Oslo Sports Trauma
RESEARCH CENTER

Øystein Bjerkestrand Lian

On the causes of patellar tendinopathy

Faculty of Medicine
University of Oslo
2007

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 499

ISBN 978-82-8072-868-5

Cover: Inger Sandved Anfinsen.
Printed in Norway: AiT e-dit AS, Oslo, 2007.

Produced in co-operation with Unipub AS.
The thesis is produced by Unipub AS merely in connection with the
thesis defence. Kindly direct all inquiries regarding the thesis to the copyright
holder or the unit which grants the doctorate.

Unipub AS is owned by
The University Foundation for Student Life (SiO)

Table of contents

Acknowledgements

This study was carried out at Oslo Sports Trauma Research Center, located at the Norwegian University of Sports and Physical Education, Oslo, Norway. I would like to thank this institution for the opportunity to carry out the research.

I would like to express my sincere gratitude to everyone who has been involved in this thesis project, directly or indirectly. In particular I would like to thank:

Roald Bahr, MD, PhD, professor and chair of the Oslo Sports Trauma Research Center and Department for Health Studies, Norwegian University of Sports and Physical Education, and my main tutor, for the opportunity to study at the Oslo Sport Trauma Research Center. His unique accessibility combined with a meticulous methodological approach has made this project possible. His personal support combined with patience and impatience has been very motivating. I would also thank him for our personal friendship.

Lars Engebretsen, MD, PhD, professor at the Oslo Orthopedic University Clinic, co-founder of the Oslo Sports Trauma Research Center. He is the best leader of an ortopeadic department I have ever met. He has been a visionary tutor in the development of this thesis with a very personal support.

Ingar Holme, Dr. philos, PhD, professor and statistician at the Oslo Sports Trauma Research Center and Department of Sports Medicine, Norwegian University of Sport and Physical Education for excellent statistical advise.

Trond Krosshaug, MSc, PhD at Oslo Sports Trauma Research Center for patiently helping me with a wide variety of technical problems.

Tone Rasmussen Øritsland, project coordinator and Unni Lund, former secretary († 2004) for the friendly help with the projects.

Kharim Khan, MD, PhD, professor at UBC, Vancouver, Canada, the most learned person in the world on the art of understanding science in tendinosis, for his support and scientific advise.

Alex Scott, PhD, UBC, Vancouver, Canada, for his enthusiastic cooperation with the theory and practical work with the biopsies in the apoptosis study.

Lars Nordsletten, MD, PhD, professor at the Oslo Orthopedic University Clinic, for all his encouragement, support and scientific knowledge.

Frede Frihagen, MD, resident at the Oslo Orthopedic University Clinic for his accurate work with the biopsies.

Kamel Farran, MD, senior orthopaedic surgeon, Kristiansund Hospital, for his enthusiasm and patience in teaching me orthopaedic surgery, and still being one of my best personal friends.

Ingrid Bahr, for hospitality and patience during late evenings and nights working together with her husband Roald.

To my colleagues at Kristiansund Hospital who have inspired and supported me to continue my work.

Thanks to my friends for their support and encouragement.

Thanks to my parents, my brother Kristian and sister Anne Berit for their relentless support throughout my life. Without them nothing of this would have been possible.

Ingun, for patience, support and being my very best friend.

Ola, Erna Agathe, Kristian, Kristine and Eirik, the very best in my life.

The main financial support came from Oslo Sports Trauma Research Center which has been established at the Norwegian University of Sport and Physical Education through generous grants from the Royal Ministry of Culture, the Norwegian Olympic Committee and Confederation of Sport, Norsk Tipping AS and Pfizer AS.

List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I. Lian Ø, Engebretsen L, Bahr R. Prevalence of jumper's knee among elite athletes from different sports – A cross-sectional study. Am J Sports Med 33: 561-567, 2005.

II. Lian Ø, Holen K, Engebretsen L, Bahr R. Relationship between symptoms of jumper's knee and the ultrasound characteristics of the patellar tendon among high level male volleyball players. Scand J Med Sci Sports 6: 291-296, 1996.

III. Lian Ø, Engebretsen L, Øvrebø RV, Bahr R. Characteristics of leg extensors in male volleyball players with jumper's knee. Am J Sports Med 24: 380-385, 1996.

IV. Lian Ø, Refsnes PE, Engebretsen L, Bahr R. Performance characteristics of volleyball players with patellar tendinopathy. Am J Sports Med 31: 408-413, 2003.

V. Lian Ø, Dahl J, Ackermann P, Frihagen F, Engebretsen L, Bahr R. Pronociceptive and antinociceptive neuromediators in patellar tendinopathy. Am J Sports Med 34: 1801-1808, 2006.

VI. Lian Ø, Scott A, Engebretsen L, Duronio V, Bahr R, Khan K. Excessive apoptosis in patellar tendinopathy in athletes. Am J Sports Med Epub Jan 23, 2007.

Definitions

Nomenclature. The nomenclature used to characterize different tendon disorders has been confusing, at least in part because of a lack of understanding of the underlying pathology. Based on previous definitions described by Jozsa and Kannus 1997, Clancy 1990, Leadbetter 1992 and Khan et al. 1998 the following terminology is used in this thesis:

Paratenonitis. Previously named "tenosynovitis", "tenovaginitis" and "peritendinitis". This is an inflammation of only the paratenon, either lined by synovium or not. The histopathologic findings consist of inflammatory cells in paratenon or peritendinous areolar tissue. The clinical signs and symptoms include the cardinal inflammatory signs with swelling, pain, crepitation, local tenderness, warmth and dysfunction.

Paratenonitis with tendinosis. Previously named "tendinitis". Characterized by paratenon inflammation associated with intratendinous degeneration. The histopathologic findings consist of inflammatory cells in the paratenon or peritendinous areolar tissue and loss of tendon collagen, fiber disorientation, vascular ingrowth, but absent or very sparse intratendinous inflammation. The clinical picture is the same as seen in paratenonitis, with frequently palpable tendon nodules, swelling and inflammatory signs.

Tendinosis. Previously named "tendinitis". Intratendinous degeneration due to different etiologic factors characterized histologically by noninflammatory intratendinous collagen degeneration with fiber disorientation and vascular ingrowth. In tendinosis there is no swelling of the tendon sheat, and there can be a palpable tendon nodule.

Tendinitis. Previously named "tendon strain" or "tendon tear". This is a symptomatic degeneration of the tendon with vascular disruption and inflammatory repair response.

Patellar tendinopathy. This term means the lesion associated with pain and tenderness at the lower point of the patella and lesions of the main body of the tendon. It can be used to describe both acute and overuse conditions, but does not assume any knowledge about the underlying pathology.

Jumper's knee. A clinically defined condition with exercise-related pain localized at the quadriceps insertion to the patella or the patellar tendon and its proximal insertion, combined with pain on palpation at the same localization.

Summary

The term "tendinopathy" describes a medical condition associated with a lesion with tendon pain and tenderness. It can be used to describe both acute and overuse conditions. Tendinopathy is assumed to be caused by overload in more or less susceptible individuals. The aim of this thesis was to study certain aspects of this disease in athletes with tendinopathy localized to their patellar tendon, and based on the findings suggest a model that can explain the relationship between a suspected chronic overload injury and the tissue response on macro and cellular level.

The aim of the study presented in Paper I was to estimate the prevalence of jumper's knee in different sports among female and male athletes, in order to correlate the prevalence to the loading characteristics of the extensor mechanism in these sports. The study was designed as a cross-sectional study. We examined approximately 50 Norwegian male and female athletes at the national elite level from different sports. The examination included an interview on individual characteristics (weight, age, height, and training background), a clinical exam and self-recorded VISA score (from 0 (worst) to 100 (best). The overall prevalence of current jumper's knee was 14.2% (87 of 613 athletes), with a significant difference between sports with different performance characteristics (range: 0-45%). In addition, 51 athletes (8%) reported previous symptoms. The prevalence of current tendinopathy was lower among women (5.6±2.2%) compared with men (13.5±3.0%; χ^2 test, p=0.042). The duration of symptoms among athletes with current tendinopathy (n=87) was 32±25 (SD) months with a VISA score of 64±19. The study shows that the prevalence of jumper's knee is high in sports characterized by high demands on speed and power for the leg extensors. The symptoms are often serious, resulting in long-standing impairment of athletic performance.

In Paper II we assessed the ultrasound characteristics of the patellar tendon in two groups of volleyball players, one group without knee symptoms and one group with symptoms of jumper's knee. Of 47 male elite players, 25 were diagnosed to have current and 7 to have had previous symptoms of jumper's knee, as determined by clinical examination. Since some players had bilateral problems, there were 34 knees with current problems and 9 with previous problems. Seven of the 30 knees with a clinical diagnosis of jumper's knee in the patellar tendon had normal ultrasound findings, and ultrasound changes believed to be associated with jumper's knee (tendon thickening, echo signal changes, irregular paratenon appearance) were observed in 12 of 51 knees without symptoms. Specific ultrasound findings such as paratenon changes, hypoechoic zones or pathologic tendon thickness proximally did not correlate significantly with the degree or the

duration of symptoms. This study suggests that the specificity and sensitivity of ultrasonography is low in the evaluation of patients with mild symptoms of jumper's knee.

In Paper III and IV, we examined the biomechanical characteristics of the extensor mechanism in athletes with jumper's knee compared with healthy controls, and described their training background and body characteristics.

In Paper III, patient and control groups (12 players in each) were selected from a population of 141 well trained male Norwegian volleyball players, of which 55 (39%) satisfied the diagnostic criteria for jumper's knee. The testing program consisted of a standing jump (SJ), a counter-movement jump (CMJ), a 15 second rebound jump test (RJ), a standing jump with a 20 kg load ($SJ_{20\,kg}$) and a load corresponding to one-half body weight ($SJ_{1/2\,bw}$). The test result of the patient group was significantly higher than that of the control group for CMJ (15% increase), power during RJ (41%), work done in SJ (12%) and CMJ (22%), and the difference between CMJ and SJ (effect of adding eccentric component). In conclusion, athletes with jumper's knee demonstrated better performance than healthy athletes in jump tests, particularly in ballistic jumps involving eccentric force generation.

In Paper IV, the purpose of the study was to examine the performance of the leg extensors in two groups of high level male volleyball players, one group with jumper's knee (n=24) and a control group (n=23) without knee symptoms. The groups were similar in age, height and playing experience, but the patient group did more specific strength training and had a higher body weight. The testing program consisted of different jump tests with and without added load. Jump height was measured using a contact mat connected to an electronic timer, whereas equipment recording load displacements was used to measure velocity, force and power during jumps with added load. The results showed that the patient group scored significantly higher than the control group on a composite jump index calculated from the individual test results.

In Paper V, we did a case-control study to examine if nerve ingrowth and altered expression of sensory and sympathetic neuromediators may play a major role in the pain pathophysiology of patellar tendinopathy, since the mechanisms behind the occurrence of cronic tendon pain is still largely unknown. Biopsies from the patellar tendon in patients with patellar tendinopathy were compared with biopsies from a control group without any previous or current knee complaints compatible with patellar tendinopathy. The biopsies were stained immunohistochemically for sensory and autonomic nerve markers. With semi-quantitative methodology the biopsies from the two groups were compared. Chronic painful patellar tendons exhibited increased occurrence

of sprouting non-vascular sensory, substance P (SP)-positive nerve fibers and decreased occurrence of vascular sympathetic nerve fibers, positive to tyroxin hydroxylase (TH ; a marker for noradrenaline). Increased occurrence of SP suggests a nociceptive and maybe also a proliferative role in tendinopathy, while the decreased occurrence of TH may reflect a decreased anti-nociceptive role. Further neuro-anatomic studies should be performed for elucidating future specific treatment of tendinopathy.

Paper VI was a case-control study to see if an apoptotic process is part of the pathophysiology in tendinopathy. Apoptosis, also called "programmed cell death", is a specific physiological response to different stimuli with distinct morphological and biochemical changes ending up with cell death. Biopsies from the patellar tendon in patients with patellar tendinopathy were compared with biopsies from a control group without any previous or current knee complaints compatible with patellar tendinopathy. The presence of apoptosis was examined with immunohistochemical methods using a polyclonal antibody recognizing active caspase-3, confirmed by labeling DNA strand breaks (F7-26 antibody) and nuclear morphology. There was a significant higher number of apoptotic cells per unit area in tendinopathic samples compared with controls. Although the tendinopathic samples displayed increased cellularity, the apoptotic index was significantly higher. This study confirms that apoptosis is a feature of tendinosis. This suggests that tenocyte death may either limit the ability of injured tendon to recover from chronic injury, or may be involved in the ongoing repair and remodeling of the chronically injured tendon.

Introduction

Anatomy

Gross anatomy

The patellar tendon extends from the lower patellar pole to the tibial tuberosity and is the extension of the common tendon of insertion of the quadriceps femoris muscle. It is about 3 cm wide in the coronal plane and 4-5 mm deep in the sagittal plane (Khan et al. 1998). The bulk of the tendon is attached to the distal two-thirds of the anterior aspect of the patella with fascicles converging in the frontal plane and parallel in the sagittal plane towards their tibial attachments (Basso et al. 2001). The length of tendon fascicles varies with longer anterior fascicles than the corresponding posterior fascicles, since the anterior bundles are attached more proximal to the patella and more distal to the tibia than the corresponding posterior bundles (Basso et al. 2001).

The tendon is surrounded by a loose areolar connective tissue called the paratenon, which functions as an elastic sleeve and permits free movement of the tendon against the surrounding tissue (Kvist et al. 1985, Hess et al. 1989). Under the paratenon the tendon is surrounded by a fine connective tissue sheath called the epitenon which on its inner side is contiguous with the endotenon. This endotenon invests each tendon fiber and binds individual fibers (Hess et al. 1989, Jozsa et al. 1991). The endotenon network allows the fiber groups to glide on each other and to carry blood vessels, nerves and lymphatics to the deeper portions of the tendon (Hess et al. 1989, Jozsa et al. 1991).

Vascular supply

The arterial supply is from three arterial pedicles on each side of the patellar tendon. Two main arcades anastomose with these pedicles, the retropatellar and the supratubercular resulting in a peritendinous network characterized by a high vascular density next to the poles of the patellar tendon. The retropatellar arch has an average diameter of 1.5 mm and courses horizontally across the fat pad in the posterior surface of the patellar tendon and is placed at the level of junction between the patella and the tendon (Soldado et al. 2002). Only the retropatellar and the supratubercular arches give rise to vessels that pierce the tendon, which means that there are two vascular segments in the arterial supply of the patellar tendon (bipolar pattern). The upper

segment of the patellar tendon is supplied by arterioles that reach the posterior surface from the retropatellar arch and enter the tendon substance from the posterior side. The inferior segment is supplied from arterioles from superficial vessels from collaterals of the supratubercular arch. These intratendinous vessels create anastomoses in the middle third of the patellar tendon (Soldado et al. 2002). In the tendon substance there is an intratendinous vascular network together with nerves and lymphatics localized to the endotenon septas (Elliott 1965, Hess et al. 1989). This intratendinous network consists of longitudinally arranged vessels with one artery followed by two veins. Small arterioles and capillaries originate from these longitudinally arteries and form the microvascular units of the tendon tissue organized to ensure an adequate metabolism in all part of the fiber fascicles (Ippolito 1986).

Cell components

The cellular elements of the patellar tendon consist of 90-95% tenoblasts and tenocytes, the rest are chondrocytes at the insertion sites, nerve and vessel cells (Jozsa and Kannus 1997). The morphologic features of young tenoblasts support the concept that these cells have a high metabolism with high synthesis of the matrix components (Jozsa and Kannus 1997). The tendon cells have the enzyme chains for all of the main pathways of energy metabolism: the Krebs cycle, anaerobic glycolysis and the pentose phosphate shunt (Ippolito 1986, Jozsa et al. 1979).

Innervation

The patellar tendon is innervated mainly by sensory nerves entering the tendon substance via the endotenon septa. Inside the tendon the nerves are relatively few in number and follow the vascular channels, anastomise with each other and finally terminate in the sensory nerve endings (Ippolito 1986, Jozsa et al. 1993). However, the innervation within the patellar tendon and the distribution of the different nerve fiber types within the patellar tendon substance is mostly unknown.

In tendon tissue in general the myelinated A-fibers innervate specialized multicellular end organs with high sensitivity to mechanical stimuli (Bray et al. 2005). The mechanoreceptors found in tendons and ligaments are important in motor control (Proske et al. 1988). The different kinds of free nerve endings, called nociceptors, are activated by mechanical, chemical and thermal stimuli and can be sensitized by repetitive activation (Schepelmann et al. 1992). Stimulation of these nociceptive fibers results in vasodilatation, increased vascular permeability and oedema, which is called “neurogenic inflammation” (Bayliss 1901, Lewis 1937). The autonomic nerve fibers are

mainly localized in networks around blood vessels in the epiligaments and loose connective tissue around the tendons and ligaments (Bray et al. 2005). Both sympathetic and parasympathetic autonomic fibers have been identified in tendons and ligaments (Bray et al. 2005). According to Bray et al. (2005), there are three groups of neurotransmitters of importance in the regulation of tendon and ligament physiology; sensory, opioid and autonomic according to their function and original nerve fiber type. They can act as neurotransmitters, hormones and paracrine factors.

Sensory neuropeptides with nociceptive and pro-inflammatory effect are substance P (SP) and calcitonin gene-related peptide (CGRP) (Ziche et al. 1990). These neurotransmitters are found in pain-transmitting C-fibres (Gibson et al. 1984, Lembeck et al. 1987, Wiesenfeld-Hallin et al. 1984). Substance P is involved in a multitude of physiological processes due to its widespread distribution, centrally and peripherally; among them are angiogenesis and vasodilatation (Konttinen et al. 1990). The autonomic nerve system can influence the sensory C-fibers by sensitizing or desensitizing the pain receptors.

Physiology

Tendons are extremely strong with an ultimate failure-stress range of 56.7±4.4 MPa (Stanish et al. 1985). According to Stanish et al. (1985), tendons may be subject to fatigue with high chronic repetitive loading, despite the fact that the cyclical loads may be well within the tendons ultimate failure-stress range. Physiological loads usually cause less than 4% increase in the length of the tendon and strain above 4% results in damage to one or more of the tendon fibre bundles, while strain in excess of 8-12% results in complete tendon rupture (strain is calculated as change in length per unit length) (Elliott 1965, Jozsa and Kannus 1997, Burstein and Wright 1994). It has been estimated that forces within the patellar tendon may reach 14.5 kN during competitive weight lifting resulting in a total patellar rupture, which corresponds to more than 17.5 times the lifter's body weight (Zernicke et al. 1977). When calculated per cross-sectional area, there is no gender difference in the tensile strength of human tendons (Becker and Krahl 1978). Forces that place highest stress on the tendon occur during eccentric muscle contraction (Fyfe and Stanish 1992, Stanish et al. 1985). The maximal muscle force that can be generated eccentrically is 1.5-2.0 times higher than the maximal isometric force, and several-fold higher than maximal concentric force, especially at high speeds (Herzog 2000). Also, the ground reaction force is different between different tasks, ranging from 2.8 times body weight during distance running to 6 times body weight during jumping in volleyball and 10 times body weight in a long jump take off

(McNitt-Gray 2000). The highest ground reaction forces are seen with ballistic drop jumps, and the resulting forces through the extensor tendons are proportional to the ground reaction force.

In a study by Basso et al. (2002), they found that under quadriceps loading there was significantly higher strain in the posterior fascicles compared with the anterior fascicles between 60 and 90 degrees of knee flexion. The material properties in the anterior and posterior fascicles were similar, except that the failure strain was significantly higher posterior. For a same amount of elongation, the shorter posterior fascicles strain more than the longer anterior fascicles. This could mean that the posterior fascicles are adapted to sustain significantly greater tensile strain before failing (Basso et al. 2002). However, in a recent study by Almekinders et al. (2002), they found that the strain increased on the anterior side but decreased on the posterior side in the central, proximal location of the tendon in dynamic measurements in the range from 0 to 60 degrees of flexion. The cross-sectional area of the tendon increases from proximal to distal (el-Khoury et al. 1992). Since shear stress is directly correlated to the cross-sectional area, the shear stress can therefore be assumed to be higher in the proximal part of the tendon compared with the distal part.

