Rubin CT, McLeod KJ. Does bone perfusion/reperfusion initiate bone remodelling and the stress fracture syndrome? *Med Hypoth* 1999;53:363-8.

Pasupathy S, Homer-Vanniasinkam S. Ischaemic preconditioning protects against ischaemia/reperfusion injury: emerging concepts. *Eur J Vasc Endovasc Surg* 2005;29:106-15.

Percy EC, Strother RT. Patellalgia. *Phys Sportsmed* 1985;13:43-59.

Plate KH. Gene therapy of malignant glioma via inhibition of tumor angiogenesis. *Cancer Metastasis Rev* 1996;15:237-40.

Powers CM, Ward SR, Chen YJ, Chan LD, Terk MR. Effect of bracing on patellofemoral joint stress while ascending and descending stairs. *Clin J Sport Med* 2004;14:206-14.

Powers CM, Ward SR, Fredericson M, Guillet M, Shellock F. Patellofemoral kinematics during weight-bearing and non-weight-bearing knee extension in persons with lateral subluxation of the patella: a preliminary report. *J Orthop Sports Phys Ther* 2003;33:677-85.

Powers CM. Rehabilitation of patellofemoral joint disorders: a critical review. *J Orthop Sports Phys Ther* 1998;28:345-53.

Post WR. Clinical assessment of malalignment: does it correlate with the presence of patellofemoral pain? *Sports Med Arthrosc Rev* 2001;9:301-5.

Post WR. Anterior knee pain - a symptom not a diagnosis. *Bull Rheum Dis* 1993;42:5-7.

Rakusan K, Ehrenburg IV, Gulyaeva NV, Tkatchouk EN. The effect of intermittent normobaric hypoxia on vascularisation of human myometrium. *Microvasc Res* 1999;58:200-3.

Reid DC. The myth, mystic, and frustration of anterior knee pain. *Clin J Sports Med* 1993;3:139-43.

Reid DC, Wilson J, Magee D. Intraosseous venous pressures in the patello-femoral pain syndrome. *Am J Knee Surg* 1990;3:80-4.

Reider B, Marshall JL, Warren RF. Clinical characteristics of patellar disorders in young athletes. *Am J Sports Med* 1981;9:270-4.

Ritter MA, Campell ED. Postoperative patellar complications with or without lateral release during total knee arthroplasty. *Clin Orthop Relat Res* 1987;219:163-8.

Roberts AH, Kewman DG, Mercier L et al. The power of non-specific effects in healing: implications for psychosocial and biological treatments. *Clin Psych Review* 1993;13:375-91.

Ryles MT, Pilmanis AA. The initial signs and symptoms of altitude decompression sickness. *Aviat Space Environ Med* 1996;67:983-9.

Sakamoto K, Kanai H. Electrical characteristics of flowing blood. *IEEE Trans Biomed Eng* 1979;26:686-95.

Sanchis-Alfonso V, Roselló-Sastre E, Revert F, Garcia A. Histologic retinacular changes associated with ischemia in painful patellofemoral malalignment. *Orthopedics* 2005;28:593-9.

Sanchis-Alfonso V, Roselló-Sastre E. Imunohistochemical analysis for neural markers of the lateral retinaculum in patients with isolated symptomatic patellofemoral malalignment. *Am J Sports Med* 2000;28:725-31.

Sanchis-Alfonso V, Roselló-Sastre E, Martinez-Sanjuan V. Pathogenesis of anterior knee pain syndrome and functional patellofemoral instability in the active young. *Am J Knee Surg* 1999;12:29-40.

Sanchis-Alfonso V, Roselló-Sastre E, Monteagudo-Castro C, Esquerdo J. Quantitative analysis of nerve changes in lateral retinaculum in patients with isolated symptomatic patellofemoral malalignment: A preliminary study. *Am J Sports Med* 1998;26:703-9.

Sandberg M, Larsson B, Lindberg LG, Gerdle B. Different patterns of blood flow response in the trapezius muscle following needle stimulation (acupuncture) between healthy subjects and patients with fibromyalgia and work-related trapezius myalgia. *Eur J Pain* 2005;9;497-510.

Sandberg M, Zhang Q, Styf J, Gerdle B, Lindberg LG (2005) Non-invasive monitoring of muscle blood perfusion by photoplethysmography: evaluation of a new application. *Acta Physiol Scand* 2005;183:335-43.

Sandberg M, Lindberg LG, Gerdle B. Peripheral effects of needle stimulation (acupuncture) on skin and muscle blood flow in fibromyalgia. *Eur J Pain* 2004;8;163-71.

Scapinelli R. Blood supply to the human patellae. *J Bone Joint Surg* 1967;49B:563-70.

Schneider U, Breusch SJ, Thomsen M, Graf J, Niethard FU. A new concept in the treatment of anterior knee pain: patellar hypertension syndrome. *Orthopedics* 2000;23:581-6.

Scott A, Khan KM, Roberts R, Cook JL, Duronio V. What do we mean by the term ''inflammation''? A contemporary basic science update for sports medicine. *Br J Sports Med* 2004;38:372–80.

Selfe J, Harper L, Pedersen I, Breen-Turner J, Waring J, Stevens D. Cold legs: a potential indicator of negative outcome in the rehabilitation of patients with patellofemoral pain syndrome. *Knee* 2003;10:139-43.