Pathology

Histopathology

The histopathological findings in biopsies from the patellar tendon in patients with tendinopathy are very consistent. Under light microscopy the biopsies are characterized by degeneration and fibrotic scarring in the tendon itself, as well as in the bone-tendinous junction (Ferretti et al. 1985, Fritschy and de Gautard 1988, Kälebo et al. 1991, Myllymäki et al. 1990, Orava et al. 1986, Raatikainen et al. 1994, Roels et al. 1978). The normal parallel collagen bundles are disorganized and replaced by degenerative tissue with increased ground substance, consisting of proteoglycans and glycosaminoglycans (Khan et al. 1996). The tenocytes lose their spindle shape and nuclei appear more rounded (Clancy 1990). There are an increased number of fibroblasts compared with normal tendons (Ferretti et al. 1983, Colosimo and Bassett 1990, Fritschy and deGautard 1993, Roels et al. 1978, Martens et al. 1982). There is also neovascularization with capillary proliferation and prominent angiogenesis (Roels et al. 1978, Colosimo and Bassett 1990, Khan et al. 1998). There are clefts in the collagen bundles, which have been assumed to represent microscopic tears in the tendon substance (Roels et al. 1978, Davies et al. 1991, Kujala et al. 1989, Raatikainen et al. 1994). In a recent presentation, Maffulli et al. (2005) reported similar

histopathological findings in tendinopathic Achilles and patellar tendons. They stated that "a common, as yet unindentified, etiopathological mechanism may have acted on both these tendon populations." This means that there may be a common pathophysiological pathway that may explain the very uniform histopathological findings in tendinopathic tissue biopsies.

One of the most striking findings is the absence of inflammatory cells. As stated by Khan et al. (1998), there are two papers coauthored by specialist pathologists who report a total absence of inflammatory cells in tissue from patients with jumper's knee, even at the periphery of abnormal tissue and in patients who had symptoms for only four months (Yu et al. 1995, Khan et al. 1996). In a study by Alfredsson et al. (2003), they used cDNA arrays and real-time quantitative polymerase chain reaction technique to study tendinosis and control tissue samples and found that several cytokines and cytokine receptors were not upregulated, indicating the absence of an inflammatory process in chronic painful Achilles tendinosis.

Cell pathology

However, one consistent finding in biopsies from tendinotic tissue is hypercellularity. In the absence of inflammatory cells, the hypercellularity must be explained by the presence of other cell types. These cells are not fully characterized.

Recently, it has been suggested that the initial pathology in tendinopathy is to the tenocyte, not the collagen fibres (Khan et al. 2000b, Yuan et al. 2003, Cook et al. 2004). Necrosis and apoptosis are the two major types of cellular death (Ameisen 1996, Lavin and Watters 1993, Sen 1992). Necrosis is characterized by rupture of the cell membrane and very often an inflammatory response and a pathological tissue reaction involving groups of adjoining cells (Ameisen 1996). Apoptosis, also called "programmed cell death," is a specific physiological response to different stimuli with distinct morphological and biochemical changes ending up with cell death, very often without a concomitant inflammatory response (Lavin and Watters 1993, Sen 1992). The apoptotic process is stimulated and inhibited by a number of influencing factors, such as hormones, cytokines and growth factors (Kiess and Gallaher 1998). At the cellular level the tendon cells are also influenced by mechanical factors, such as repetitive loading and stretching (Skutek et al. 2003, Barkhausen et al. 2003, Arnoczky et al. 2002). In a study by Yuan et al. (2002), they found excessive apoptosis at the edge of torn rotator cuff tendons compared with controls. However, in this study the mean age of the patients was more than 60 years and they had a rupture of the rotator cuff. Tendon rupture may result from a different pathological process compared to tendinosis. This means that the findings by Yuan et al. (2002) cannot necessarily

explain the pathology found in tendinopathic tissue biopsies. In a study by Scott et al. (2005) they showed that apoptosis could occur in response to short term, high strain mechanical loading in a rat tibialis anterior model. This means that there is evidence for a connection between mechanical factors and apoptosis both at the cellular level and at the isolated tendon level. These findings suggest that apoptosis may be a factor in tendon overload injuries. However, it is still unknown whether there is a connection between mechanical factors and apoptosis in vivo in humans. This problem was explored in Paper VI.

Vascular pathology

Another consistent histopathological finding in tendinotic tissue biopsies is neovascularization with capillary proliferation and prominent angiogenesis (Roels et al. 1978, Colosimo and Bassett 1990, Khan et al. 1998). This neovascularization may be a part of the remodeling process, but is assumed to weaken the mechanical stability by proteolysis of the extra-cellular matrix by the invading endothelial cells (Petersen et al. 2004b). Angiogenesis is controlled by many stimulatory and inhibitory proteins acting on invading endothelial and smooth muscle cells (Ferrara 1999). One of the most important angiogenetic factors is vascular endothelial cell growth factor (VEGF) (Senger et al. 1983). High VEGF concentrations have been demonstrated in degenerative tendon tissue compared with healthy Achilles tendons (Pufe et al. 2001, Petersen et al. 2004a). In response to VEGF stimulation vascular and smooth muscle cells produce matrix metalloproteinases (MMPs) (Wang and Keiser 1998, Sato et al. 2000). The protease inhibitor tissue inhibitor of metalloproteinase-3 (TIMP-3) blocks VEGF from binding to its receptor VEGFR-2, thereby reducing the effect of VEGF (Qi et al. 2003). This means that there are interactions between VEGF and MMPs and TIMPs resulting in weakened material properties in the tendon in degenerative tendon disease (Pufe et al. 2005). Another regulatory pathway of VEGF production is by the transcription factor hypoxia inducible factor-1 (HIF-1). VEGR is upregulated by HIF-1, and HIF-1 is upregulated by hypoxia (Maxvell et al. 2001, Ferrara 1999). In a study by Petersen et al. (2004b), they found that mechanical stress induced HIF-1 and VEGF in isolated tendon cells. This means that both hypoxia and mechanical factors influence the expression of VEGF. The role of VEGF and HIF-1 in the angiogenetic process seen in biopsies from patients with patellar tendinopathy is not known.

Healing processes

The reparative processes in tendinosis are also poorly understood. Whether tendinosis is a primary degenerative condition, or if there are simultaneous degenerative and reparative processes within the tendon substance is unknown. Many growth factors and matrix molecules with different biological effects can be found in the tendon substance with different temporal expression (Dahlgren et al. 2005). Both insulin-like growth factor-1 (IGF-1) and transforming growth factor ß1 (TGF-ß1) are produced by tenoblasts, and in vitro these two growth factors increase cell proliferation and the synthesis of collagen and proteoglycans (Abrahamsson et al. 1991, Letson and Dahners 1994, Tsuzaki et al. 1994). Whether these growth factors are up-regulated in tendinotic tissue is not known. If there is an increased expression of IGF-1, this may, at least in part, explain the hypercellularity found in biopsies from tendinotic tissue. An increased expression of IGF-1 would also indicate an ongoing reparative process within the tendon tissue.

Pain mechanisms

In the absence of inflammatory cells, the substrate for pain production is confusing. In biopsies from degenerated facet joints and degenerated intervertebral discs it has been shown that there is in-growth of nociceptive nerve fibers (Freemont et al. 1997, Coppes et al. 1997, Konttinen et al. 1990). It is not known whether this is part of the pain mechanism in tendinopathy. In a study by Bjur et al. (2005), they examined the innervation pattern of the normal and tendinotic Achilles tendon and found SP and CGRP in the paratendinous loose connective tissue and to some extent in the tendon tissue proper intimately associated with small blood vessels. However, as described earlier, the innervation and distribution of the different nerve fiber types within the patellar tendon substance is unknown. The pain mechanisms in patellar tendinopathy are also mostly unknown. These issues were the focus of Paper V.

Diagnosis of patellar tendinopathy

The diagnosis of jumper's knee is based on a history of pain localized to the lower patellar pole or insertion of the quadriceps tendon in connection with athletic activity and distinct palpation tenderness corresponding to the painful area (Blazina et al. 1973). The diagnosis of patellar tendinopathy requires that, in addition to a typical history and clinical signs, there are structural changes in the tendon, as demonstrated by MR, ultrasound or tendon biopsies. Nevertheless, in the clinical setting the diagnosis is often based on a typical history and clinical findings alone.

In fact, when the current research projects were started, the relationship between imaging findings and symptoms had not been clarified. Previously the diagnostic precision by use of ultrasound was assumed to be high, since several studies had shown a near-perfect correlation between preoperative ultrasound changes and surgical findings (Raatikainen et al. 1994, Orava et al. 1986, Kälebo et al. 1991, King et al. 1990, Karlsson et al. 1992). However, as these studies were carried out in a selected patient group (i.e. almost all of them had disabling symptoms who did not respond to non-operative treatment), the results should be interpreted carefully when applied to other patient populations.

The only previous study comparing the clinical and ultrasound-based diagnosis of jumper's knee was done by Myllymäki et al. (1990). Of 62 knees with characteristic symptoms of jumper's knee, they reported no hypoechoic changes in 31 (50%). However, to our knowledge, there is no available information on the histopathological changes in patients with Roels' grade I, II or IIIa disease. In spite of lack of this information, attempts had been made to correlate ultrasound changes and anatomical findings to the clinical staging of the disease (Fritschy and DeGautard 1988, Jerosch et al. 1990). Jerosch and Schröder (1990) suggested that a relationship exists between the severity of the pathological changes and certain ultrasound characteristics. However, their study did not include corresponding histopathological examinations, which means that their conclusions were based on assumptions. In Paper II, we have examined the ultrasound characteristics of the patellar tendon among high-level volleyball players with and without jumper's knee.

To assess the severity of the disease Roels' clinical grading system (Roels et al. 1978) has been used. It is assumed that this grading system reflects the clinical seriousness of the disease, but the system is based more on clinical experience than research. In describing patients with jumper's knee, we proposed a modification to Roels' clinical grading system. There are several patients who are able to play matches and practice despite having pain throughout the activity, but for whom there is no available classification category according to Roels et al. (1978). We therefore suggested splitting grade III into grade IIIa for patients with pain during activity, but who are still able to train and play matches, and grade IIIb for those with disabling pain (Table 1). This modification would enable a more precise patient classification in future epidemiological and clinical studies.

Table 1. Classification of jumper's knee according to symptoms as outlined by Roels et al. (1978) as modified by us.

	Roels et al. (1978)	Our classification
Grade I	*Pain* at the infrapatellar or suprapatellar region *after practice* or after an event	Same
Grade II	*Pain at the beginning of the activity, disappearing after warm-up and reappearing after completion of activity*	Same
Grade III	*Pain remains during and after activity* and the patient is *unable to participate* in sports	IIIa: *Pain during and after activity, but the patient is able to participate* in sports at the same level
		IIIb: Pain during and after activity and the *patient is unable to participate* in sports at the same level
Grade IV	*Complete rupture of the tendon*	Same

In order to assess the severity of the condition, athletes diagnosed with patellar tendinopathy can self-record their VISA score (Visentini et al. 1998). This is a validated pain and function score with a best score of 100 (no symptoms) and lowest score of 0 (maximum symptoms), which has been developed specifically for this purpose and has been shown to be a valid measure of symptoms (Robinson et al. 2001).

Epidemiology of jumper's knee

The prevalence of jumper's knee across different sports is mostly unknown. However, early studies from volleyball have shown that among male players at the elite level the prevalence is 40-50 % (Ferretti et al.1983, Ferretti et al. 1990). Publications from studies on the outcome after surgery suggest that the prevalence may be high in sports with high demands on speed and power, such as volleyball, soccer and athletics (Karlsson et al. 1991, Raatikainen et al.1994, Martens et al. 1982). Raatikainen et al. (1994) from Finland described 182 patients undergoing surgery for jumper's knee and found that 46% were from athletics, 37% from volleyball, 5% from soccer and the rest from other sports. On the other hand, Martens et al. (1982) from Belgium found that only 8% of his 90 surgically treated patients were from athletics, while 34% were volleyball players and 32% soccer players. Furthermore, Karlsson et al. (1992) from Sweden reported that of 81 patients they treated for jumper's knee, only 9% were volleyball players, while 37% were from athletics and 27% from soccer. In all of the three studies described, basketball

accounted for less than 10% of patients. As illustrated by the conflicting results from these (Karlsson et al. 1992, Raatikainen et al. 1994, Martens et al. 1982) and other studies (for a complete review of surgical studies, see Coleman et al. 2000), is not possible to estimate prevalence from case series, since the population at risk is unknown. The differences observed in the proportion of patients from different sports may simply reflect how popular these sports are in the different countries. To our knowledge, there are no previous reports on the prevalence of jumper's knee across different sports, nor is the severity and duration of symptoms well described across sports. This issue was therefore examined in Paper I.

Intrinsic risk factors for patellar tendinopathy

In general, risk factors for sports injuries are traditionally divided into internal, personal, risk factors and external, environmental, risk factors which can act either alone or in combination (Lorentzon 1988, Stanish 1984, van Mechelen et al. 1992). In tendon overuse injuries, an interaction between these two categories is common (Harvey 1983, Williams 1986).

According to Hess et al. (1989), almost any orthopaedic disorder that causes a variation from normal anatomic position and resulting vector forces on a tendon may cause an overuse syndrome. The most common intrinsic factors suggested in tendon overuse injuries are said to be alignment abnormalities, leg length discrepancy, muscle weakness and imbalance, decreased flexibility, joint laxity, gender, age, overweight and predisposing diseases (Hess et al. 1989, Micheli 1983, Renström 1988, Heiser et al. 1984, Kannus et al. 1987, Drinkwater 1988). Most of these references are review articles and none of them specifically address patellar tendinopathy. As stated by Lorentzon (1988); in general, it should be stressed that this area is highly conjectural and that many plausible hypotheses lack substantial evidence. It is claimed that in elite athletes a leg length discrepancy of more than 5 to 6 mm may cause symptoms (Michaeli 1983, Renström 1988). However, the clinical significance of leg length discrepancy is uncertain and further investigations in athletes providing substantiating data are needed before any firm conclusions can be drawn (Lorentzon 1988). Muscle imbalance means that there is an asymmetry between the agonist and the antagonist muscles in one extremity, asymmetry between the extremities, or a difference with an anticipated normal value (Grace 1985). The actual magnitude of what constitutes balance and imbalance has never been accurately defined and may actually be dependent on anatomic region involved, type of sport, age, size and gender (Grace 1985). There is some evidence that certain conditioning programs can reduce the injury rates related to muscle weakness or imbalance (Heiser et al. 1984), but other studies could not find any relationship

between muscle weakness or imbalance and injury (Grace 1985). As far as we know, there are no studies investigating the connection between patellar tendinopathy and muscle imbalance. Moreover, there are no studies to provide conclusive evidence on whether reduced flexibility is the cause or the consequence of tendon injuries (Jozsa and Kannus 1997).

Gender

According to Kannus et al. (1987) and Drinkwater (1988), there is a higher incidence of tendon overuse injuries among females compared with men. Women have less muscle mass per unit body weight than equally trained men, and their overall muscle strength averages about two-thirds that of men (Drinkwater 1988). Jozsa and Kannus (1997) suggest on a theoretical basis that these factors together with female risk factors in body anatomy and biomechanics (i.e., wider hips and more mobile joints) may predispose women to overuse injuries. Ferretti (1986) also presented the results from a sample of 26 volleyball players selected from 93 players diagnosed with jumper's knee in a random cohort of 407 volleyball players participating in the Italian Volleyball Championship. The selection criteria were not described and there was no control group. They found no difference in the prevalence of jumper's knee between males and females. In other words, there is limited epidemiological evidence to substantiate the claim for a gender bias in overuse tendon injury risk. This issue was studied in Paper I.

Antropometric data, strength and flexibility

Data on intrinsic factors for patellar tendinopathy are conflicting, and mostly related to static biomechanical characteristics (Ferretti et al. 1984, Kujala et al. 1986, Kujala et al. 1987). In a study by Hunter and Pole (1987), they suggest that "patellar tendinitis" can be caused by tight hamstring and quadriceps muscles and treated by flexibility training. However, this study does not give any information on flexibility measurements or specific outcome measures to support their suggestions.

In a study by Witvrouw et al. (2001), they followed 138 students without any knee complaints at inclusion for two years. At inclusion all students were evaluated for leg alignment characteristics, muscular tightness, and muscular strength. The leg length alignment characteristics were obtained by clinically measuring the leg length discrepancy, Q-angle and the medial tibial intercondylar distance. Isokinetic strength of the quadriceps and hamstring muscles were evaluated on a dynamometer. The tightness of the hamstrings and quadriceps femoris muscles were measured goniometrically. Nineteen of these 138 students developed "patellar tendonitis" based on clinical

and ultrasonographic examinations. Univariate and stepwise discriminant function analysis were performed on different measurements, and the only significant factor was muscular flexibility, with the patellar tendonitis patients being less flexible in the quadriceps and hamstring muscles ($p< 0.05$). To explore this issue, stretching and warm-up habits were compared between athletes with jumper's knee and controls in Paper III and IV.

In a study by Ferretti et al. (1984) among 407 male volleyball players they found a small peak in incidence between 20 and 25 years and an incidence peak at the third year of play, but concluded that age and years of play were not significant factors in producing jumper's knee. Age and years of play as intrinsic predisposing factors are examined in Papers I, III and IV.

In another study by Ferretti et al. (1983), primarily on histological findings in biopsies from athletes with jumper's knee, they also report that out of 18 knees treated surgically, two patients had patella alta and eight had a vastus medialis obliquus dysplasia. However, none of these patients were characterized further in the text, and the diagnostic criteria used were not described.

Ferretti (1986) also presented the results from a sample of 26 volleyball players selected from 93 players diagnosed with jumper's knee in a random cohort of 407 volleyball players participating in the Italian Volleyball Championship. The selection criteria were not described and there was no control group. Evaluation of the knee alignment, alignment of the extensor mechanism, position of the patella, characteristics of the tibial tuberosity, rotation of the femur, rotation of the tibia, degree of constitutional instability, characteristics of the foot or morphotype, did not give conclusive results with regard to predisposing intrinsic factors.

Leg length and patellar position

In the same study by Ferretti (1986) they assessed the position of the patella both clinically and radiographically using the method of Insall and Salvati (1971), and concluded that the patella was "slightly high" in four out of 26 athletes diagnosed with jumper's knee. However, they did not specify whether this finding was based on clinical or radiographic methods, or both.

In contrast, in a series of papers by Kujala et al. (1986, 1987, 1989) they found more leg length inequality and patella alta in patients with jumper's knee compared to controls. They compared 20 athletes diagnosed with jumper's knee with a control group of 20 athletes with normal knees and found a significantly higher mean value for lower leg length inequality in the athletes with jumper's knee compared with the control group (7.3 mm $\pm$ 4.2 mm vs. 3.0 mm $\pm$ 2.3 mm,

$p<0.001$) (Kujala et al. 1986). In the same study, they measured patellar height using two different methods. The Insall-Salvati method relates the length of the patellar tendon to the length of the patella (Insall and Salvati 1971), while the method described by Blackburne and Peel (1977) measures the ratio between the shortest distance from the distal end of the articular surface of the patella and the tibial plateau to the length of the articular surface of the patella. Using the Insall-Salvati method they found a significantly higher position of the patella in the patient group, but no significant difference with the Blackburne-Peel method. It should be noted that in this study 13 of the 20 athletes in the patient group were volleyball players, while only four out of 20 in the control group were volleyball players, which reduces the validity of this study. In a later study they used radiographic methods and found that the leg length inequality among athletes diagnosed with jumper's knee to be 5.8 ± 4.5 mm compared to 3.0 ± mm in a control group (Kujala et al. 1987). In this cohort of 57 athletes with jumper's knee there were 37 volleyball players, three basketball players, four long distance runners and five orienteerers. Ten athletes were not characterized with regard to type of activity. In the athletes with jumper's knee the injury was located on the side with the longer leg in 17 of 27 (63%) of cases. The same group of athletes had the injury located to the takeoff leg in 30 cases and on the other side in 18 cases. Those who could determine their take-off leg when jumping and whose lower leg inequality was at least 5 mm, the takeoff leg was the longer in 15 cases and the shorter leg in seven cases. However, they provided no information on the connection between types of sport or takeoff technique, nor whether these were statistical significantly differences.

In a final study by the same group (Kujala et al. 1989), they studied the extensor mechanism in 32 male competitive volleyball players and a control group of 49 young males. In this study they used both the Insall-Salvati index and the Blackburne-Peel index to evaluate the height of the patella, and concluded that there was a slight, but significant ($p<0.05$) tendency to patella alta according to the Blackbourne-Peel index, but no difference based on the Insall-Salvati index. In this study the control group was selected from volunteers at the beginning of their military service, making selection bias possible. The internal validity in this study is substantially reduced since the control group was not representative with regard to other known factors that could render them susceptible to jumper's knee. As a conclusion, based on this series of studies, there are conflicting results on the relationship between patella alta and jumper's knee. However, a methodological limitation with these studies is the fact that the patient group and the control group were from different sports. In this thesis, the position of the patella was examined in Paper II, using the Insall-Salvati index, comparing athletes with patellar tendinopathy with controls from the same sport and with identical training background.

In all of the previous studies described, the main study focus was on static biomechanical parameters. In Paper III and IV we have examined dynamic characteristics of the extensor mechanism, which may have a stronger effect as predisposing internal factors since they reflect the loading pattern during training and competition.

Patellar impingement

Johnson et al. (1996) postulated that impingement of the inferior patellar pole against the patellar tendon during knee flexion is responsible for "patellar tendonitis". They studied 24 patients diagnosed with patellar tendonitis and concluded that there was impingement of the inferior patellar pole against the patellar tendon by examining the involved knee in a position of 60º of flexion. In this study they were able to demonstrate kinking between the patella and the patellar tendon, but the reproducibility of their positioning protocol was questioned by the authors themselves. In another study by Schmid et al. (2002), they examined 19 knees diagnosed with patellar tendinopathy with positive MRI findings and a typical history and clinical findings. The control group was 32 asymptomatic knees. They obtained dynamic sagittal images from full extension to 100º of flexion with and without activation of the quadriceps muscle and measured the tendon-patella angle, anteroposterior diameter of the tendon, signal-to-noise ratio, the shape of the inferior patellar pole and the location of the patellar tendon insertion. They found no significant difference between the groups of the tendon-patella angle at any angle, with or without quadriceps muscle activation. The insertion site of the patellar tendon differed significantly with a more posterior insertion being more common in symptomatic knees, but not the shape of the inferior pole of the patella. The volume and the signal -to-noise ratio of zones of increased intratendinous signal, as well as the anteroposterior diameter of the proximal patellar tendon were increased in symptomatic knees. The conclusion of this study was that the data could not support the theory that patellar tendinopathy is caused by patellar impingement, because no difference was detected between symptomatic and asymptomatic knees. In this study, the MR examination protocol differed from the protocol used by Johnson et al. (1996), since the images were obtained through a larger range of motion, with a larger number of measurements at different angles of knee flexion with and without activation of the quadriceps muscle. This means that the study protocol in the study by Schmid et al. (2002) is more valid with regard to the problem they investigated in these studies.

Extrinsic risk factors for patellar tendinopathy

Extrinsic predisposing factors act externally on the human body (Nigg 1988). The most common extrinsic factors are thought to be training errors, excessive loads on the body, poor environmental conditions and poor equipment (Nigg 1988, James et al. 1978, Renström and Johnsen 1985, Smart et al. 1980, Ferretti et al. 1984). Training errors are assumed to contribute to 60 to 80% of tendon and other overuse injuries (James et al. 1978, Renström and Johnsen 1985, Smart et al. 1980), and the main problems are thought to be too high intensity and too fast progression. And as stated by Leadbetter (1992), a sport injury is likely to occur when the athlete changes the mode or use of the involved part of the body. This is called "the principle of transition". However, most papers on this subject are theoretical assumptions and mostly related to running injuries.

Training load

In one of the previously described studies by Ferretti et al. (1984), they examined 407 volleyball players from different playing levels and found the overall prevalence of previous or current symptoms of jumper's knee to be 23% (74 men and 19 women). Of those athletes playing five times a week or more, the prevalence was 41%. There was a near linear relationship between the prevalence of jumper's knee and the number of weekly training and playing sessions. However, they did not find any significant correlation between career duration and the prevalence of jumper's knee.

Floor hardness

The ground reaction forces during landing and take-off can be quite different on different surfaces. The impact force or the force at first contact is much higher for running on asphalt compared with running on grass or sand (Nigg 1988). The ground reaction force is at the same magnitude for those different surfaces, and it is therefore speculated that these high-impact forces are one of the causes of overuse injuries (Nigg 1988). Ferretti et al. (1984) found that 60.7% of the players with jumper's knee played on a cemented or linoleum floor, while only 4.7% of those diagnosed with jumper's knee played on a parquet floor, suggesting a positive correlation between the hardness of the floor and the prevalence of jumper's knee among volleyball players. In line with this, it has recently been shown that the prevalence of jumper's knee among elite beach volleyball players playing on sand is only 9%, considerably lower than for indoor volleyball players (Bahr and Reeser 2003).

As stated previously, the ground reaction force is 6 bw during jumping in volleyball and 10 bw in a long jump take-off (McNitt-Gray 2000). The highest ground reaction forces are seen with ballistic drop jumps, and the resulting forces through the extensor tendons are proportional to the ground reaction force. This may explain the correlation between the number of weekly training sessions and the prevalence of jumper's knee as shown by Ferretti et al. (1984). Other predisposing external factors for jumper's knee than hardness of the floor and number of weekly training sessions have not been examined.

Methodological considerations

From a methodological point of view, predisposing factors for overuse injuries are traditionally divided into external and internal factors. However, this model is unidimensional and does not take into account the dynamic interactions between different risk factors. As stated by Bahr et al. (2003), there is also a need to identify the mechanisms by which the injuries occur, and to consider the temporal dimension in a dynamic multicausal model. One such model is described by Meeuwisse (1994).

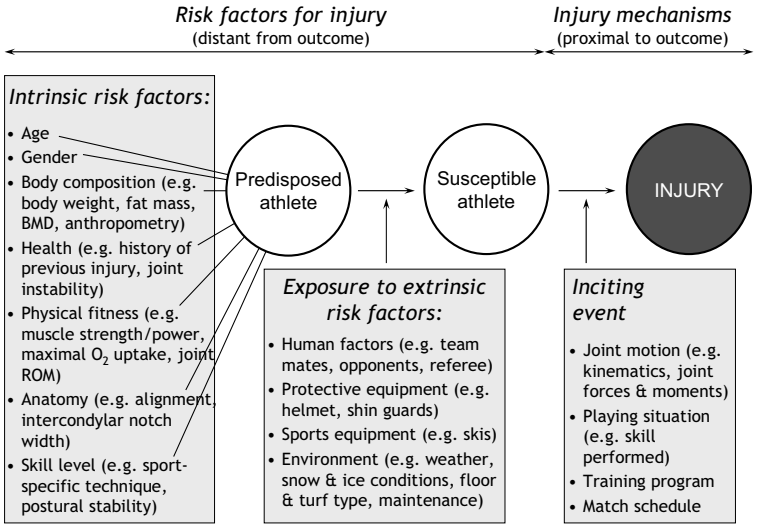


Figure 1. A dynamic, multifactorial model of sports injury etiology as presented by Meeuwisse (1994) and modified by Bahr and Holme (2003) and Bahr and Krosshaug (2005).

This model was mainly developed to describe the etiology of acute injuries. Meeuwisse (1994) states that it is the presence of both intrinsic and extrinsic risk factors that renders the athlete susceptible to injury, but that these factors are not necessarily sufficient to produce injury. In his model the risk factors define a specific predisposition to injury, but there has to be a final inciting event to result in an injury. A specific final event can usually not be identified in the case of overuse injuries, such as patellar tendinopathy. The onset of symptoms is typically gradual and the pathological processes within the tissue may even start a long time before symptoms occur. Therefore, in overuse injuries it may be necessary to study more distant etiological factors to establish a basic understanding of the early pathological processes and in that way be able to establish prophylactic and treatment procedures. Thus, the conceptual model by Meeuwisse (1994) cannot be applied directly to explain the etiology of overuse injuries, but has to be modified to characterize the etiologic factors for overuse injuries. This is highlighted by Bahr and Krosshaug (2005), who emphasize the need to use a comprehensive model, which accounts for the events leading to the injury situation as well as to include a description of whole body and joint biomechanics at the time of injury. In their model different intrinsic and extrinsic factors affect load and load tolerance, and can be used to study the interaction between the different factors causing injury (Bahr and Krosshaug 2005). They state that the key point to consider with regard to biomechanical factors is that they must explain how the event either resulted in a

mechanical load in excess of that tolerated under normal circumstances or reduced the tolerance levels to a point at which a normal mechanical load cannot be tolerated (Bahr and Krosshaug 2005, Mcintosh 2005).

However, the connection between a biomechanical load and the biologic response at the cellular level within the tendon substance is poorly understood. This connection is suggested by Khan et al. (1998), who have described a theoretical model on how tendon injury may precipitate a vicious cycle ("tendinosis cycle") of further injury, modified from Leadbetter (1992). In this model he suggests that an increased demand on the tendon causes microdamage with inadequate repair resulting in inadequate collagen and matrix production. In turn, this results in tenocyte death from excessive strain with further reduction in collagen and matrix production and a predisposition to further injury (Khan et al. 1998). In this model the tendon loading conditions can be regarded as an extrinsic inciting event, and Khan et al. (1998) suggests that there is a correlation between tendon overload and a pathologic response on the cellular level with tenocyte death. Interestingly, he even suggests that susceptible tenocytes may die as a result of excessive strain. In other words, he hypothesizes that there is a connection between a defined biomechanical loading of tendons (strain) and a physiological well-defined response, namely cellular death.

However, all these models are theoretical, and there is an obvious need for specific studies to establish evidence-based models. The overall aim of the present thesis was to examine potential risk factors for patellar tendinopathy and to examine some of the possible cellular responses to these risk factors.

Study aims

Based on the literature outline provided above, the aims of this thesis were as follows:

1. To estimate the prevalence of jumper's knee in different sports, in order to correlate the prevalence to the loading characteristics of the extensor mechanism in these sports and to assess the duration and severity of the symptoms (Paper I).

2. To investigate if there is a gender difference in the prevalence of jumper's knee (Paper I).

3. To compare anthropometric characteristics as risk factors for jumper's knee between athletes with jumper's knee with non-symptomatic controls (Paper I, III, IV).

4. To compare sport history and training background as risk factors between athletes with jumper's knee and non-symptomatic controls (Paper I, III, IV).

5. To characterize differences in the performance ability of the leg extensors in athletes with jumper's knee compared with a control group without knee symptoms (Paper III, IV).

6. To characterize the ultrasound findings of the patellar tendon in athletes diagnosed with jumper's knee compared with non-symptomatic athletes (Paper II).

7. To study some potential pain mechanisms in patellar tendinopathy (Paper V).

8. To study the histopathological findings in biopsies from patients with jumper's knee compared with a control group without knee symptoms (Paper VI).

Methods

Interview and clinical examination

Study populations and interviews

Paper I. This study was designed as a cross-sectional study among Norwegian athletes at the national elite level from different sports. Male athletes from eight different sports were examined; athletics (high jump, 100 and 200 m sprint), basketball, ice hockey, orienteering, road cycling, soccer, team handball, volleyball and wrestling. In addition, female athletes from two of the same sports were examined; team handball and soccer. We wanted to examine approximately 50 athletes in each sport, to provide a precision of 2-7% (proportion standard error) for the prevalence estimate in each group. In the team sports (basketball, ice hockey, team handball and soccer), elite division teams from the largest cities were invited to take part in the investigation, and all invited teams agreed to take part. The teams were examined towards the end of their competitive season. In the individual sports (athletics, orienteering, road cycling, wrestling), we asked athletes participating in the national championships, which were organized during the peak competition season, to take part in the study. All athletes who were present when we visited their team and all athletes we approached in the individual sports agreed to take part in the study.

Paper II and IV. This cohort study was carried out during an international volleyball tournament in Oslo, Norway in May 1994. The tournament was played 2 months after the end of the regular league season with teams competing in classes according to their level of play. The six Norwegian teams participating in the men's elite division in the tournament were invited to take part in the study. These were amateur teams that otherwise competed in the top division of the Norwegian Volleyball Federation (NVBF) leagues. The teams consisted of 53 players and of these, 47 (89%) consented to participate in an interview, a clinical examination, and an ultrasound examination of both knees. Each player went through an interview, and both knees were examined. They were asked about present and former knee injuries and complaints, specifically about symptoms of jumper's knee. Their symptoms were classified according to criteria by Roels et al. (1978), and Blazina et al. (1973). The 47 players who consented to take part were tested with a series of standardized jump and power tests described below. Their patellar tendons were also examined ultrasonographically.

Paper III. In this case-control study the patient and control groups were recruited from division I and II teams in the Norwegian Volleyball Federation (NVBF) leagues, which consisted of 16 men's teams with a total of 164 licensed players. Of these, 141 players participated in two tournaments in September 1989 just prior to the start of the indoor season and these players were interviewed during the tournaments. The athletes in this study were asked about warmup and stretching habits, type of floor in their normal training gym, type of shoe normally worn during volleyball training, as well as data on present and former knee injuries to ensure an identical matching as possible. All players with current knee complaints or a history of previous injury consented to go through a clinical interview and a standard knee examination. Players with current symptoms of jumper's knee were encouraged to report at the testing station for jump testing if they satisfied the following criteria: 1) Symptoms from the patellar tendon only; and 2) No history of intraarticular pathology (positive patella grinding test, positive meniscal tests, instability, locking, 'giving way' or joint effusion), rheumatic disease, previous fractures in the knee region, previous knee surgery or previous corticosteroid injections in or around the patellar tendon. A total of 12 players of those who reported for jump testing satisfied the criteria for inclusion in the patient group and successfully completed the standardized jump testing program. Also, a matched control group consisting of 12 players without knee pain consented to undergo an identical testing program. The control group consisted of players with no history of knee pain and a normal knee examination. The players in the control group were actively recruited to undergo the jump testing programs among team members of the injured players and the players were individually matched with respect to age, function (middle blocker, outside hitter, setter), playing experience and training level.

Paper V and VI. The patient group was selected among athletes from different sports who had failed conservative treatment for patellar tendinopathy. The diagnosis was based on a typical history and clinical findings combined with positive MRI findings compatible with tendinosis to ensure that the biopsies were taken from an area which was assumed to contain pathological tissue. The duration of symptoms had to be more than 3 months.

The control group was selected from patients with tibia fractures from low-energy trauma treated with marrow-nailing. These patients could not have current or previous knee complaints compatible with previous or current patellar tendinopathy. All individuals in both groups had to be more than 18 years old to ensure closed epiphyses. Exclusion criteria in both groups were previous surgical treatment in or around the same knee, previous corticosteroid injections in or

around the same knee, previous serious traumatic events affecting the same knee, all types of rheumatic disease and degenerative knee disorders.

Each patient went through a standardized interview, and the information requested from each athlete included age, height, weight and number of years participating in organized athletic training. Patients were asked to report the number of training hours per week during the competition season (sport specific training, weight training, jump training and other types of training). In order to assess the severity of the condition, the athletes diagnosed with current patellar tendinopathy also self-recorded their VISA score (Visentini et al. 1998).

Diagnostics

Standard form

In all studies information requested from the athletes included age, height, weight, number of years participating in organized training, years of participation at the elite level, total number of training hours per week, number of hours sports specific training per week, weight training and jump training (plyometric training) done each week.

Each athlete went through a standard knee examination and clinical interview on present and former knee injuries and complaints. The following diagnostic criteria for jumper's knee were used: History of pain localized to the lower patellar pole or insertion of the quadriceps tendon in connection with volleyball play and distinct palpation tenderness corresponding to the painful area (Blazina et al. 1973). Previous jumper's knee was diagnosed based on history alone.

In order to assess the severity of the condition, the athletes diagnosed with current jumper's knee in study III and IV were classified according to Roels et al. (1978) as modified by us (see Table 1, p. 18)

In order to assess the severity of the condition in paper IV, V and VI, the athletes diagnosed with current patellar tendinopathy self-recorded their VISA score (Visentini et al. 1998). This is a validated pain and function score with a best score of 100 (no symptoms) and lowest score of 0 (maximum symptoms), which has been developed specifically for this purpose and has been shown to be a valid measure of symptoms (Robinson et al. 2001).

Biomechanical testing

Paper III. In the first biomechanical study, the testing program was carried out using the Ergojump® equipment (KB Ergotest, Mikkeli, Finland), which consists of a contact mat connected to an electronic timer/computer (Bosco and Komi 1979, Bosco et al. 1983, Komi and Bosco 1978, Sale 1990). The equipment measures the flight time of each jump, and the jump height (in cm) is calculated from this. In addition, power (W) is calculated from flight and contact times during rebound jumping (Bosco et al. 1983). The jumps performed were standing jump (SJ), counter-movement jump (CMJ), standing jump with a 20 kg load ($SJ_{20\ kg}$), standing jump with a load corresponding to one-half body weight ($SJ_{1/2\ bw}$), and a 15-s rebound jump test (RJ). As described by Komi and Bosco (1978), standing jumps were performed with the subjects starting from a stationary semi-squatting position with 90° knee flexion. No counter movement was allowed with any body segment, and hands are kept fixed on the hips. In the counter-movement jumps the subjects started the movement from a stationary erect position with knees fully extended and they were then required to bend down to approximately 90° knee flexion before starting the upward motion of the jump. The 15-s rebound jump test consisted of continuous counter-movement jumps, where the subjects were encouraged to jump as high and as fast as possible for 15 s. Rebound jumping was also performed with hands fixed on the hips, and in each jump squatting down to approximately 90° knee flexion. In particular, care was taken to ensure that there was no counter-movement in the standing jumps and that the subjects landed with straight legs. The best out of three technically correct attempts was recorded and used for the statistical analysis, except for the 15-s rebound jump test, which was performed only once.

Paper IV. In the second biomechanical study, the players went through a standardized jump and power testing program. The testing program was performed using a contact mat connected to a computer (Intervall A/S, Oslo, Norway). The jumps performed were SJ, CMJ, $DJ_{45\ cm}$, $SJ_{20\ kg}$, $SJ_{1/2\ bw}$, $SJ_{1/1\ bw}$, and a RJ. $DJ_{45\ cm}$ was a drop jump from a dropping height of 45 cm. Otherwise the performance of the different jumps was the same as described in Paper III. In addition, during the execution of the $SJ_{1/2\ bw}$ and $SJ_{1/1\ bw}$ tests, average velocity, force and power during the jump were measured using the Ergopower system (Ergotest Technology AS, Langesund, Norway). The equipment measures the displacement of gravitational loads, in this case barbells, as external resistance (Bosco et al. 1995). The vertical displacements of the loads are monitored with mechanical and sensor arrangements. When the subject moves the loads, the signal from the sensor interrupts the microprocessor every 3 mm of displacement. Thus, it is possible to calculate

velocity, acceleration, force, power, and work corresponding to the load displacements. The system has been shown to be adequate in terms of its accuracy and reproducibility (Bosco et al. 1995).

Figure 2. Illustration of the experimental setup for the jump tests. During all tests the players jumped on a contact mat connected to a computer, making it possible to compute jumping height (Bosco et al. 1983).

Ultrasound examination

Ultrasonography was performed using a 7.5 MHz real-time, linear array probe (Model Sonoline SI 400, Siemens, Germany). A stand-off gel mattress was used to enhance the image. The players were scanned in a supine position with the knee in about 30 degrees of flexion to ensure an extended tendon (Kälebo et al. 1991, Fornage 1987). All ultrasound examinations were performed by an experienced ultrasonographer who was blinded to the patients' history and the results of the clinical examination. The patellar tendon was examined for any of the following

changes: Hypo- or hyperechoic zones, signal changes in the anterior surface or the posterior margin, and bursa appearance. Care was taken to hold the probe perpendicular to the tendon (Kälebo et al. 1991, Fornage 1987). The length of any hypoechoic zones was recorded. Prints of the images were also obtained for future reference.

The lengths of the patella and patellar tendon were measured using longitudinal scans. Similar to the Insall-Salvati index (Insall and Salvati 1971), an index of patella length to patellar tendon length was calculated. Finally, the proximal and mid-part width and thickness of the tendon were measured using transverse scans (Fig. 3). Assuming an ellipsoid shape, the proximal and mid-part cross-sectional areas of the tendon were calculated as: $\pi \times (W/2) \times (T/2)$, where W is the width and T is the thickness of the tendon.