Selfe J, Kärki A, Stevens D. A review of the role of circulatory deficit in the genesis of patellofemoral pain. *Phys Ther Rew* 2002;7:169-72.

Shalaby M, Almekinders LC. Patellar tendinitis: the significance of magnetic resonance imaging findings. *Am J Sports Med* 1999;27:345-9.

Siegel M, Siqueland B, Noyes F. The use of computerized thermography in the evaluation of non-traumatic anterior knee pain. *Orthopedics* 1987;10:825-830.

Slater RN, Spencer JD, Churchill MA, Bridgeman GP, Brookes M. Observations on the intrinsic blood supply to the human patella: disruption correlated with articular surface degeneration. *J R Soc Med* 1991;84:606-7.

Slater H, Arendt-Nielsen L, Wright A, Graven-Nielsen T. Sensory and motor effects of experimental muscle pain in patients with lateral epicondylalgia and controls with delayed onset muscle soreness. *Pain* 2005;114:118-30.

Stanitski CL. Anterior knee pain syndromes in the adolescent. *Instr Course Lect* 1994;43: 211-20 .

Strobel M, Stedtfelt H 1990 Evaluation of the femuropatellar joint. In: Strobel M, Stedtfelt H (eds) Diagnostic evaluation of the knee, pp 183-198. Berlin, Springer-Verlag.

Svensson E. Application of a rank-invariant method to evaluate reliability of ordered categorical assessment. *J Epid Biostat* 1998;4:403-9.

Svensson E. Ordinal invariant measures for individual and group changes in ordered categorical data. *Statistics Med* 1998;17: 2923-36.

Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res* 1985;198:43-9.

The international patellofemoral study group. Patellofemoral semantics. *Am J Knee Surg* 1997;10:92-5.

Thomas M, Lundeberg T. Does acupuncture work? *Pain Clinical updates* 1996;4:1-4.

Thomeé R, Renström P, Karlsson J, Grimby G. Patellofemoral pain syndrome in young women. *Scand J Med Sci Sports* 1995;5:237-44.

Urwin M, Symmons D, Allison T, Brammah T, Busby H, Roxby M, Simmons A, Williams G. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomic sites, and the relation to social deprivation. *Ann Rheum Dis* 1998;57:649-55.

Uematsu S, Edwin D, Jankel W, Kozikowski J, Trattner M. Quantification of thermal asymmetry. Part 1: Normal values and reproducibility. *J Neurosurg* 1988;69:552-5.

Vahasarja V. Prevalence of chronic knee pain in children and adolescents in northern Finland. *Acta Paediatr* 1995;84: 803-5.

Van Tiggelen D, Witvrouw E, Roget P, Cambier D, Danneels L, Verdonk R. Effect of bracing on the prevention of anterior knee pain – a prospective randomized study. *Knee Surg Sports Traumatol Arthrosc* 2004;12:434-9.

Waisbrod H, Treiman N. Intra-osseous venography in patellofemoral disorders. A preliminary report. *J Bone Joint Surg Br* 1980;62:454-6.

Wang J, Ver Donk P, Elewaut D, Veys EM, Verbruggen G. Homeostasis of the extra cellular matrix of normal and osteoarthritic human articular cartilage chondrocytes in vitro. *Osteoarthritis Cartilage* 2003;11:801-9.

Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, Strandness DE Jr, Taylor LM. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 1996;94:3026-49.

Welsh RP. Patellofemoral arthralgia, overuse syndromes of the knee, and chondromalacia patella. *Can Fam Physician* 1985;31:573-6.

Werner S, Arvidsson H, Arvidsson I, Eriksson E. Electrical stimulation of vastus medialis and stretching of lateral thigh muscles in patients with patello-femoral symptoms. *Knee Surg Sports Traumatol Arthrosc* 1993;1:85-92.

Werner S, Knutsson E, Eriksson E. The effect of taping the patella on concentric and eccentric torque and emg of knee extensor and knee flexor muscles in patients with patello-femoral pain syndrome. *Knee Surg Sports Traumatol Arthrosc* 1993;1:169-77.

Wetzner SM, Bezreh JS, Scott RD, Bierbaum BE, Newberg AH. Bone scanning in the assessment of patellar viability following knee replacement. *Clin Orthop* 1985;199:215-19.

Wilkinson IB, Webb DJ. Venous occlusion plethysmography in cardiovascular research: methodology and clinical applications. *Br J Cli Pharmacol* 2001;52:631-46.

Williamson L, Yudkin P, Livingstone R. Hay fever treatment in general practice: a randomised controlled trial comparing western acupuncture with sham acupuncture. *Acupunct Med* 1996;14:6-10.

Witvrouw E, Lysens R, Bellemans J, Cambier D, Cools A, Danneels L, Bourgois J. Which factors predict outcome in the treatment program of anterior knee pain? *Scand J Med Sci Sports.* 2002;12:40-6.

Wojtys EM, Beaman DN, Glover RA, Janda D. Innervation of the human knee joint by substance-P fibers. *Arthroscopy* 1990;6:254-63.

Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004;140:441-51.

Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjork E. Towards a mechanism-based classification of pain? *Pain* 1998;77:227-9.

Yates C, Grana WA. Patellofemoral pain – a prospective study. *Orthopedics* 1986;9:663-7.

Zhang Q, Lindberg LG, Kadefors R, Styf J. A non-invasive measure of changes in blood flow of the human anterior tibial muscle. *Eur J Appl Physiol* 2001;85:567-71.