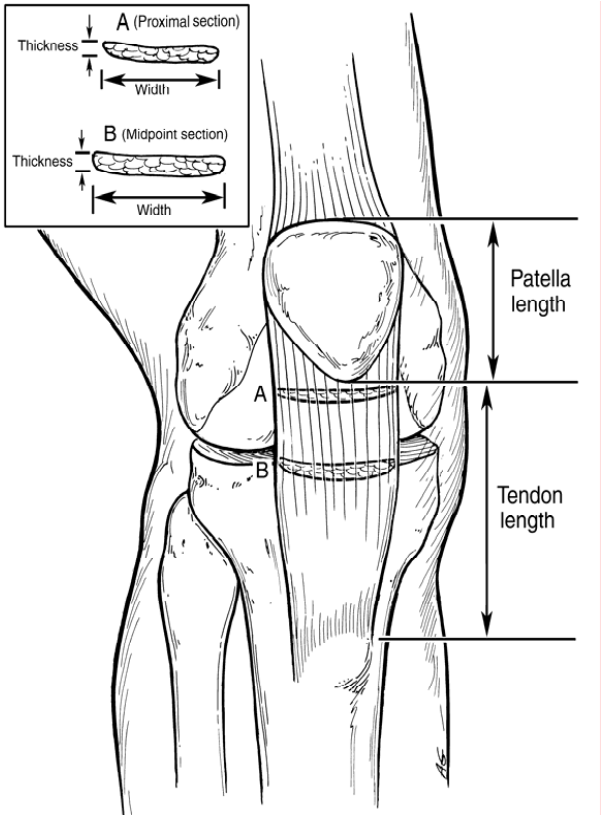


Figure 3. Measurements of patellar length, and patellar tendon length, width and thickness of the patellar tendon as made on ultrasound scans.

Immunehistochemistry

Surgical technique

The surgical exposure was identical in the two groups, the patient group with patellar tendinopathy and the control group with tibia fracture, with a straight medial or lateral parapatellar incision, splitting of the paratenon and exposure of the patellar tendon. In both groups the biopsies were taken with the proximal limit at the bone-tendon junction. In the control group the biopsies were taken with a width of at least five mm and a length of at least 20 mm from the middle portion of the tendon. In the patient group the biopsies were taken in the same manner, since the pathological tissue was confined to the middle and proximal part of the tendon. The biopsies were taken with full thickness of the tendon in the anterior-posterior direction.

Biopsy procedure

The biopsy handling was identical in the two groups. Immediately after the surgical procedure, the biopsies were transferred to Zamboni solvent (Zamboni and De Martino 1967). The biopsies were stored in this solution for 4-24 hours, and then washed in 0.1 M phosphate-buffered NaCl (PBS), pH 7.2, with 15% sucrose (weight/volume) and 0.1% natriumazide. The biopsies were then stored in PBS at 4 °C for a minimum of 48 hours. They were stored in this way for later immune-histochemical analyses.

Nerve staining and analyses

The samples were sectioned at 15 μm on a Leitz cryostat and frozen sections were mounted directly on Super-Frost/Plus glass slides and stained using the avidin-biotin or the haematoxylin-eosin systems, for immunohistochemistry and light microscopy, respectively.

Immunohistochemistry

The slides were rinsed for 10 min in PBS. Incubation with 10% normal goat serum in PBS for 30 min blocked nonspecific binding. Subsequently, the sections were incubated overnight in a humid atmosphere at +8C° with primary antisera for protein gene product 9.5 (PGP, 1:10000, Ultraclone, UK), a general nerve marker, substance P (SP, 1:10000, Peninsula Laboratories, USA) and tyrosine hydroxylase (TH, 1:5000, Peninsula Laboratories, USA), a rate-limiting enzyme

reflecting the occurrence of noradrenaline (NA). After incubation with the primary antisera, the sections were rinsed in PBS (3x5 min) and then incubated with biotinylated goat anti-rabbit antibodies (1:250, Vector Laboratories, CA, USA) for 40 min at room temperature. Finally, the sections were incubated for 40 min with Cy3-conjugated avidin (1:5000, Amersham International plc, UK). Control staining was performed by omitting the primary antiserum. A Nikon epifluorescense microscope (Eclipse E800, Yokohama, Japan) was used for the analyses. The occurrence of PGP, SP and TH was subjectively assessed and pictures were taken for subsequent semi-quantitative analyses.

Semi-quantitative analysis

After the subjective assessment, the following steps identified in an earlier study (Ackermann et al. 2002) were applied in order to optimize the semi-quantitative analysis: The patellar tendon biopsies were sectioned longitudinally and the sections were numbered consecutively from the dorsal to the ventral aspect. Three sections from different levels, i.e. ventral, middle and dorsal parts of the tendon were chosen to represent the full thickness of the tendon. Staining was performed simultaneously for all sections to be compared. For microscopic analysis, a video camera system (DXM 1200, Nikon) was attached to the epifluorescence microscope and connected to a computer. From each section, one image from the microscopic field (20x objective) exhibiting the strongest immunofluorescence was stored in the computer. Thereafter, the images were analyzed using the software Easy Analysis (Technooptik, Sweden). The software denotes and considers all positively stained nerve fibers beyond a defined threshold of fluorescence intensity. The results were expressed as the fractional area occupied by positive fibers in relation to the total area. The fluorescent/total area was determined in three images in each biopsy of the patient and control groups, respectively. In the microscopic analysis, the mean interobserver coefficient of variation was 9.8 % and the intraobserver variation was 9.6%. For statistical analysis, the mean fluorescent/total area was calculated for each of the ten biopsies from both the patient and the control group.

Apoptosis assessment

Light microscopic appearance

5 μm sections were routinely stained for H&E (general morphology) and Alcian Blue (sulphated glycosaminoglycans) and viewed at 100 to 630x magnification on a Zeiss Axioplan upright microscope.

Detection of apoptosis and assessment of caspase activation

Apoptosis was assessed using a monoclonal antibody against single-stranded DNA breaks (F7-26; Chemicon, Temecula, U.S.A.), as well as with a polyclonal antibody against the active (cleaved) form of caspase-3 (Asp 175; Cell Signaling), and propidium iodide staining (Sigma-Aldritch) for nuclear morphology. Of these methods, the cleaved caspase-3 antibody yielded the most specific and reproducible labeling of apoptotic cells in tonsil tissue (serving as a positive control), and was thus used for systematic quantification. The sections were cleared, quenched in 3% hydrogen peroxide, incubated in protein-free block for 15 min, then left overnight with the antibody diluted 1:50 in 0.1% bovine serum albumin in tris buffered saline (TBS). Slides were then sequentially exposed in a dark, moist chamber to horse radish peroxidase-conjugated goat-anti-rabbit (1:100, 30 min), fluorescyl-tyramide amplification reagent (DAKO Diagnostics, Glostrup, Denmark), anti-fluroescein-horse radish peroxidase, and finally 3,3'-diamino-benzidine (Vector Laboratories, Burlingame, U.S.A.) for 5', with 3x5' washes in TBS between each step. Bouin's fixed tonsil with or without the primary antibody was used as positive or negative control, respectively.

Image analysis

The identity of slides was masked with black tape. Using a 40x objective lens, the tissue section was illuminated with halogen or fluorescent light (488 nm wavelength) and respective areas of positive F7-26 or propidium iodide staining were captured at 1392 x 1045 pixels with a digital camera (Retiga Exi 1394, Qimaging Corp, Burnaby, Canada). For quantitation of apoptosis, fifteen random areas (0.30 mm^2 each) from the proximal region were digitized. Cells were considered positive only if the labeling was dense and suggestive of apoptotic morphology. A standard exposure time (50ms) was used through, and the contrast was not digitally adjusted.

Ethics

Study II, III, IV, V and VI were approved by the Regional Ethical Committee for Medical Research. In all six studies participation was voluntary and consent was obtained.

Statistics

In paper IV, in order to evaluate the performance ability of the leg extensors for each player a composite jump index was calculated by rating each player's result on a scale from 0 to 100 on each of the following jump tests: SJ, CMJ, CMJ-SJ, DJ, RJ, $SJ_{20\ kg}$, $SJ_{1/2\ bw}$ (power) and $SJ_{1/1\ bw}$ (power), where 0 represents the lowest test score among all the players tested and 100 the best score. The overall score was computed as the average of the results from each of these eight scores. Descriptive data are given as means ± SD and/or range unless otherwise noted. Comparisons of continuous data between groups were done using analysis of variance or unpaired t-tests, as noted in the results. Prevalence was compared between groups using Pearson chi-square tests. In paper IV proportions are reported with the corresponding SE, where relevant. In paper IV multiple logistic regression was used to test the effect of potential risk factors for jumper's knee (age, height, weight, experience at elite level, volume of sports specific training, weight training and jump training), adjusting for differences between sports. An alpha level of 0.05 was considered significant.

In Paper VI, for quantitation of apoptosis, the following variables were compared using caspase-3-labeled tissue sections; total number of positive cells in all areas, number of positive fields, average number of positive cells per field, and Apoptotic Index (% positive cells in all fields).

Results and discussion

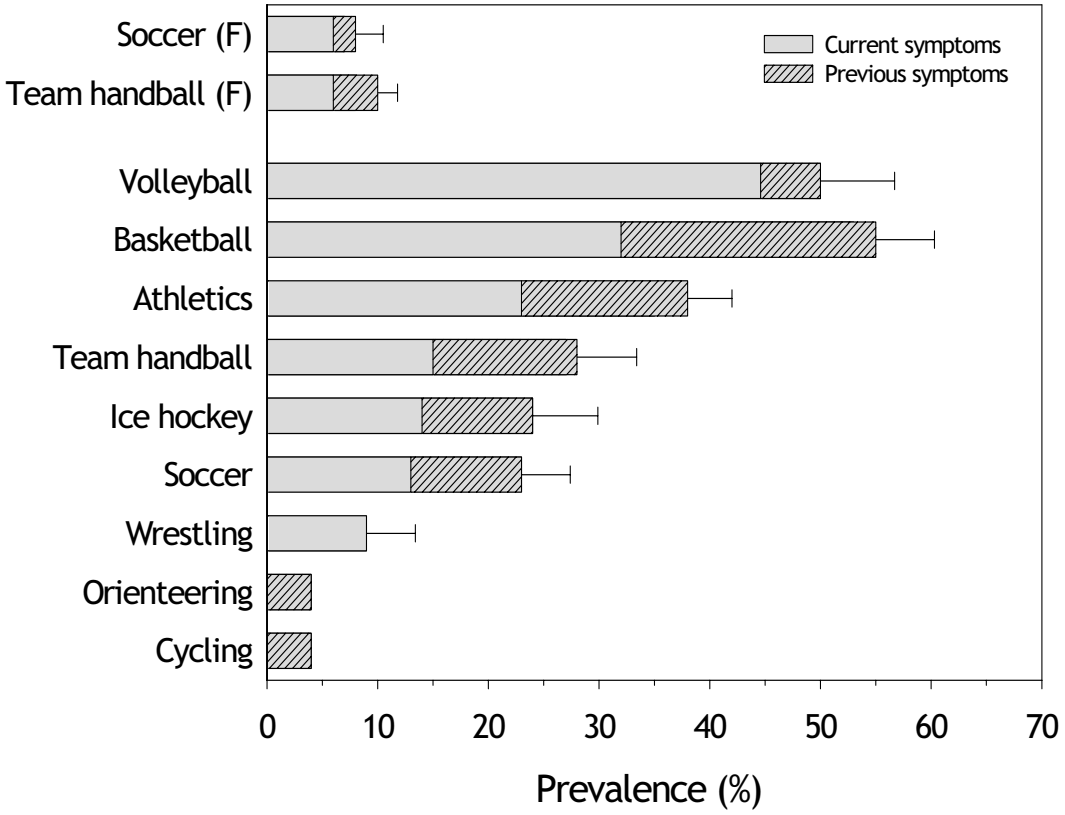
Prevalence data

Results

Paper I. The overall prevalence of current jumper's knee was 14.2±1.4% (87 of 613 athletes). Of the 87 athletes with current symptoms, 37 had bilateral symptoms, while 30 athletes had symptoms from the right side only and 15 players had symptoms from the left side only. This means that the prevalence of current jumper's knee affecting the right knee was 10.9% (67 players) and of the left knee 9.3% (57 players). In addition, 51 athletes (8.3%) reported previous symptoms of jumper's knee affecting one or both legs, resulting in a prevalence of current or previous symptoms of 22.5% (138 of 613 athletes). Only one athlete diagnosed with current jumper's knee localized the pain to the quadriceps tendon insertion at the upper patellar pole, the rest localized the pain to the patellar tendon.

As shown in Fig. 4, there were significant differences in the prevalence of current jumper's knee ($\chi 2$ test, $p<0.001$), as well as in the prevalence of previous symptoms ($\chi 2$ test, $p<0.001$). The prevalence of current symptoms was highest in volleyball with 44.6±6.6% and basketball with 31.9±6.8% while there were no cases in cycling or orienteering.

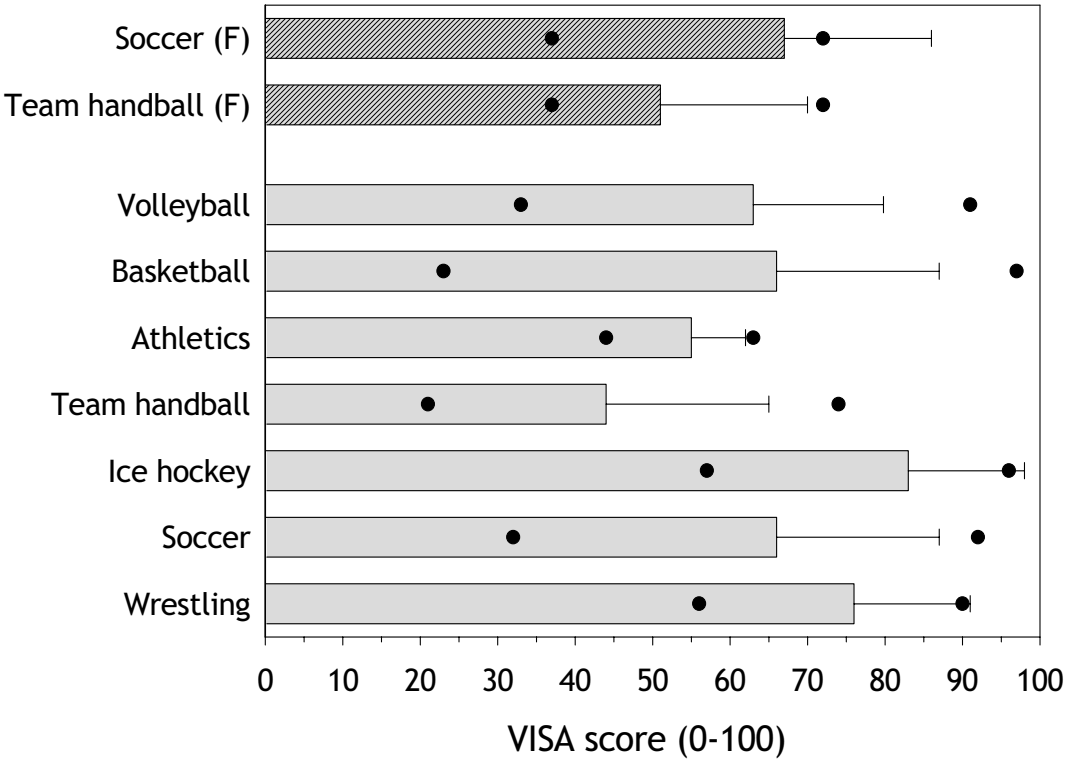
Figure 4. Prevalence (%) of current (white bars) and previous (hatched bars) symptoms of jumper's knee. The results for female athletes (F) are shown in the two upper bars, the rest of the results are for male athletes. Error bars denote SE.



The mean symptom duration among athletes with current jumper's knee was 32±25 months (range: 1-144 months, n=87). There was a significant difference in symptom duration between the different sports (ANOVA, p=0.04).

The mean VISA score reported across sports and genders was 64±19. As seen in Fig. 5, the VISA score reported by players with current symptoms of jumper's knee was significantly different between sports (ANOVA, p=0.003). The lowest VISA score was reported by male team handball players and the highest by ice hockey players.

Figure 5. VISA scores for players with current symptoms of jumper's knee in the various sports groups. For players with bilateral symptoms, the lowest value (worst knee) has been used. The top two hatched bars show the results for female athletes (F) from soccer and team handball, the open bars show the results for male athletes. No results are given for orienteering and cycling, since there were no athletes with current symptoms in these groups. The bars and error bars denote the mean and SD. In addition, the filled circles show the lowest and highest value in each group.



Paper III. In Paper III we examined 16 men's Division I and II teams with a total of 164 licensed players. Of these, 141 players participated in two tournaments in September 1989 just prior to the start of the indoor season and these players were interviewed during the tournaments. 55 players (38%) were diagnosed with current jumper's knee.

Paper IV. Of the 47 players participating in the study, 24 players (51.0%) were clinically diagnosed with current jumper's knee affecting at least one side. Twenty players (42.6%) had never experienced problems from any knee, whereas 3 players reported having had previous knee problems identified as jumper's knee (6.4%). The severity of symptoms among those with current jumper's knee (n=33 knees) was classified as grade I in 6 knees, grade II in 18 knees and grade IIIa in 9 knees. The onset of symptoms was gradual in 31 knees (94%) and acute in 2 knees, and

the duration of symptoms reported by the players with current complaints of jumper's knee was 3.5±2.4 (0.1-10) yrs. The age at symptom onset was 18.8±2.8 yrs (13.5-25.9).

Discussion

The main finding of Paper I was that the overall prevalence of jumper's knee was 14% across the sports included. In addition, 8% of the athletes reported previous symptoms, indicating that every fifth elite athlete is affected by jumper's knee during their athletic career. The prevalence varied between sports—from no cases in cycling and orienteering to 45% with current symptoms in male volleyball. In Paper III the prevalence of current jumper's knee was 38% and in Paper IV 51%. These prevalence figures probably represent *minimum* estimates since the athletes with the most serious problems, those who could not participate in training or competition, were not included in the studies. We do not know the number of athletes who were too disabled to be included. This may be a significant source of error, particularly in the individual sports, where it is more likely that an athlete would withdraw or not even enter the national championships if he thought that he could not perform fully. Also, an unknown number of athletes may have retired early because of jumper's knee, and some may have settled for a career on a lower level of performance because they could not tolerate the heavy training and competition load at the elite level. Thus, the elite samples we were able to study represent the survivors, and the true career prevalence is higher than that reported here as an overall result across the sports included.

It should also be noted that the mean duration of the symptoms was 32 months with a mean VISA score of 64. The information on the duration of the symptoms is based on memory, which means that the precision of this information is uncertain. Nevertheless, it seems clear that even with this limitation, there is no doubt that the majority of patients have played with symptoms for several years. This means that this condition can severely interfere with athletic performance, and even threaten an athletic career.

Another methodological limitation which must considered when interpreting the results is that the results are based on clinical examination alone, except in study II where we did an ultrasound examination. For practical reasons, we were not able to do MR or ultrasound imaging in the other studies to confirm the presence of structural tendon changes. This means that to be recorded as having current symptoms of jumper's knee, the athlete had to report a painful tendon during athletic activity with corresponding palpation tenderness. It may be argued that this definition is unspecific, since we do not know for certain that the tendon was the source of the pain in all cases. For instance, we could not rule out cases with referred pain, principally from the

distal aspects of the articular surface of the patella. In fact, a number of studies have shown that the correlation between clinical findings and ultrasound (Myllymäki et al. 1990, Cook et al. 2000a, Khan et al. 1997, Khan et al. 1999) or MR (Davies et al. 1991, Bodne et al. 1988, Khan et al. 1996) examinations is low, and even that symptoms and tendon changes come and go independently (Cook et al. 2000a, Cook et al. 2001). A significant number of athletes have or develop visible tendon changes without symptoms of jumper's knee and some have significant pain without detectable tendon changes (Cook et al. 2001). Thus, we would argue that the current clinical definition provides the most valid estimate for the prevalence of jumper's knee, since it will detect all players with tendon symptoms during athletic performance.

To our knowledge, there are no previous reports on the prevalence of jumper's knee across different sports, although a number of case series presenting the outcome after surgical treatment indicate that the majority of patients are from sports with high demands on speed and power (Karlsson et al. 1991, Raatikainen et al. 1994, Martens et al. 1982)

As expected, in the present study the prevalence was high in volleyball and basketball (55% reporting current or previous jumper's knee), sports characterized by high demands on speed and power. The maximal muscle force that can be generated eccentrically is 1.5-2.0 times higher than the maximal isometric force, and several-fold higher than maximal concentric force, especially at high speeds (Herzog 2000). Also, the ground reaction force is different between different tasks, ranging from 2.8 times body weight during distance running to 6 bw during jumping in volleyball and 10 bw in a long jump take off (McNitt-Gray 2000).The highest ground reaction forces are seen with ballistic drop jumps, and the resulting forces through the extensor tendons are proportional to the ground reaction force. Therefore, it is reasonable to suggest a connection between the loading pattern of the knee extensors and the prevalence of jumper's knee. This seems to match the prevalence distribution seen in the present and previous studies, with the highest in basketball and volleyball (high jump volume and eccentric load), then athletics (sprinters and jumpers, high load, but less volume), followed by team handball, soccer and ice hockey (less jumping, some sprinting) and low prevalence among orienteerers (high volumes of running, but no sprinting) and road cycling (high volumes of concentric work, no ballistic loading).

Gender

Results

Paper I. The prevalence of current jumper's knee was lower among women with 5.6±2.2% (6 of 107 team handball and soccer players) compared with a combined prevalence of 13.5±3.0% (18 of 133) in the corresponding male sports (χ^2 test, p=0.042). However, there was no difference (t-test, p=0.48) in the duration of symptoms between female (22±12, n=6) and male athletes (28±21, n=55). Also, there was no gender difference in VISA score. The VISA score in female team handball and soccer was 59±15, compared with 58±23 in the same male sports (ANOVA, p=0.9).

The number of years of participation in organized training was 15.2±5.1, with 6.1±4.2 years at the elite level. The number of hours with sport-specific training was 11.8±3.9. There was no significant gender difference in these variables between athletes with current jumper's knee and those without.

Discussion

Gender as a risk factor for jumper's knee had not been studied before in contrast to acute knee injuries, particularly ACL tears (Myklebust et al. 1998, Arendt and Dick 1995). The prevalence of current symptom was 5.6% among female team handball and soccer players compared with 13.5% in the corresponding male sports. The question is what the cause of the apparent gender difference is. We chose team handball and soccer to examine the gender difference, since these are sports which in Norway are played at an equally high performance level by men and women, where we therefore thought player experience and training volumes would be similar. Also, we expected a relatively high prevalence of jumper's knee in these sports. As seen from Table 4 in Paper I, the training volumes (15-17 h/week total training time) and background (15-18 years of organized training, 5-7 years at the elite level) were similar between men and women. The difference in prevalence may be attributed to a number of other factors. It is well documented that the jumping ability and force-generating capacity is lower among women than men (McNitt-Gray 2000). So, even if the number of sprints and jumps may be similar between men and women playing the same sports, the lower prevalence may simply reflect that the forces that are transmitted through the quadriceps and patellar tendons are lower among women.

Antropometrical data

Results

In Paper I athletes with current jumper's knee weighed more (83.6 kg±11.6 vs. 77.3 kg±11.9, $p<0.001$) and were taller (186±9.5 cm vs. 181±9.2 cm, $p<0.001$).

In male soccer the jumper's knee group was significant taller than the others (186 ±4.3 cm vs.183 ±5.5 cm, $p=0.05$). Otherwise, there were no other significant differences between those with jumper's knee compared with those without within each sport with regard to age, height and weight. In a logistic regression model which included gender, sport, age, height, weight, training background, and the volume of the different types of training, only weight training and jump training were significant factors.

In Paper III there was no difference between the groups with regard to age, height and weight.

In Paper IV players with jumper's knee had a significantly higher body weight than the controls, but there was no difference in height and age.

Discussion

Age was not a significant risk factor for jumper's knee in any of the present studies. Among volleyball players there was no significant difference in height between players with jumper's knee compared with controls. In the overall material in Paper I (prevalence study), the athletes with jumper's knee were significantly taller, but within each specific sport there was only significant difference in height among male soccer player. In a logistic regression model which included gender, sport, age, height, weight, training background, and the volume of the different types of training, only weight training and jump training were significant factors. As a conclusion, height is not a significantly associated risk factor for jumper's knee. In Paper I and IV athletes with jumper's knee were significantly heavier than those without jumper's knee. We did not examine body composition, but it seems unlikely that the body weight difference observed was due to differences in body fat in such a well-trained population of players. The players with jumper's knee reportedly trained significantly more with weights than the others in study II and IV. This weight training by itself means a higher total loading of the extensor apparatus, and the anticipated effect of this training is also to increase muscle mass and jumping ability.

Sports history and training background

Results

Paper I. The number of years of participation in organized training was 15.2±5.1, with 6.1±4.2 years at the elite level. The number of hours with sport-specific training was 11.8±3.9. There was no significant difference in these variables between athletes with current jumper's knee and those without. However, athletes with current jumper's knee did significantly more weight training (3.5±2.4 h/week vs. 2.5±2.1, $p<0.001$) and jump training (1.1±1.8 h/week vs. 0.5±1.0, $p<0.001$).

The comparison between athletes with current jumper's knee and those without within each specific sport showed that in basketball, the athletes with jumper's knee did significantly more sport-specific training than those without jumper's knee (14.7±2.7 h/week vs. 12.3 ±2.5 h/week, $p=0.005$). In male handball the athletes with jumper's knee did significantly more plyometric training compared with those without jumper's knee (0.7±1.0 h/week vs. 0.2±0.3 h/week, $p=0.01$). In a logistic regression model which included gender, sport, age, height, weight, training background, and the volume of the different types of training, only weight training and jump training were significant factors.

Paper III. In this study the players with jumper's knee did a significantly higher number of weekly training sessions compared with the athletes without jumper's knee. There was no difference between the groups with regard to number og seasons played, weight training, jump training, warm-up time or stretching time.

Paper IV. The characteristics of the players and their training background are shown in Table 2. The prevalence of current jumper's knee was significantly higher among outside hitters (68%) and middle blockers (64%) compared with utility players (28%) or setters (18%).

*Table 2. Characteristics of players with current symptoms of jumper's knee (n=24), and without history of jumper's knee (n=20). Values are means ± SD. *Significantly different from players without history of jumper's knee (unpaired t-tests).*

	Current jumper's knee	No history of jumper's knee	Significance level (p)
Organized volleyball training (yrs)	8.0±2.8	7.5±3.6	0.55
Training at senior level (yrs)	6.8±2.5	5.7±3.6	0.28
Training at elite level (yrs)	2.5±2.6	2.2±3.2	0.70
Volleyball training (h/wk)	7.7±2.1	7.4±1.6	0.53
Weight training (h/wk)	4.5±2.8*	2.3±2.3	0.009
Jump training (h/wk)	0.4±0.9	0.6±1.1	0.53
Sum training (h/wk)	12.6±4.2	10.3±3.9	0.06
Stretching during warm-up (min)	3.4±3.0	3.1±2.7	0.71
Stretching after training (min)	6.2±5.8	7.1±3.9	0.55

Discussion

Epidemiological studies on extrinsic factors have shown that the hardness of the playing surface and an increased frequency of training sessions correlate positively with the prevalence of jumper's knee (Ferretti et al. 1984, Ferretti 1986). This is supported by the results in Paper I, which shows a small, but significant difference in training volume between players with and without symptoms. In Paper II we found no difference between the groups in the total amount of specific volleyball training, since all the players were selected from a well-trained group with a similar training history. In Paper I, athletes with jumper's knee did significantly more jump training. In the same study the sport with the highest prevalence of jumper's knee was basketball (55% reporting current or previous jumper's knee), a sport characterized by high demands on speed and power. In this sport, athletes with current jumper's knee did significantly more sport-specific training than those without jumper's knee. In other words, there is substantial evidence to suggest a link between the total load on the tendon and the prevalence of jumper's knee.

Volleyball involves approximately 60 maximal jumps per hour of play, and previous studies have shown that the prevalence of jumper's knee increases with increased frequency of training (Ferretti et al. 1984, Neri 1991). The tactics of the game require middle blockers jump more than others, and it has been shown that they have a higher prevalence of jumper's knee (Neri 1991). We did find that the prevalence of jumper's knee was significantly higher among outside hitters and middle blockers compared to utility players and setters. This is not surprising, since outside

hitters and middle blockers perform a much higher number of maximal jumps than setters as a result of their function on the team. In line with this, it has recently been shown that the prevalence of jumper's knee among elite beach volleyball players is only 9%, considerably lower than in indoor volleyball players (Bahr and Reeser 2003). The explanation for this difference in prevalence is probably that jumping and landing in soft sand is less demanding on the tendon than is jumping on indoor playing surfaces. Thus, there is reason to suggest that the prevalence of jumper's knee in volleyball players is closely related to the volume of jumping and playing surface hardness.

The players with jumper's knee reportedly trained more with weights than the others (Paper I and IV). In Paper I, a logistic regression model which included gender, sport, age, height, weight, training background, and the volume of the different types of training, only weight training and jump training were significant factors. This weight training by itself means a higher total loading of the extensor apparatus, and the anticipated effect of this training is also to increase muscle mass and jumping ability. This is supported by the fact that the players with jumper's knee had a higher body weight than those without jumper's knee.

However, in the present studies we do not have detailed information on the training history of the players at the time they were first injured. At that time there may have been differences in e.g. training volume or intensity that we were unable to detect in a cross-sectional study, and longitudinal studies are necessary to examine in detail how training programs may lead to tendon overload.

Biomechanical data

Results

Paper III. The players from the patient and control groups came from the same teams, used the same type of shoe, and trained and played on the same type of gym floor. The characteristics of the patient group and the matched control group who underwent the jump testing program are shown in Table 3.

*Table 3. Characteristics of patient group (n=12) and control group (n=12). Values are means ± SD. *Significant difference between groups.*

	Patient group	Control group
Age (yrs)	23.7 ± 3.0	24.8 ± 4.6
Height (cm)	189.3 ± 7.0	187.9 ± 4.9
Weight (kg)	*84.1 ± 5.6	79.2 ± 3.7
No. of seasons played	7.2 ± 2.2	8.5 ± 2.8
No. of training sessions per week	4.6 ± 1.2	4.3 ± 1.1
Weight training (h/wk)	1.0 ± 1.0	1.0 ± 0.6
Jump training (h/wk)	0.3 ± 0.7	0.5 ± 0.5
Warm-up time (min)	19 ± 7	20 ± 3
Stretching time (min)	6 ± 4	5 ± 3

In the jump tests the patient group performed better than the control group in the counter-movement jump, the standing jump with a 20 kg load, and the 15-second rebound jump test. Also, the work done in counter-movement and standing jump was greater in the patient group, as was the difference between jump height in counter-movement and standing jumps.

Paper IV. The jumper's knee group scored significantly higher than the control group on the composite jump score (50.3 vs. 39.2, p=0.02), and significant differences were also observed for work done in the drop jump, and average force and power in the standing jumps with half and full body weight loads.

Thirty-seven players (79%) reported using a right-left step-close takeoff technique in the spike jump, whereas 10 players (21%) used a left-right takeoff. Only one player reported preferring the right leg when landing after the attack, whereas 31 players (66%) reported a balanced landing technique, and 15 players (32%) reported favoring their left leg when landing. The takeoff and landing techniques among the players with current jumper's knee are shown in Table 4.

Table 4. Takeoff and landing technique in spike jump among players with current jumper's knee on the right and left side.

	Right knee (n=22)	Left knee (n=11)
Right-left takeoff	20	11
Left-right takeoff	2	0
Right-left landing	0	0
Left-right landing	6	4
Simultaneous landing	16	7

Discussion

The main finding of these studies was that the groups of players with jumper's knee performed better in standardized series of jump and power tests compared with the control groups.

Dynamic characteristics such as jumping capacity and loading of the extensor mechanism are by definition possible intrinsic predisposing factors for jumper's knee. However, data on intrinsic disposing factors for jumper's knee is limited and it is not known why some players have problems, whereas others do well despite almost identical external predisposing factors, such as high training and jumping volumes. There is no convincing evidence in support of suggestions that injury may be associated with malalignment of the extensor mechanism of the knee, patella alta, abnormal patella laxity or other structural abnormalities (Ferretti et al. 1984, Ferretti 1986, Kujala et al. 1986, Kujala et al. 1989, Kujala et al. 1987, Torstensen et al. 1994). However, the problem may be related to the performance characteristics of the leg extensors. Players who jump well load their tendons more than others and this may lead to a greater risk of injury. Our data seem to indicate that this is the case, because the patient group in both studies performed better compared with the control group.

In Paper III it is interesting to note that the test results did not differ between the groups for all modes of jumping. The standing jump is designed as a "pure" concentric movement, and the results for unloaded jumping did not differ between the groups. However, for the counter-movement jump, which consists of a ballistic movement of a rapid eccentric muscle action immediately followed by a maximal concentric contraction, there was a significant difference between the groups. We also observed a significant difference in the 15-second rebound jump test, which consists of a series of ballistic jumping movements. Consequently, it may be suggested that the main difference between the groups could be the way in which they were able to utilize the eccentric pre-stretch component of the ballistic motion to increase their jumping height.

However, we could not reproduce these results in Paper IV. Paper III included a smaller number of players, and in a case-control study it is possible that a selection bias may have occurred. However, the performance of the players with jumper's knee in Paper III in the counter-movement jump test and the rebound jump test was significantly better than the results of the players in Paper IV. This suggests that the injured players in the first study had a highly developed leg extensor apparatus, which may implicate a stronger predisposition towards jumper's knee.

The right knee was affected twice as often as the left knee (Paper IV). The majority of the players used a right-left step-close takeoff technique, and none of the players reportedly preferred the right leg when landing after the attack. In fact, 20 of the 22 players with current jumper's knee on the right side used a right-left takeoff technique. This suggests that a relationship may exist between the takeoff technique and jumper's knee, and that the forces sustained during takeoff may be of considerable importance. In order for a right-handed player to obtain proper alignment of the upper body for an effective spike, the preferred technique involves placing the right foot first and about 45º externally rotated (Selinger and Ackermann-Blount 1986). When using this takeoff technique, the deceleration work is mostly done with the right leg, subjecting it to higher eccentric loading than the left leg. Also, when these high loads are imposed, the right leg may be in a state of functional malalignment. The preferred takeoff technique results in a valgus position of the right leg, a greater flexion angle of the knee, as well as external rotation of the tibia relative to the femur. It is possible that these factors result in a more unfavourable loading pattern of the right knee with respect to development of jumper's knee. Motion analysis and direct force measurements are necessary to study this phenomenon in more detail. Based on the present studies there is reason to suggest an overall better jumping capacity, especially in jumps with an eccentric component, as important intrinsic predisposing factors for jumper's knee.

For the injured athletes to have been able to jump higher than the control subjects, a larger vertical impulse must have been produced. Force was not measured directly in Paper III, but it is likely that the force transfers through the patellar tendon were larger as well. From previous studies of volleyball players, it is known that good jumpers are characterized by a shorter contact time and higher peak force during take-off (Selinger and Ackermann-Blount 1986). Thus, the difference in peak force is likely to be larger than the difference in the jump result alone would seem to indicate. Since more than 50% of the work done in jumping is produced by the knee extensors (Luhtanen and Komi 1978), it seems reasonable to conclude that the differences

observed in jumping height reflects a true increase in the force transfer through the patellar tendon.

The jumping ability of the players, 40-45 cm in a counter-movement jump, may not seem impressive. However, the jumping mode tested differs from the techniques used when playing volleyball. In a spike jump players usually employ an approach run of two steps, a step-close take-off technique and a full arm swing, thereby adding another 55-65% to their counter-movement result (Bahr et al. 1992). There is a close correlation between the results of a counter-movement jump and a spike jump (r=0.96) (Bahr et al. 1992), and based on this relationship the spike jump of this group of injured players may be estimated to range from 55 to 92 cm. The forces involved during take-off and landing are also larger than during the standard test situation used in the present study (Bahr et al. 1992).

In Paper IV the composite jump index was designed as an overall indicator of a player's ability to load the extensor apparatus during conditions ranging from slow-speed concentric (standing jump with added load) to high-speed ballistic (rebound jumps). The dynamic testing program was selected to resemble the various loading conditions imposed on the leg extensors during different jumping and cutting movements used in the game of volleyball. The significant difference observed between the groups in the composite jump index may be taken as an indication that the leg extensor apparatus in the group with jumper's knee may be subjected to higher loads during volleyball play, as well. There were significant differences between the players with current jumper's knee and those without both in average force and average power in standing jumps with added loads corresponding to one-half and whole body weight. Consequently, the forces acting on the tendon or the rate of force development during jumping may surpass the adaptive abilities of the tendon.

The study designs have some limitations which must be borne in mind when interpreting the results. It is possible that the selection of athletes to the patient group was biased, since diagnostic criteria were based on a typical history and clinical findings alone. However, we included only athletes with a typical history of patellar tendon pain in the patient group, and care was taken to exclude athletes with evidence of additional or other pathology. In Paper III the matching of the control players from the same teams based on age, function, playing experience and training level was felt to be the best way to minimize the risk of a selection bias. While the study format allowed us to match the patient and control groups carefully with respect to diagnosis and factors believed to be of importance in the development of jumper's knee, it also

resulted in a small sample size, and the results therefore needed to be validated in a larger population of athletes as in Paper IV.

The jump testing protocol is a standard program which has been shown to be highly reproducible (Sale 1990). The tests are functional, designed to give an estimate of performance at different speeds and loads, much in the same way that different demands are placed on the leg extensors for given tasks during the actual game of volleyball. The tests were familiar to the examiners as well as many of the teams, who use the same tests on a regular basis to check the efficacy of their training programs. Pain inhibition during jump testing among the players in the patient group is possible. The players did not express any problems and even if this occurred, it would appear not to invalidate the results, since the patient group still performed better than the control group.

An interesting observation in this connection is that athletes with longstanding complaints from what is supposed to be an overload condition perform better in dynamic tests with high resemblance to the movements and loading mechanisms of the extensor apparatus which is supposed to be the reason to the injury compared with asymptomatic athletes. However, whether the athletes with jumper's knee actually have reduced performance level compared with their preinjury level or not can only be answered through longitudinal studies. Since the athletes with jumper's knee perform better compared with controls in dynamic testing procedures even with serious symptoms for many years we can not explain their reduced performance level by reduced performance of their extensor mechanism. The problems the athletes with reports are correlated to their experiences of pain. This means that there is reason to suggest a connection between a high jumping capacity and high training volumes and the pain mechanisms within the tendon. It is also reason to suggest a correlation between an overload condition giving specific histopathological changes that can explain the pain mechanisms since the histopathological findings are consistent and uniforme (Roels et al. 1978, Karlsson et al. 1991, Colosimo and Bassett 1990, Bassett et al. 1980, Khan et al. 1998).

Ultrasound data

Results

Paper II. Palpation tenderness was found in a number of players who did not complain of symptoms of jumper's knee, and the predictive value of pain on isometric contraction was low (Table 5). Previous Osgood-Schlatter's disease was reported in 2 cases among those with current jumper's knee (34 knees), and in 8 of 60 knees without current symptoms (n.s.)

Table 5. Clinical findings in 34 knees with current jumper's knee and 51 knees without symptoms. Knees with previous symptoms (n=9) only were excluded from the analysis.

Test	Test result	Current symptoms (n=34)	No symptoms (n=51)
Palpation tenderness	Negative	-	39
	Slight	9	6
	Moderate	12	6
	Strong	13	-
Pain on isometric contraction (0°)	No	24	48
	Yes	10	3
Pain on isometric contraction (30°)	No	29	51
	Yes	5	-
Pain on isometric contraction (90°)	No	31	51
	Yes	3	-
Chondromalacia tests	Negative	27	43
	Positive	7	8

Tendon changes observed by ultrasonography

Table 6. Dimensions of the patellar tendon and patella in athletes with (n=30 knees) or without (n=51) current symptoms of jumper's knee. Knees with previous symptoms or symptoms from the quadriceps tendon only were excluded from the analysis (n=13). Values are means ± SD.

	No symptom	Current symptoms	Significance level (P)*
Tendon length (mm)	52±5	53±7	0.29
Patella length (mm)	38±3	39±3	0.79
Insall-Salvati index	0.75±0.10	0.73±0.08	0.46
Proximal thickness (mm)	3.8±1.1	6.2±2.2	<0.001
Proximal width (mm)	33±3	33±4	0.65
Proximal area (mm)	99±29	161±60	<0.001
Midpoint thickness (mm)	3.9±0.7	4.1±0.5	0.21
Midpoint width (mm)	36±3	37±6	0.003
Midpoint area (mm2)	108±20	120±19	0.08

**Unpaired t-test.*

The degree of clinical symptoms could not be reliably predicted from the changes observed in paratenon appearance or by the presence of hypoechoic changes. The length of the hypoechoic zone was 11.5±4.2 mm among those without symptoms, and 10.0±0.0 mm, 14.4±2.8 mm and 20.1±8.4 mm among those with grade I, II and IIIa symptoms, respectively (n.s., ANOVA).

No increase was observed in proximal tendon thickness or length of any echoic changes observed in relation to the duration of current symptoms of jumper's knee.

Discussion

The main finding of this study was that the prevalence of jumper's knee and ultrasound changes in the patellar tendon was high, approximately 50%, but that the correlation between symptoms and ultrasound changes was low. In the present study, 7 of the 30 knees with a clinical diagnosis of jumper's knee in the patellar tendon had normal ultrasound findings. On the other hand, we found ultrasound changes believed to be associated with jumper's knee (tendon thickening, echo signal changes, irregular paratenon appearance) in 12 of 51 knees without current or previous symptoms.

The findings in the present study have later been confirmed by others. In a cross-sectional cohort study by Cook et al. (1998), they assessed the sonographic patellar tendon appearance in 320 athletes from different sports (basketball, cricket, netball and Australian rules football) without any current or previous complaints compatible with jumper's knee compared with 27 nonathletic individuals as controls. In the asymptomatic group of athletes they found hypoechoic changes in the tendon in 22% and in 4% in the control group, in 30% of male and 14% of female athletes without symptoms, and in 32% of asymptomatic basketball players compared with 9% in the other sports (all $p<0.05$). In another study by Cook et al. (2000b) they studied the patellar tendons in 134 elite 14- to 18-year old female (n=64 and male (n=70) basketball players and 29 control swimmers (17 female and 12 male) clinically and ultrasonographically. Of tendons categorised clinically as "never patellar tendinopathy", 22% had an ultrasonographic hypoechoic region.

To evaluate the ability of ultrasonography to predict eventual symptoms Khan et al. (1997) compared patellar tendon sonographic findings at baseline and at follow-up in female basketball players with and without symptoms of jumper's knee. They concluded that patellar tendon sonographic hypoechoic areas can resolve, remain unchanged or expand in active sports-women without predicting symptoms of jumper's knee. Cook et al. (2000a) did a longitudinal study on 52 elite junior basketball players with an ultrasonographic evaluation at baseline and after 16 months. All tendons were asymptomatic at baseline and 10 had hypoechoic changes at baseline and 42 were ultrasonographically normal at baseline. The relative risk for developing symptoms of jumper's knee was 4.2 greater in case tendons than in control tendons. Half of the abnormal tendons in women became ultrasonographically normal in the study period. Based on their data

they suggest that the presence of an ultrasonographic hypoechoic area is associated with a great risk of developing symptoms of jumper's knee. They concluded that neither qualitative nor quantitative analysis of baseline ultrasonographic images made it possible to predict which tendons would develop symptoms or resolve ultrasonographically. In another study by Cook et al. (2001), they used a longitudinal study design to examine whether or not the presence of a hypoechoic lesion in an asymptomatic patellar tendon conferred a risk for developing jumper's knee compared with a tendon that was ultrasonographically normal. They followed 46 patellar tendons over 47 ± 12 months. Eighteen tendons had hypoechoic changes at baseline and 28 were ultrasonographically normal. Five tendons resolved ultrasonographically in the study period. Seven normal tendons at baseline developed hypoechoic changes but only two became symptomatic. Analysis of ultrasonography at baseline and clinical outcome showed that there was no association between baseline ultrasound changes and symptoms at followup. There was no statistical significant relationship between ultrasonographic patellar tendon abnormalities and clinical outcome in elite male athletes. As a conclusion from the available studies there is ample evidence to state that the relationship between symptoms and clinical findings of jumper's knee and the ultrasound changes is weak.

Several authors have described the histopathological changes in the patellar tendon obtained from surgical specimens in patients with disabling jumper's knee, and their observations usually include tearing of tendon fibers, regeneration with fibroblast proliferation, myxomatous degeneration, and capillary proliferation without any inflammatory response (Roels et al. 1978, Karlsson et al. 1991, Colosimo and Bassett 1990, Bassett et al. 1980, Khan et al. 1998). However, these observations are from patients with disabling symptoms (grade IIIb), among whom conservative treatment methods have failed. The correlation between ultrasound findings and histopathology in patients with patellar tendinopathy has been studied by Khan et al. (1996). In this study, 28 knees diagnosed with patellar tendinopathy planned for surgical treatment underwent an ultrasonographic examination. Control biopsies were taken from 39 cadaver knees. All knees diagnosed with patellar tendinopathy had an ultrasonographically abnormal zone at the proximal patellar tendon and histopathological examination revealed mucoid degeneration in all these tendons and in three of 39 (8%) in the cadaver knees. This study correlates the histological findings in biopsies from patients clinical diagnosed with patellar tendinopathy combined with simultaneous typical ultrasonographic findings, and describes a very close correlation between this subgroup of athletes with patellar tendinopathy and a specific histopathologic finding (mucoid degeneration). All the previous mention studies on histopathology present results from a

cohort of patients with disabling symptoms (grade IIIb), among whom conservative treatment methods have failed.

However, to our knowledge, there is no available information on the histopathological changes in patients with Roels' grade I, II or IIIa disease. In spite of lack of this information, attempts have been made to correlate ultrasound changes and anatomical findings to the clinical staging of the disease (Fritschy and DeGautard 1988, Jerosch et al. 1990). Jerosch and Schröder (1990) suggested that a relationship exists between the severity of the pathological changes and certain ultrasound characteristics. More serious disease is assumed to be associated with wide-spread thickening of the tendon, echoic changes and surface irregularities. The correlations made in these studies are based on assumptions since the ultrasound findings are not correlated to corresponding histopathologic findings in the same individuals. In the present study we found no correlation between the presence of surface changes suggesting paratenon pathology, and either the presence of symptoms or the degree or duration of symptoms. This suggests that paratenon changes do not necessarily constitute a sign of more serious clinical disease.

Several studies have shown near-perfect correlation between preoperative ultrasound changes and surgical findings (Raatikainen et al. 1994, Orava et al. 1986, Kälebo et al. 1991, King et al. 1990, Karlsson et al. 1992). However, as these studies were carried out in a selected patient group, i.e., almost all of them had disabling symptoms (grade IIIb) who did not respond to non-operative treatment, the results should be interpreted carefully when applied to other patient populations. Indeed, the results of the present study and that of Myllymäki et al. (1990) show that the correlation between ultrasound changes and symptoms is weak among athletes with less serious symptoms. Karlsson et al. (1992) studied 91 patients with grade III symptoms and hypoechoic changes on ultrasound examination. When the patients were grouped according to the length of the hypoechoic zones, only 6.6% of the patients with changes of <10 mm needed surgical treatment, whereas 38.5% of those with changes of >20 mm subsequently needed surgical treatment (Karlsson et al. 1992). This suggests that the length of the hypoechoic zone may be a significant factor in planning treatment. However, we did not find any correlation between clinical staging and the length of the hypoechoic changes, nor could we find any relationship with the duration of symptoms. Since there appears to be a correlation between the size of the hypoechoic area and the effect of nonoperative treatment, but no correlation between size and clinical staging or duration of symptoms, this may be one reason why the relationship between clinical stage and effect of non-operative treatment may be difficult to predict. As a

conclusion from the present study specific ultrasound findings could neither be used to predict the clinical grade of the disease, nor the duration of symptoms.

When comparing normal tendons and tendons with symptoms of jumper's knee, we found a significant difference between the asymptomatic and symptomatic players in antero-posterior tendon thickness, particularly in the proximal part of the tendon, the location where most of the echoic changes were observed. Several studies involving surgery have found that in the majority of the cases the pathological process is localized in the proximal posterior part of the tendon (Roels et al. 1978, Ferretti 1986, Karlsson et al. 1991, Colosimo and Bassett 1990, Bassett et al.1980). MRI studies have shown that the antero-posterior diameter of the normal tendons increases slightly from proximal to distal (el-Khoury et al. 1992). Since stress/strain resistance is correlated to the cross-sectional area, this may explain why the pathological process usually starts in the proximal part of the tendon. The length of tendon fascicles varies with longer anterior fascicles than the corresponding posterior fascicles since the anterior bundles are attached more proximal to the patella and more distal to the tibia than the corresponding posterior bundles (Basso et al. 2001). For a same amount of elongation, the shorter posterior fascicles strain more than the longer anterior fascicles (strain=elongation/gauge length) (Basso et al. 2002), which may explain why the pathological process is localized to the posterior part of the tendon.

No difference in the tendon length or the modified Insall-Salvati index could be detected between symptomatic and asymptomatic groups of knees. This suggests that players with longer tendons are not predisposed to jumper's knee in contrast to Kujala et al.(1986, 1987), who reported a significantly higher proportion with patella alta among those with jumper's knee compared to controls. However, their reports included much fewer volleyball players in the control groups than in the patient groups, and this fact may have skewed their results and reduced the external validity of their studies.

Innervation

Results

Patient characteristics. The mean age was 30 years (24-34 years, n=10) in the patient group and 29 years (19-43 years, n=10) in the control group. In the patient group, the mean number of years participating in organized training was 17 (10-28 yrs, n=10), and the mean number of total training hours per week was 14 (6-24 h, n=10). The mean VISA score was 42 (15-65, n=10), and the mean duration of symptoms was 36 months (5-120 months, n=10).

Microscopy

The morphologic appearance of the painful tendons in the tendon proper differed significantly compared to the controls. The proper tendinous tissue exhibited signs of tendinosis (collagen degeneration, fiber disorientation, hypercellularity, angiogenesis, and absence of inflammatory cells) in all but one of the patients, whereas only a few of the controls exhibited early signs of tendinosis.

Semi-quantitative assessment of tenocyte morphology and of angiogenesis was performed according to the Bonar scale (Cook et al. 2004). Tenocyte changes occurred in all but one of the painful tendons, whereras only 5 of 14 controls exhibited these changes ($p=0.006$). Angiogenesis, considered to be the last histological sign of tendinopathy (Cook et al. 2004), was found in 4 of 11 painful tendons, but in none of the controls ($p=0.038$).

Immunohistochemistry

Overall, the subjective immunohistochemical assessment confirmed the morphologic appearance. However, it also provided more detailed information about sensory (SP) and sympathetic (TH) nerve fiber occurrence in the patellar tendon. Thus, the majority of the painful tendons exhibited an increased number of nerve fibers positive to SP and notably decreased levels of TH.

Sensory nerves

Closer subjective analyses showed that the increased number of SP-positive fibers in the painful tendons occurred mainly as thin, varicose, non-vascular nerve terminals within the tendon proper. Notably, these SP-positive nerves in the painful tendons were found over a larger area, more spread out within the tendon than in the controls. The SP positive nerve fibers seen as free nerve endings interspersed between the proper collagen fibers, often accompanying the loose connective tissue ingrowth within the tendon proper of the painful tendons. Contrary to what one might have expected, no differences were noted between the groups regarding the small subpopulation of vascular SP-positive fibers. In both groups, SP was regularly seen in larger nerve bundles.

Sympathetic nerves

Subjective analyses demonstrated not only a great difference in the occurrence of TH-expressing nerve fibers between patients and controls, but also in their morphological distribution. In both

groups, TH-positive nerves were present as free nerve endings throughout the tendon proper but, unlike the sensory nerves, the majority of the TH-nerves were distinctively related to the blood vessels. In the patients, there was a distinct decrease in the occurrence of TH-positive nerves. Some TH-positive free nerve endings were still seen, but the vessel-related TH nerves were significantly diminished in the patients.

General nerve occurrence

The neuronal localisation of SP- and TH-staining was confirmed by positive immunoreactivity for PGP, a general nerve marker. The subjective analyses of PGP showed a higher nerve fiber occurrence in the chronic pain group compared to the controls. Nerves existed both as vascular and non-vascular free nerve endings and in larger bundles.

Semi-quantitative immunohistochemistry

Computerized image analysis of SP, TH and PGP expression showed similar differences in occurrence as assessed subjectively, although all results were not statistically significant. The occurrence of SP was 22% ($p=0.567$) and that of PGP 54% ($p=0.098$) higher in the chronic painful tendons than in the controls. The occurrence of TH in the chronic painful tendons was 53% lower than in the controls ($p =0.018$).

Discussion

This study demonstrates that nerve fibers expressing sensory (SP) and sympathetic neuromediators (TH) appear to differ between patients with painful patellar tendinopathy and healthy controls. Most notably, an increased number of SP-positive non-vascular nerve endings and a vascularly related decrease in TH were seen.

The sensory neuropeptide, substance P, has a strong proinflammatory function, such as increased angiogenesis and vasopermeability, in addition to its role in nociception. The increased number of sensory nerves seen as sprouting free nerve endings in the painful tendons may, at least partly, explain the pain. The fact that the increased number of SP fibers was not seen around blood vessels was somewhat surprising, since one might have expected a strong connection, similar to that seen in healing tendons. Instead, the existence of free nerve endings indicated that the main function of SP in tendinopathy is nociceptive rather than vasoactive.

The reduction in TH, vascular noradrenaline, suggests a role in pain modulation. Noradrenaline as a peripheral and vascular pain modulator is a topic of ongoing research. Notably, a similar pattern of decreased vascular TH and increased free SP positive nerve fibers is seen in patients with painful rheumatoid arthritis (Straub et al. 2002).

The mean VISA score of 42 combined with a mean symptom duration of three years and histopathological findings characteristic of severe tendinosis mean that the patient group is characterized by chronic and severe complaints of patellar tendinopathy.

Variation between biopsies was high, and the semi-quantitative analysis confirmed only one of the three subjective analyses of the neuromediators in question. However, the trends all pointed in the same direction. The semi-quantitative method only takes the fields with highest density of immunofluorescence into account, thus overlooking histological differences, such as extensive nerve sprouting. The semi-quantitive analysis should therefore only be regarded as a complement to the subjective analysis.

In conclusion, the results demonstrate a differentiation in the sensory and sympathetic neuromediator pattern in painful tendinopathic tendons. The dominance of nonvascular SP nerve endings, as well as the decrease of the anti-nociceptive modulator, noradrenaline, suggests a pathophysiological regulation of pain. These neuropeptides, known to be essential for normal healing, exhibit a disturbed balance that may contribute to the degenerative processes of tendinopathy.

Apoptosis

Results

Clinical characteristics. The mean age was 30 years (24-34 years, n=23) in the patient group and 29 years (19-43 years, n=11) in the control group. In the patient group, the mean number of years participating in organized training was 17 (10-28 yrs, n=23), and the mean number of total training hours per week was 14 (6-24 h, n=23). The mean VISA score was 42 (15-65, n=23), and the mean duration of symptoms was 36 months (5-120 months, n=23).

Light microscopic appearance. Biopsies from patients with a clinical history of tendon pain consistently revealed tendinosis, including areas of hypocellularity, as well as neovascularization with intimal hyperplasia, and collagen disarray and degeneration. Increased amounts of

glycosaminoglycan were localized to areas of fibrocartilagenous metaplasia or to the neointima of the vessel. Inflammatory cells were virtually absent.

Apoptosis in normal and overused tendons. Apoptotic tenocytes were identified using all three methods (F7-26, propidium iodide, caspase-3) both in normal and pathological tendon, and each method showed that apoptosis represented a small minority of total cell counts (< 1%). Apoptosis was predominantly found in fibroblast-like cells in the tendon proper. Clusters of 5 to 10 apoptotic cells were observed in the tendinosis samples, compared to scattered or no cells in the controls.

The number of apoptotic cells per unit area (4.5 mm^2) was 0.91 ± 0.81 in tendinosis samples and 0.21 ± 0.21 in controls (p=0.026). There were more areas with apoptotic cells in the tendinosis tissue (3.7 ± 0.20 vs 1.9 ± 1.2, p=0.006). In addition, fields from tendinosis patients that displayed positive staining had more apoptotic cells than positive fields from controls (3.1 ± 2.2 vs 1.5 ± 0.89, p=0.006). Although the tendinosis samples displayed increased numbers of fibroblastic cells (52 ± 32 nuclei/mm^2 vs 31 ± 16 nuclei/mm^2, p=0.021), the apoptotic index was higher (0.42 ± 0.38 % vs 0.17 ± 0.16 %, p =0.014).

Discussion

The results showed a significantly higher number of apoptotic cells per unit area and a significantly higher apoptotic index in biopsies from the patellar tendons in patients with patellar tendinopathy compared with controls. The caspases are members of a family of cysteine proteases with a sequential activation and amplification system eventually causing apoptosis (Salvesen 2002). Since caspase-3 is one of the terminal proteins in the caspase activation system (Boatright and Salvesen 2003), this finding denotes an increased apoptotic activity in the patellar tendon in patients with patellar tendinopathy compared with controls.

The caspases are synthesized as inactive zymogens and it is essential that the caspases remain inactive until the apoptotic signal is received (Boatright and Salvesen 2003). Apoptosis is typically triggered by a variety of cellular stresses including ischemia-reperfusion and oxidative stress, loss of extracellular matrix contact, excessive cytosolic calcium, cytoskeletal disruption, mechanical trauma, and others. Alternatively, disappearance of excessive fibroblasts during tissue remodelling is a normal, physiological response (Grinnell et al. 1999). In tendinopathy, the mechanisms underlying apoptosis and caspase-3 activation, and whether or not it represents a pathological or a physiological process, are not currently known. How early in the pathogenesis of tendinosis apoptosis arises remains an important question.

The link between mechanical loading conditions and the pathophysiological response in tendinopathy is obscure, and currently there is insufficient evidence to provide a direct explanation for the possible connection between the loading pattern and the in vivo pathological response (Scott et al. 2005). Paper III and Paper IV show that volleyball players with jumper's knee have better jumping ability and power generation than players who do not report symptoms from their tendons, presumably because they subject their knee extensors to higher loads when jumping and landing. Also, prevalence is higher in sports that require frequent jumping as shown in Paper I, and among athletes who train more (Ferretti et al.1984). Thus, there is reason to believe that there is a connection between the tendon loading pattern and the pathology within the tendon substance. In a study by Yuan et al. (2002), excessive apoptosis was observed at the edge of torn rotator cuff tendons in elderly patients compared with controls. This has led to the proposal that tendinosis may begin as a degenerative process involving tenocyte death (Yuan et al. 2003). In support of this model, Skutek et al. (2003) suggested that mechanical stretching of tendon fibroblasts activates cell signaling pathways leading to apoptosis. However, once ruptured the supraspinatus tendon would likely not receive excessive tensile loads, therefore other mechanisms such as oxidative stress, hypoxia, or remodelling may predominate in later stages. In another study, Barkhausen et al. (2003) found that different repetitive cyclic longitudinal stress patterns resulted in different cellular reactions dependent on the strength of the applied stress. Repetitive stress applied during one day stimulated both proliferation and apoptosis (Barkhausen et al. 2003). Our data show the number of tenocytes was increased overall, but there were also discrete areas of apoptosis and hypocellularity, suggesting that death and proliferation may be occurring simultaneously in response to repetitive loading, similar to the finding by Barkhausen et al. (2003).

One of the consistent histological findings in biopsies in tendons from patients with patellar tendinopathy is the scarcity of inflammatory cells (Karlsson et al. 1991, Khan et al. 2000a, Martens et al. 1982). In a study by Alfredsson et al. (2003), cDNA arrays and real-time quantitative polymerase chain reaction technique were used to study tendinosis and control tissue samples. Several cytokines and cytokine receptors were not upregulated, suggesting the absence of an extrinsic inflammatory process in chronic painful Achilles tendinosis.

If the primary pathology were a partial rupture, one might have expected the presence of an inflammatory response since this is the case with acute, total tendon ruptures. However, in time cellular inflammation would be expected to diminish and evolve into a typical post-inflammatory reparative response as seen in tendons and other connective tissues (increased

glycosaminoglycans and collagen synthesis, neovascularisation, hypercellularity and apoptosis of fibroblasts). In keeping with this picture, the extent of cell death observed in the current study would not be expected to trigger an inflammatory response, particularly given the poor vascularisation of tendons.

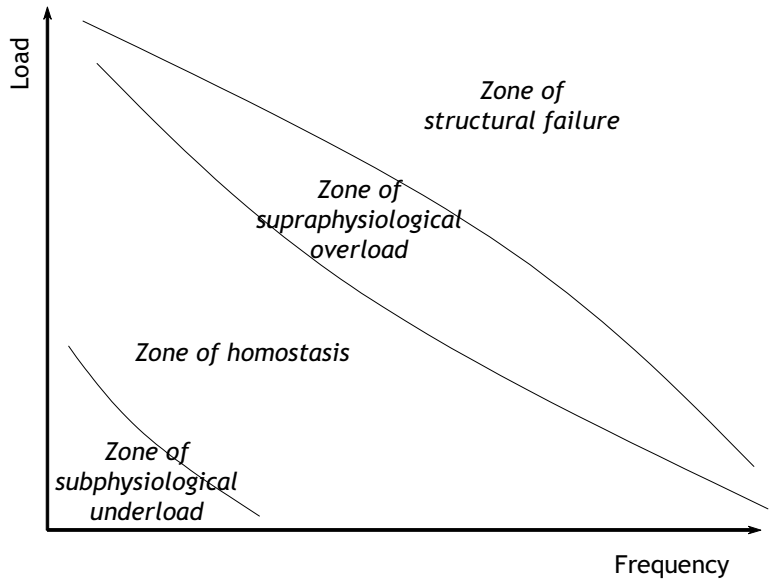
This study contributes a novel insight toward understanding the pathology of tendinosis, namely, that there is evidence of increased apoptosis in association with degenerate, non-ruptured tendon compared to controls. However, there remain several limitations that must temper conclusions. Firstly, our cross-sectional study sheds no light on whether apoptosis preceded or followed the development of tendinosis. Secondly, our data were obtained in young sports people with chronic patellar tendinosis – we may not extend our conclusions beyond this population as yet.

A model for the causation of patellar tendinopathy

Tissue homeostasis model

Dye (2005) has presented a model on the pathophysiology of patellofemoral pain. In this model he states that certain high loading conditions may induce loss of tissue homeostasis by exceeding the safe load acceptance capacity of the tissue, leading to symptomatic damage.

Figure 6. This figure describes the relationship between structural adaptation and the frequency and loading of a joint. The figure is reproduced from Dye (2005).



In this model, Dye (2005) describes a zone of load acceptance called "zone of homeostasis". By increasing the load and frequency beyond this limit the tissue will enter a zone of physiological overload, where there is gradual adaptation of tissue properties to the increased load. However, if even greater load and/or frequency is applied, structural damage will occur. The zone between subphysiological underload and supraphysiological overload is termed "the envelope of function".

Dye's model for patellofemoral pain assumes that the main causative factors are load and frequency. This seems to be the case for patellar tendinopathy, as well. Early epidemiological studies on volleyball players have shown that training frequency correlates positively with the

prevalence of patellar tendinopathy (Ferretti et al. 1984, Ferretti 1986). Moreover, sports characterized by high demands on speed and power have a higher prevalence of patellar tendinopathy (Paper I). When groups of athletes from the same sports and teams were compared, differences in total or jump training volume could be detected between asymptomatic and symptomatic athletes, at least in some cases (Paper I). However, in Paper II we found no difference between groups in the total amount of specific volleyball training. It also follows from the results that there are asymptomatic athletes who report very high training volumes and symptomatic athletes who train much less. Thus, the model above does not fully explain why some athletes develop tendinopathy and other athletes from the same team do not, despite being exposed to the same training load and frequency. Other factors must also play a significant role, either alone or by modifying tendon load or load tolerance.

Risk factor model

In order to account for interactions between different internal and external risk factors, as well as to relate these to the mechanisms by which the injuries occur, a dynamic multicausal model has been developed (Meeuwisse 1994, Bahr and Holme 2003, Bahr and Krosshaug 2005). However, this model has mainly been applied to describe the etiology of injuries with a sudden onset, resulting from a specific, identifiable event. Clinical experience suggests that such an acute trauma rarely can be recalled in cases of patellar tendinopathy, but that symptoms develop gradually over weeks and months. Thus, when applying the Meeuwisse model to explain the etiology of overuse injuries, some modifications are necessary. Mainly, this relates to the description of the injury mechanisms, the final link in the chain of leading to injury. In the case of overuse injuries, the injury mechanism is represented by the training and competition program the athlete has followed during the period the injury has developed, keeping in mind that pathology may even develop within the tissue long before symptoms occur. Thus, factors which describe the tendon loading conditions during this period, such as training volume, training frequency and type, changes in the training program, type of sport, need to be characterized to describe the injury mechanisms for overuse injuries. Different intrinsic and extrinsic factors can affect load and load tolerance, and these interactions must therefore be accounted for.

Based on the available evidence, the causes of patellar tendinopathy can be summarized as shown in Figure 7.

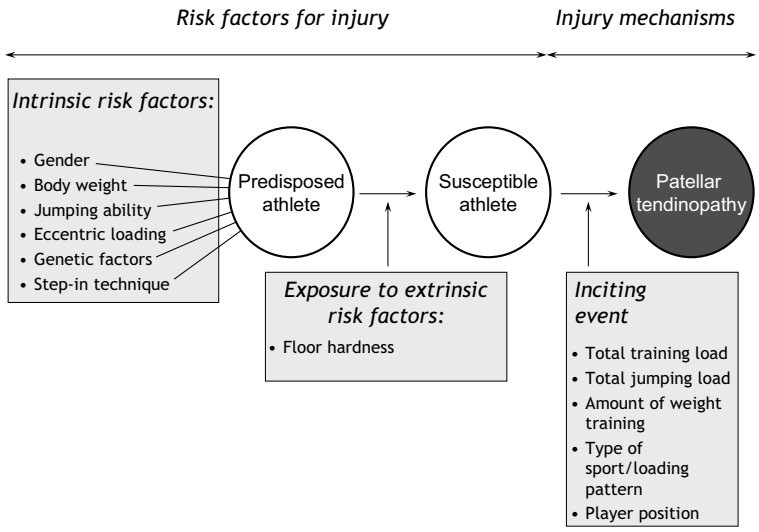


Figure 7. A dynamic, multifactorial model of the etiology of patellar tendinopathy.

Male gender is an intrinsic risk factor, because the prevalence of current jumper's knee in female handball and female soccer was 2.4 times lower compared with the corresponding male sports (Paper I). Body weight appears to be an intrinsic risk factor, because athletes diagnosed with jumper's knee weighted significantly more compared with asymptomatic athletes (Paper I and IV). In the biomechanical studies (Paper III and VI), players with jumper's knee performed better in standardized series of jump and power tests compared with the control groups. In Paper IV we found a correlation between the takeoff technique and jumper's knee. The right knee was affected twice as often as the left knee. The majority of the players used a right-left step-close takeoff technique, and none of the players reportedly preferred the right leg when landing after the attack. In fact, 20 of the 22 players with current jumper's knee on the right side used a right-left takeoff technique. This means that the leg doing the eccentric work is mostly affected. This finding may be related to the observations in Paper III, where the patient group appeared to be more effective in counter-movement jumps compared with the controls. Better eccentric performance during the decelerating part of the step-in will result in a better jumping ability, and consequently, higher tendon load when jumping.

Genetic factors are probably also of importance as shown by Mokone et al. (2006), who found that individuals with an A2 allele of the α1 type V collagen gene (COL5A1) were less likely to develop symptoms of chronic Achilles tendinopathy. However, the authors state that this

association does not prove a causal relationship, since there may be other closely linked genes involved (Mokone et al. 2006). Age was not a significant risk factor for jumper's knee in any of the present studies.

Ferretti et al. (1984) suggested a positive correlation between the hardness of the floor and the prevalence of jumper's knee among volleyball players. In line with this, it has recently been shown that the prevalence of jumper's knee among elite beach volleyball players playing on sand is only 9%, considerably lower than for indoor volleyball players (Bahr and Reeser 2003). Thus, the hardness of the floor can be regarded as an extrinsic risk factor for jumper's knee. Other suggested risk factors for jumper's knee have not been well documented yet.

Inciting event

In chronic overload injuries there is not a well defined inciting event. However, Paper I shows a small, but significantly higher training volume in players with symptoms of jumper's knee compared to asymptomatic controls. Volleyball players with jumper's knee reportedly also trained more with weights (Paper I and IV). The overall prevalence of current and previous jumper's knee was significant higher in sports characterized by ballistic movements, speed and power (Paper I). A combination of all these factors may—in an athlete predisposed by intrinsic and extrinsic risk factors—result in structural tendon damage. Thus, the loading characteristics determined by the training and competition program may be regarded as the inciting event in jumper's knee.

In the model described above, internal and external risk factors act together to make the individual susceptible to tendinopathy. For example, a volleyball player with a specific jumping technique will need to perform a certain amount of specific training on a specific floor hardness to develop tendinopathy. In our experience, the first symptoms of jumper's knee often occur after a period with increased training loads in a young athlete who is selected to a team or a training camp at a higher level of play. These talented young athletes may, from one week to the next, move from a relatively "safe" training environment—for example, practice two to three days a week, no weight lifting—to an elite club or sports school that practices daily, including intensive weight and jump training. Talented athletes are also likely to possess superior jumping ability which, when coupled with sudden increases in strength, muscle mass, and training load, further amplifies their risk of developing tendinopathy. In this setting the increased training load may be regarded as the inciting event, bringing the tendon tissue out of the envelope of function, ending up with structural damage.

Mechanotransduction

However, the link between loading conditions and structural damage is obscure. Koskinen et al. (2004) have shown that physical activity can influence the activity of local matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) in vivo, and suggest that this may be of importance in extracellular adaptation to exercise in tendon tissue. In a study by Miller et al. (2005), they found an increased synthesis of collagen in the patellar tendon after a single acute bout of strenuous, non-damaging exercise. They hypothesize that this increased collagen production may be due to some common signalling pathway transducing the mechanical stimuli into anabolic events (Miller et al. 2005). Langberg et al. (2006) showed that patients with Achilles tendinosis treated with 12 weeks of eccentric training increased their collagen synthesis rate, but the collagen metabolism in healthy controls was not affected by eccentric training. They suggest that this might indicate an inadequate adaptation of tissue strength to the activity level in tendinosis, with a subsequent tissue injury (Langberg et al. 2006). Olesen et al. (2006) have shown that loading of the plantaris tendon in rats resulted in upregulation of IGF-1 and procollagen. They suggest that the IGF-1 system probably is involved in regulation of the collagen synthesis in tendon in response to mechanical loading (Olesen et al. 2005). Lavagnino et al. (2005) have shown that tendon cells could establish an internal cytoskeletal tension through interactions with the extrecellular environment. Alterations in this tension could control the expression of both catabolic and anabolic genes (Lavagnino et al. 2005). Studies on isolated tendon cells in vitro have shown that stress deprivation results in up-regulation of interstitial collagenase, while application of a tensile load inhibits mRNA expression of interstitial collagenase, probably through the same cytoskeletally based mechanotransduction mechanism (Arnoczky et al. 2002). In a study by Mokone et al. (2005), they found that persons with variants of the tenacin-C gene with 12 and 14 guanine-thymidine repeats appeared to have a 6-fold risk of developing Achilles tendon injuries. Since mechanical signals can alter the synthesis of tenacin-C (Chiquet 1999), and tenacin-C can regulate cell-matrix interactions, the author speculate if this protein may be of importance in a possible apoptotic model of tendinopathy (Mokone et al. 2005). Arnoczky et al. (2002) have also shown, at the cellular level, that cyclic strain induces activation of stress-activated protein kinases (SAPK), possibly by a calcium-dependent mechanotransduction pathway. Since SAPK activation are important upstream regulators of the apoptosis cascade in different cell lines, they speculate if this mechanotransduction pathway may induce apoptosis and be part of the etiology in tendon overload injuries (Arnoczky et al. 2002). Scott et al. (2005) have shown that high-strain mechanical loading rapidly induced tendon apoptosis in an ex vivo rat tibialis anterior model. In Paper VI, we found excessive apoptosis in tendon biopsies from patients with patellar

tendinopathy compared with controls. This means that both at the molecular, cellular and isolated muscle-tendon level, as well as in vivo, there is reason to suggest a connection between biomechanical factors and specific anabolic and catabolic biologic responses, among them excessive apoptosis, through a mechanotransduction pathway.

In conclusion, the present model connects the loading pattern and specific extrinsic and intrinsic factors which can modify load or load tolerance to specific histopathological findings through a mechanotransduction pathway, ending up with structural damage and pain. The different anabolic and catabolic processes may be specific to the different loading conditions, initially probably in a reversible way. Understanding these relationships may be key factors to establish effective preventive measures.

Conclusions

Based on the results of the papers presented in this thesis, the conclusions are as follows:

1. The overall prevalence of current and previous jumper's knee was significantly higher in sports characterized by ballistic movements, speed and power. The condition is in most cases chronic, and athletes report significant symptoms and disability, particularly related to sport.

2. The prevalence of current jumper's knee among males was 2.4 times higher than females in comparable sports.

3. Athletes diagnosed with jumper's knee weighted significantly more compared with asymptomatic athletes, while age was not identified as a significant risk factor for jumper's knee.

4. Training volume was somewhat higher in players with symptoms of jumper's knee than controls. Also, players with jumper's knee reportedly trained more with weights.

5. Players with jumper's knee performed better in standardized series of jump and power tests compared with controls.

6. The prevalence of ultrasound changes in the patellar tendon was high among elite volleyball players, approximately 50%, but the correlation between symptoms and ultrasound changes was low.

7. Nerve fibers expressing sensory (SP) and sympathetic neuromediators (TH) appear to differ between patients with painful patellar tendinopathy and healthy controls. An increased number of SP-positive non-vascular nerve endings and a vascularly related decrease in TH were seen in patients.

8. Biopsies from the patellar tendons in patients with patellar tendinopathy displayed evidence of increased apoptosis than healthy controls.

References

Abrahamsson SO, Lundborg G, Lohmander LS. Recombinant human insulin-like growth factor-1 stimulates in vitro matrix synthesis and cell proliferation in rabbit flexor tendons. *J Orthop Res.* 1991;9:495-502.

Ackermann PW, Ahmed M, Kreicbergs A. Early nerve regeneration after achilles tendon rupture--a prerequisite for healing? A study in the rat. *J Orthop Res.* 2002;20:849-856.

Alfredsson H, Lorentzon M, Bäckman S, Bäckman A, Lerner U. cDNA-arrays and real-time quantitative PCR techniques in the investigation of chronic Achilles tendinosis. *J Orthop Res.* 2003;21:970-975.

Almekinders LC, Vellema JH, Weinhold PS. Strain patterns in the patellar tendon and the implications for patellar tendinopathy. *Knee Surg Sports Traumatol Artrosc.* 2002;10:2-5.

Ameisen JC. The origin of programmed cell death. *Science.* 1996;272:1278-1279.

Arendt E, Dick R. Knee injury patterns among men and women in collegiate basketball and soccer. NCAA data and review of literature. *Am J Sports Med.* 1995;23:694-701.

Arnoczky SP, Tian T, Lavagnino M, Gardner K. Ex vivo static tensile loading inhibits MMP-1 expression in rat tail tendon cells through a cytoskeletally based mechanotransduction mechanism. *J Orthop Res.* 2004;22:328-333.

Arnoczky SP, Tian T, Lavagnino M, Gardner K, Schuler P, Morse P. Activation of stress-activated protein kinase (SAPK) in tendon cells following cyclic strain: the effect of strain frequency, strain magnitude and cytosolic calcium. *J Orthop Res.* 2002;20:947-952.

Bahr R, Hallén J, Medbø JI. *Testing av styrke, spenst og hurtighet.* Oslo: Universitetsforlaget; 1992.

Bahr R, Holme I. Risk factors for sport injuries--a methodological approach. *Br J Sports Med.* 2003;37:384-392.

Bahr R, Kannus P, van Mechelen W. Epidemioplogy and Prevention of Sports Injuries. In: Kjær M, Krogsgaard M, Magnusson P, Engebretsen L, Woo S, eds. *Textbook of Sports Medicine.* Oxford: Blackwell Science; 2003:299-314.

Bahr R, Krosshaug T. Understanding injury mechanisms: a key component of preventing injuries in sport. *Br J Sports Med.* 2005;39:324-329.

Bahr R, Reeser JC; Federation Internationale de Volleyball. Injuries among world-class professional beach volleyball players. The Federation Internationale de Volleyball beach volleyball injury study. *Am J Sports Med.* 2003;31:119-125.

Barkhausen T, van Griensven M, Zeichen J, Bosch U. Modulation of cell functions of human tendon fibroblasts by different repetitive cyclic mechanical stress patterns. *Exp Toxicol Pathol.* 2003;55:153-158.

Bassett FJI, Soucacos PN, Carr WA. *Jumper's knee: patellar tendinitis and patellar tendon rupture.* In: Anonymous AAOS symposium on the athlete's knee. St.Louis: CV Mosby; 1980:96-106.

Basso O, Johnson DP, Amis AA. The anatomy of the patellar tendon. *Knee Surg Sports Traumatol Artrosc.* 2001;9:2-5. Erratum in: *Knee Surg Sports Traumatol Artrosc.* 2001;9:56.

Basso O, Amis AA, Race A, Johnson DP. Patellar tendon fiber strains: their differential responses to quadriceps tension. *Clin Orthop Relat Res.* 2002;400:246-253.

Bayliss WM. On the origin from the spinal cord of the vasodilator fibres of the hind limb and on the nature of these fibres. *J Physiol.* 1901;26:173-209.

Becker W, Krahl H. *Die tendopathien.* Stuttgart: G Thieme; 1978.

Bjur D, Alfredson H, Forsgren S. The innervation pattern of the human Achilles tendon: studies of the normal and tendinosis tendon with markers for general and sensory innervation. *Cell Tissue Res.* 2005;320.201-206.

Blackburne JS, Peel TE. A new method of measuring patellar height. *J Bone Joint Surg Br.* 1977;59B:241-242.

Blazina ME, Kerlan RK, Jobe FW, Carter VS, Carlson GJ. Jumper's knee. *Orthop Clin North Am.* 1973;4:665-673.

Boatright KM, Salvesen GS. Mechanisms of caspase activation. *Curr Opin Cell Biol.* 2003;15:725-731.

Bodne D, Quinn SF, Murray WT. et al. Magnetic resonance images of chronic patellar tendinitis. *Skeletal Radiol.* 1988;17:24-28.

Bosco C, Komi PV. Mechanical characteristics and fiber composition of human leg extensor muscles. *Eur J Appl Physiol Occup Physiol.* 1979;41:275-284.

Bosco C, Luhtanen P, Komi PV. A simple method for measurement of mechanical power in jumping. *Eur J Appl Physiol Occup Physiol.* 1983;50:273-282.

Bosco C, Belli A, Astrua M. et al. A dynamometer for evaluation of dynamic muscle work. *Eur J Appl Physiol Occup Physiol.* 1995;70:379-86.

Bray RC, Salo PT, Lo IK, Ackermann P, Rattner JB, Hart DA. Normal Ligament Structure, Physiology and Function. *Sports Med Artrosc Rev.* 2005;13:3:127-135.

Burstein AH, Wright TM. Mechanical behaviour of materials. In: Burstein AH, Wright TM, eds. *Fundamentals of Orthopaedic Biomechanics.* Boltimore: Williams and Wilkins; 1994;108.

Chiquet M. Regulation of extracellular matrix gene expression by mechanical stress. *Matrix Biol.* 1999;18:417-426.

Clancy WG. Tendon trauma and overuse injuries. In: Leadbetter WB, Buckwalter JA, Gordon SL, eds. *Sport-Induced Inflammation: Clinical and Basic Science Concepts.* Park Ridge: AAOS; 1990:609.

Coleman BD, Kahn KM, Maffulli N, Cook JL, Wark JD. Studies of surgical outcome after patellar tendinopathy: clinical significance of methodological deficiencies and guidelines for future studies. Victorian Institute of Sport Tendon Study Group. Scand *J Med Sci Sports.* 2000;10:2-11.

Colosimo AJ, Bassett FH 3rd. Jumper's knee. Diagnosis and treatment. *Orthop Rev.* 1990;19:139-149.

Cook JL, Khan KM, Harcourt PR. Et al. Patellar tendon ultrasonography in asymptomatic active athletes reveals hypoechoic regions: a study of 320tendons. Victorian Institute of Sport Tendon Study Group. *Clin J Sports Med.* 1998;8:73-77.

Cook JL, Khan KM, Kiss ZS, Purdam CR, Griffiths L. Prospective imaging study of asymptomatic patellar tendinopathy in elite junior basketball players. *J Ultrasound Med.* 2000a;19:473-479.

Cook JL, Khan KM, Kiss ZS, Griffiths L. Patellar tendinopathy in junior basketball players: a controlled clinical and ultrasonographic study of 268 patellar tendons in players aged 14-18 years. *Scand J Med Sci Sports*. 2000b;10:216-220.

Cook JL, Khan KM, Kiss ZS, Coleman BD, Griffiths L. Asymptomatic hypoechoic regions on patellar tendon ultrasound: A 4-year clinical and ultrasound followup of 46 tendons. *Scand J Med Sci Sports*. 2001;11:321-327.

Cook JL, Feller JA, Bonar SF, Khan KM. Abnormal tenocyte morphology is more prevalent than collagen disruption in asymptomatic athletes' patellar tendons. *J Orthop Res*. 2004;22:334-338.

Coppes MH, Marani E, Thomeer RT, Groen GJ. Innervation of «painful» lumbar discs. *Spine*. 1997;22:2342-2350.

Dahlgren LA, Mohammed HO, Nixon AJ. Temporal expression of growth factors and matrix molecules in healing tendon lesions. *J Orthop Res*. 2005;23:84-92.

Davies SG, Baudouin CJ, King JB, Perry JD. Ultrasound, computed tomography and magnetic resonance imaging in patellar tendinitis. *Clin Radiol*.1991;43:52-56.

Drinkwater B. Training of female athletes. In: Dirix A, Knuttgen HG, Tittel K, eds. *The Olympic Book of Sports Medicine*. Oxford: Blackwell Scientific Publications; 1988:309-327.

Dye S. The pathophysiology of patellofemoral pain: a tissue homeostasis perspective. *Clin Orthop Relat Res*. 2005;436:100-110.

el-Khoury GY, Wira RL, Berbaum KS, Pope TL Jr, Monu JU. MR imaging of patellar tendonitis. *Radiology*. 1992;184:849-854.

Elliot DH. Structure and function of mammalian tendon. *Biol Rev*. 1965;40:392-421.

Ferrara N. Molecular and biological properties of vascular endothelial growth factor. *J Mol Med*. 1999;77:527-543.

Ferretti A. Epidemiology of jumper's knee. *Sports Med*. 1986;3:289-295.

Ferretti A, Ippolito E, Mariani P, Puddu G. Jumper`s knee. *Am J Sports Med*. 1983;11:58- 62.

Ferretti A, Papandrea P, Conteduca F. Knee injuries in volleyball. *Sports Med*. 1990;10:132-138.

Ferretti A, Puddu G, Mariani PP, Neri M. The natural history of jumper's knee. Patellar and quadriceps tendonitis. *Int Orthop.* 1985;8:239-242.

Feretti A, Puddu G, Mariani PP, Neri M. Jumper's knee: An epidemiological study of volleyball players. *Physician Sportsmed.* 1984;12:97-103.

Fornage BD. The hypoechoic normal tendon. A pitfall. *J Ultrasound Med.* 1987;6:19-22.

Freemont AJ, Peacock TE, Goupille P, Hoyland JA, O'Brien J, Jayson MI. Nerve ingrowth into diseased intervertebral disc in chronic back pain. *Lancet.* 1997;350:178-181.

Fritschy D, de Gautard R. Jumper's knee and ultrasonography. *Am J Sports Med.* 1988;16:637-640.

Fyfe I, Stanish WD. The use of eccentric training and stretching in the treatment and prevention of tendon injuries. *Clin Sports Med.* 1992;11:601-624.

Gibson SJ, Polak JM, Bloom SR. et al. Calcitonin gene-related peptide immunoreactivity in the spinal cord of man and eight other species. *J. Neurosci.* 1984;4:3101-3111.

Grace TD. Muscle imbalance and extremity injury: A perplexing relationship. *Sports Med.* 1985;2:77-82.

Grinnell F, Zhu M, Carlson MA, Abrams JM. Release of mechanical tension triggers

apoptosis of human fibroblasts in a model of regressing granulation tissue. *Exp Cell Res.* 1999;248:608-619.

Harvey JS Jr. Overuse syndromes in young athletes. *Clin Sports Med.* 1983;2:595-607.

Heiser TM, Weber J, Sullivan G, Clare P, Jacobs RR. Prophylaxis and management of hamstring muscle injuries in intercollegiate football players. *Am J Sports Med.* 1984;12:368-370.

Herzog W. Mechanical properties and performance in skeletal muscles. In: Ed. V Zatziorsky, ed. *Biomechanics in sport*, Encyclopaedia of sports medicine, Vol. IX. Oxford: Blackwell Science; 2000.

Hess GP, Cappiello WL, Poole RM, Hunter SC. Prevention and treatment of overuse tendon injuries. *Sports Med.* 1989;8:371-384.

Hunter SC, Poole RM. The cronically inflamed tendon. *Clin Sports Med.* 1987;6:371-388.

Insall J, Salvati E. Patella position in the normal knee joint. *Radiology.* 1971;101:101-104.

Ippolito E. Biochemistry and metabolism. In: Perucia L, Postacchini F, Ipplito E, eds. *The tendons: Biology-pathology-clinical aspects*. Milano: Editrice Kurtis; 1986:37-46.

James SL, Bates BT, Osternig LR. Injuries to runners. *Am J Sports Med*. 1978;6:40-50.

Jerosch J, Castro WHM, Sons HU, Winkelmann W. Möglichkeiten der Sonographie beim Patellaspitzen-Syndrom. *Ultraschall Med*. 1990;11:44-47.

Jerosch VJ, Schröder M. Ergebnisse der diagnostischen sonographie bei verletzungen des kniegelenkes. *Sportverl Sportschad*. 1990;4:139-46.

Johnson DP, Wakeley CJ, Watt I. Magnetic resonance imaging of patellar tendonitis. *J Bone Joint Surg Br*. 1996;78:452-457.

Jozsa L, Balint J, Kannus P, Järvinen M, Letho M. Mechanoreceptors in human myotendinous junction. *Muscle Nerve*.1993;16:453-457.

Jozsa L, Balint BJ, Reffy A, Demel Z. Histochemical and ultrastructural study of adult human tendon. *Acta Histochem*. 1979;65:250-257.

Jozsa L, Kannus P. *Human tendons*. Champaign, Illinois; Human Kinetics: 1997.

Jozsa L, Kannus P, Balint BJ, Reffy A. Three-dimensional ultrastructure of human tendons. *Acta Anat*. 1991;142:306-312.

Kannus P, Niittymäki S, Järvinen M. Sports injuries in woman: a one-year prospective follow-up study at an outpatient sports clinic. *Br J Sports Med*. 1987;21:37-39.

Karlsson J, Kälebo P, Goksör L-Å, Thomee R, Swärd L. Partial rupture of the patellar ligament. *Am J Sports Med*. 1992;20:390-394.

Karlsson J, Lundin O, Lossing IW, Peterson L. Partial rupture of the patellar ligament. Results after operative treatment. *Am J Sports Med*. 1991;19:403-408.

Kälebo P, Swärd L, Karlsson J, Peterson L. Ultrasonography in the detection of partial patellar ligament ruptures (jumper's knee). *Skeletal Radiol*. 1991;20:285-289.

Khan KM, Bonar F, Desmond PM. et al. Patellar tendinosis (jumper's knee): findings at histopathologic examination, US, and MR imaging. Victorian Institute of Sport Tendon Study Group. *Radiology*. 1996;200:821-827.

Khan KM, Cook J, Kiss ZS. et al. Patellar tendon ultrasonography and jumper's knee in female basketball players: A longitudinal study. *Clin J Sport Med.* 1997;7:199-206.

Khan KM, Cook JL, Maffulli N, Kannus P. Where is the pain coming from in tendinopathy? It may be biochemical, not only structural, in origin. *Br J Sports Med.* 2000a;34:81-83.

Khan KM, Cook J, Taunton J. Overuse tendinosis, not tendonitis: part 1: A new paradigm for a difficult clinical problem. *Phys Sports Med.* 2000b;28:38-48.

Khan KM, Maffulli N, Coleman BD, Cook JL, Taunton JE. Patellar tendinopathy: some aspects of basic science and clinical management. *Br J Sports Med.* 1998;32: 346-355.

Khan KM, Visentini PJ, Kiss ZS. et al. Correlation of ultrasound and magnetic resonance imaging with clinical outcome after patellar tenotomy: prospective and retrospective studies. Victorian Institute of Sport Tendon Study Group. *Clin J Sports Med.* 1999;129-137.

Kiess W, Gallaher B. Hormonal control of programmed cell death/apoptosis. *Eur J Endocrinol.*1998;138:482-491.

King JB, Perry DJ, Mourad K, Kumar SJ. Lesions of the patellar ligament. *J Bone Joint Surg Br.* 1990;72:46-48.

Komi PV, Bosco C. Utilization of stored elastic energy in leg extensor muscles by men and women. *Med Sci Sports.* 1978;10:261-265.

Konttinen YT, Grønblad M, Antti-Poika I. et al. Neuroimmunohistochemical analysis of peridiscal nociceptive neural elements. *Spine.* 1990;15:383-386.

Koskinen SO, Heinemeier KM, Olesen JL, Langberg H, Kjaer M. Physical exercise can influence local levels of matrix metalloproteinases and their inhibitors in tendon-related connective tissue. *J Appl Physiol.* 2004;96:861-864.

Kujala UM, Aalto T, Österman K, Dahlstrøm S. The effect of volleyball playing on the knee extensor mechanism. *Am J Sports Med.* 1989;17:766-769.

Kujala UM, Friberg O, Aalto T, Kvist M, Österman K. Lower limb asymmetry and patellofemoral joint incongruence in the etiology of knee exertion injuries in athletes. *Int J Sports Med.* 1987;8:214-220.

Kujala UM, Österman K, Kvist M, Aalto T, Friberg O. Factors predisposing to patellar chondropathy and patellar apicitis in athletes. *Int Orthop.* 1986;10:195-200.

Kvist M, Jozsa L, Järvinen M, Kvist H. Fine structural alterations in chronic Achilles paratenonitis in athletes. *Pathol Res Pra*ct. 1985;180:416-423.

Langberg H, Ellingsgaard H, Madsen T. et al. Eccentric rehabilitation exercise increases peritendinous type I collagen synthesis in humans with achilles tendinosis. *Scand J Med Sci Sports.* 2006;19:1-6.

Lavagnino M, Arnoczky SP. In vitro alterations in cytoskeletal tensional homeostasis control gene expression in tendon cells. *J Orthop Res.* 2005;23:1211-1218.

Lavin M, Watters D, Eds. *Programmed cell death – the cellular and molecular biology of apoptosis*. Chur. Switzerland; Harwood Academic Publ: 1993.

Leadbetter WB. Cell-matrix response in tendon injury. *Clin Sports Med.* 1992;11:533-578.

Lembeck F, Donnever J, Colpaert FC. Increase of substance P in primary afferent nerved during chronic pain. *Neuropeptides.* 1987;1:175-180.

Letson AK, Dahners LE. Influence of growth factor combinations on ligament healing. *Trans Orthop Res Soc.* 1994;19:17.

Lewis T. The nocifensor system of nerves and its reactions. *BMJ.* 1937;194:431-435.

Lorentzon R. Causes of injuries: Intrinsic factors. In: Dirix A, Knuttgen HG, Tittel K, eds. *The Olympic Book of Sports Medicine.* Oxford: Blackwell Scientific Publications; 1988:376-390.

Luhtanen P, Komi RV: Segmental contribution to forces in vertical jump. Eur J Appl Physiol *Occup Physiol.* 1978;38:181-188.

Maffulli N, Testa V, Capasso G. et al. Similar Histopathological Picture of Tendinopathic Achilles and patellar Tendons. ISAKOS Congress. 2005; Paper 110.

Martens M, Wouters P, Burssens A, Mulier JC. Patellar tendinitis: pathology and results of treatment. *Acta Orthop Scand.* 1982;53:445-450.

Maxwell PH, Pugh CW, Ratcliffe PJ. Activation of the HIF pathway in cancer. *Curr Opin Genet Dev.* 2001;11:293-299.

McIntosh AS. Risk compensation, motivation, injuries, and biomechanics in competitive sport. *Br J Sports Med.* 2005;39:2-3.

McNitt-Gray JL. Musculoskeletal loading during landing. In: Ed. V Zatziorsky, ed. *Biomechanics in sport.* Vol. IX, Encyclopaedia of sports medicine. Oxford: Blackwell Science; 2000.

Meeuwisse WH. Assessing causation in sports injury: A multifactorial model. *Clin J Sports Med.* 1994;4:166-170.

Micheli LJ. Overuse injuries in children`s sports: the growth factor. *Orthop Clin North Am.* 1983;14:337-360.

Miller BF, Olesen JL, Hansen M. et al. Coordinated collagen and muscle protein synthesis in human patellar tendon and quadriceps muscle after exercise. *J Physiol.* 2005;567:1021-1033.

Mokone GG, Schwellnus MP, Noakes TD, Collins M. The COL5A1 gene and Achilles tendon pathology. *Scand J Med Sci Sports* 2006;16:19-26.

Mokone GG, Gajjar M, September AV et al. The guanin-thymine dinucleotide repeat polymorphism within the tenacin-C gene is associated with achilles tendon injuries. *Am J Sports Med.* 2005;33:10016-1021.

Myklebust G, Maehlum S, Holm I, Bahr R. A prospective cohort study of anterior cruciate ligament injuries in elite Norwegian team handball. *Scand J Med Sci Sports* 1998;8:149-153.

Myllymäki T, Bondestam S, Suramo I, Cederberg A, Peltokallio P. Ultrasonography of jumper's knee. *Acta Radiol.* 1990;31:147-149.

Neri M. Studio epidemiologico sul ginocchio del salvatore nel pallavolista. *J Sports Traumatol Rel Res.* 1991;13:95-101.

Nigg B. Causes of injuries: Extrinsic factors. In: Dirix A, Knuttgen HG, Tittel K, eds. *The Olympic Book of Sports Medicine.* Oxford: Blackwell Scientific Publications; 1988:363-375.

Olesen JL, Heinemeier KM, Haddad F et al. Expression of insuline-like growth factor 1, insuline-like growth factor binding proteins, and collagen mRNA in mechanically loaded plantaris tendon. *J Appl Physiol.* 2006;101:183-188.

Orava S, Österback L, Hurme M. Surgical treatment of patellar tendon pain in athletes. *Brit J Sports Med.* 1986;20:167-169.

Petersen W, Pufe T, Zantop T, Tillmann B, Tsokos M, Mentlein R. Expression of VEGFR-1 and VEGFR-2 in degenerative Achilles tendons. *Clin Orthop Relat Res.* 2004a;420:286-291.

Petersen W, Varoga D, Zantop T, Hassenpflug J, Mentlein R, Pufe T. Cyclic strain influences the expression of the vascular entothelial growth factor (VEGF) and the hypoxia inducible factor 1 alpha (HIF-1alpha) in tendon fibroblasts. *J Orthop Res* 2004b;22:847-853.

Proske U, Schaible HG, SchmidtRF. Joint receptors and kinaesthesia. *Exp Brain Res.* 1988;72:219-224.

Pufe T, Petersen WJ, Mentlein R. Tillmann BN. The role of vasculature and angiogenesis for the pathogenesis of degenerative tendon disease. *Scand J Sports Med.* 2005;15:211-222.

Pufe T, Petersen W, Tillmann B, Mentlein R. The angiogenic peptide vascular endothelial growth factor is expressed in foetal and ruptured tendons. *Virchows Arch.* 2001;439:579-585.

Qi JH, Ebrahem Q, Moore N. et al. Anand-Apte B. A novel function for tissue inhibitor of metalloproteinase-3 (TIMP3): inhibition of angiogenesis by blockage of VEGF binding to VEGF receptor-2. *Nat Med.* 2003;9:407-415.

Raatikainen T, Karpakka J, Puranen J, Orava S. Operative treatment of partial rupture of the patellar ligament. A study of 138 cases. *Int J Sports Med.* 1994;15:46-49.

Renstrøm P. Diagnosis and management of overuse injuries. In: Dirix A, Knuttgen HG, Tittel K, eds. *The Olympic Book of Sports Medicine*. Oxford: Blackwell Scientific Publications; 1988;446-468.

Renstrøm P, Johnson RJ. Overuse injuries in sports. A review. *Sports Med.* 1985;2:316-333.

Robinson JM, Cook JL, Purdam C. et al; Victorian Institute Of Sport Tendon Study Group. The VISA-A questionnaire: a valid and reliable index of the clinical severity of Achilles tendinopathy. *Br J Sports Med.* 2001;35:335-341.

Roels J, Martens M, Mulier JC, Burssens A. Patellar tendinitis (jumper's knee). *Am J Sports Med.* 1978;6:362-368.

Sale DG. Testing strength and power. In: MacDougall JD, Wenger HA, Green HJ, eds: *Physiological testing of the high-performance athlete*. Champaign, Illinois: Human Kinetics; 1990;21-106.

Salvesen GS. Caspases and apoptosis. *Essays Biochem*. 2002;38:9-19.

Sato Y, Abe M, Tanaka K. et al. Signal transduction and transcriptional regulation of angiogenesis. *Adv Exp Med Biol*. 2000;476:109-115.

Schepelmann K, Messlinger K, Schaible HG, Schmidt RF. Inflammatory mediators and nociception in the joint: excitation and sensitization of slowly conduction afferent fibers of cat`s knee by prostaglandin I2. *Neuroscience*. 1992:50:237-247.

Schmid MR, Hodler J, Cathrein P, Duewell S, Jacob HA, Romero J. Is impingement the cause of jumper's knee? *Am J Sports Med*. 2002;30:388-395.

Scott A, Khan KM, Heer J, Cook JL, Lian O, Duronio V. High strain mechanical loading rapidly induces tendon apoptosis: an ex vivo rat tibialis anterior model. *Br J Sports Med*. 2005;39:e25.

Selinger A, Ackermann-Blount J. *Power volleyball*. New York: St. Martin's Press; 1986.

Sen S. Programmed cell death: concept, mechanism and control. *Biol Rev Cam Philos Soc*. 1992;67:287-319.

Senger DR, Galli SJ, Dvorak AM et al. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science*. 1983;219:983-985.

Skutek M, van Griensven M, Zeichen J, Brauer N, Bosch U. Cyclic mechanical stretching of human patellar tendon fibroblasts: activation of JNK and modulation of apoptosis. *Knee Surg Sports Traumatol Artrosc*. 2003;11:122-129.

Smart GW, Taunton JE, Clement DB. Acilles tendon disorders in runners – a review. *Med Sci Sports Exerc*. 1980;12:231-243.

Soldado F, Reina F, Yuguero M, Rodriguez- Baeza A. Clinical anatomy of the arterial supply of the human patellar ligament. *Surg Radiol Anat*. 2002;24:177-182.

Stanish WD, Curwin S, Rubinovich M. Tendinitis: the analysis and treatment for running. *Clin Sports Med* 1985;4:593-609.

Stanish WD. Overuse injuries in athletes: a perspective. *Med Sci Sports Exerc*. 1984;16:1-7.

Straub RH, Gunzler C, Miller LE, Cutolo M, Scholmerich J, Schill S. Anti-inflammatory cooperativity of corticosteroids and norepinephrine in rheumatoid arthritis synovial tissue in vivo and in vitro. *FASEB J*. 2002;16:993-1000.

Torstensen ET, Bray RC, Wiley JP: Patellar tendinitis: a review of current concepts and treatment. *Clin J Sports Med*. 1994;4:77-82.

Tsuzaki M, Brigman BE, Xiao H. IGF-1 and TGF-B drive tendon cell DNA synthesis. *Trans Orthop Res Soc*. 1994;19:18.

van Mechelen W, Hlobil H, Kemper HC. Incidence, severity, aetiology and prevention of sports injuries. A review of concepts. *Sports Med*. 1992;14:82-99.

Visentini PJ, Khan KM, Cook JL, Kiss ZS, Harcourt PR, Wark JD. The VISA score: an index of severity of symptoms in patients with jumper's knee (patellar tendinosis). Victorian Institute of Sport Tendon Study Group. *J Sci Med Sport*. 1998;1:22-28.

Wang H, Keiser JA. Vascular endothelial growth factor upregulates the expression of matrix matalloproteinases in vascular smooth muscle cells: role of flt-1. *Cirk Res*. 1998;83:832-840.

Wiesenfeld-Hallin Z, Høkfelt T, Lundberg JM. Immunoreactive calcitonon gene-related peptide and substance P coexist in sensory neurons of the cat: evidence from combined immunohistochemistry and acetylcholinesterase staining. *Neurosci. Lett*. 1984,57:125-130.

Williams JPG. Achilles tendon lesions in sport. *Sports Med*. 1986;3:114-135.

Witvrouw E, Bellemans J, Lysens R, Danneels L, Campier D. Intrinsic risk factors for the development of patellar tendinitis in an athletic population. A two-year prospective study. *Am J Sports Med*. 2001;29:190-195.

Yu JS, Popp JE, Kaeding CC, Lucas J. Correlation of MR imaging and pathological findings in athletes undergoing surgery for chronic patellar tendinitis. *AJR Am J Roentgen*ol. 1995;165:115-118.

Yuan J, Murrell GA, Wei AQ, Wang MX: Apoptosis in rotator cuff tendonopathy. *J Orthop Res*. 2002;20:1372-1379.

Yuan J, Wang MX, Murrell GA. Cell death and tendinopathy. *Clin Sports Med*. 2003;4:693-701.

Zamboni L, De Martino C. Buffered picric acid-formaldehyd: a new, rapid fixative for electrone microscopy. *J. Cell. Biol.* 1967;35:148.

Zernicke RF, Garhammer J, Jobe FW. Human patellar-tendon rupture: a kinetic analysis. *J Bone Joint Surg Am*. 1977;59:179-183.

Ziche M, Morbidelli L, Pacini M, Geppetti P, Alessandri G, Maggi CA. Substance P stimulates neovascularization in vivo and proliferation of cultured endothelial cells. *Microvasc. Res.* 1990;40:264-278.