


Risk Factors for Jumper's Knee

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Dissertation for the degree philosophiae doctor (PhD)
at the University of Bergen

2014

Dissertation date: 12.09.14

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Scientific environment

This study has been conducted at and funded by the Oslo Sports Trauma Research Center. The Oslo Sports Trauma Research Center was established at the Norwegian School of Sport Sciences in 2000 as a research collaboration between the Department of Orthopaedic Surgery, Oslo University Hospital, and the Norwegian School of Sport Sciences. The main objective of the Oslo Sports Trauma Research Center has been to develop a long-term research program on sports injury prevention.

Kysthospitalet i Hagevik, Department of Orthopaedic Surgery, at Haukeland University Hospital, Bergen, Norway has partially funded the candidate's salary.

Acknowledgements

This study was carried out at Oslo Sports Trauma Research Center and 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, directly or indirectly. In particular I would like to thank:

My main supervisor, Roald Bahr, MD, PhD, professor and chair of Oslo Sports Trauma Research Center: Without your academic knowledge, wisdom and belief in me this thesis would never have been finished. You are the best supervisor I could ever have had. I appreciate all the discussions we have had about what matters in life: volleyball and tendons.

Agnar Tegnander MD, PhD and member of Oslo Sports Trauma Research Center. You have been a positive and supportive company on our trips to Sand for four years to perform the ultrasound examinations.

Kari Indrekvam MD, PhD and professor of the University of Bergen and hospital director of Kysthospitalet i Hagevik: Thank you for giving me the opportunity four and a half years ago, and for helping me find the balance of combining surgery and research.

Lars Engebretsen, MD, PhD, professor and co-founder of the Oslo Sports Trauma Research Center. I admire you because you set the standard for combining orthopedic surgery and research.

Thanks to all coaches and students at ToppVolley Norway (TVN). I have visited beautiful Sand many times during the five years of data collection. The enthusiasm at TVN is unique. Thanks to Øyvind Marvik, for his positive response and back-up through the years; Hans Åge Andahl for helping organize testing, Arvid Wigestrånd and Per-Arne Haarr for hosting me during testing weeks and for all good

conversations about volleyball. The students at TVN are the best students a researcher could dream of.

Karim Kahn, MD, PhD, you are probably the best tendon researcher in the world. Thank you for the input when designing this study, and your positive feedback during these years.

Aasne Hoksrud MD, PhD, we started our research careers together and you have supported me ever since.

Ingar Holme, Dr. philos, PhD, professor and statistician at Oslo Sports Trauma Research Center, thank you for excellent statistical advice and not giving up trying to teach me statistics.

Thank you to all my colleges at Oslo Sports Trauma Research Center for their inspiring work. You are one of the best research groups in the world, and I have always been motivated after our meetings. Special thanks to the “seniors” Grethe Myklebust, Thor Einar Andersen, Tron Krosshaug, May-Arna Risberg, Kathrin Steffen, Tonje Wåle Fløernes, Asbjørn Årøen and Øystein Lian.

Thank you Tone Øritsland, project coordinator, for the friendly help with the projects.

My dear colleagues at Kysthospitalet i Hagevik, you have taught me the skills of orthopedics. The quality of your work is excellent and I have still a lot to learn. I have appreciated all stimulating discussions during the last years.

To my parents and to my sister; you have always been invaluable an unwavering support to me in all kinds of ways.

My wife, Renate, my love and best friend; together we raise the loveliest children in the world. Hanna, Selma, Nora, Markus and Lisa: you are the light of my life.

Bergen, February 2014.

Abstract

Background

The prevalence of jumper's knee is high in sports characterized by high demands on leg extensor speed and power, such as volleyball, basketball, football and athletics. A prevalence up to 50% has been reported among male, elite volleyball players. The complex process from a healthy tendon to jumper's knee is not fully understood. Jumper's knee is usually described as an overuse injury, although previous studies on risk factors are not conclusive. Previous cross-sectional studies among volleyball players have found that athletes with jumper's knee have higher body mass compared to asymptomatic controls, suggesting a relationship between body composition and jumper's knee. The "jumper's knee paradox", where symptomatic athletes appear to perform better in a counter movement jump (CMJ) compared to asymptomatic controls, is not fully understood. Tendons adapt to mechanical loading, albeit not always adequately. Tendon structural changes from childhood to adulthood are not well investigated, and there is a need for prospective studies examining the response to intensive training during adolescence. In many athletes with symptoms of jumper's knee, ultrasound or MRI imaging of the painful tendons will reveal morphological abnormalities, typically as localized tendon thickening with hypoechoic areas and increased vascularity. However, it is not clear whether the presence of ultrasound changes in asymptomatic tendons precede (and predict) future tendon problems.

Aims

First, we wanted to study whether training load and competition load as well as body composition or change of body composition represented a risk factor for developing jumper's knee (Paper I). Furthermore, we wanted to investigate jumping ability and change of jumping ability as potential risk factors for developing jumper's knee (Paper

II). We also wanted to investigate the relationship between the development of ultrasound changes in the patellar and quadriceps tendons and symptoms of jumper's knee, as well as the medium-term effects of intensive training on tendon thickness among adolescent athletes (Paper III).

Methods

Papers I-III were based on a prospective cohort study with a total data collection period of 5 years. All participants were recruited from the same cohort, players entering the Toppvolley Norway (TVN) program, but the time and duration of inclusion differed between participants. TVN is located in Sand, Norway and combines an elite volleyball training program with a three-year senior high boarding school program. All students at TVN were eligible for this study. In Paper I & II only athletes without jumper's knee at baseline were included, while Paper III also included athletes with pre-existing jumper's knee. The diagnosis of jumper's knee was based on a clinical examination alone. All athletes were examined twice a year. Training volume and match exposure were recorded prospectively on a weekly basis. Body composition was assessed by measuring height and weight, waist circumference and through skin fold caliper tests. Jumping ability was tested on a portable force plate and included two different jumps (CMJ and standing jump (SJ)). An ultrasound examination was done twice a year as long as students remained at TVN using grey-scale and color Doppler.

Main results

Altogether, 192 students were registered in the school record at TVN during the 5-year study period. Nearly one in three boys developed jumper's knee during their time at TVN (32%) compared to only 8% of the girls (Paper I).

Paper I: Athletes developing jumper's knee had higher total training volume and tendon load compared to those who remained asymptomatic. A multivariate regression

analysis showed that match exposure was the strongest sports-related predictor for developing jumper's knee with an OR of 3.88 (95% CI 1.80 to 8.40) for every extra set played per week. Volleyball training had an OR 1.72, (95% CI 1.18 to 2.53) when combined with match exposure and gender. We did not detect any significant differences in body composition at the time of inclusion or change of body composition during the study period between players who developed jumper's knee and those who did not developed jumper's knee. Males had three to four times higher risk of developing jumper's knee compared to females, independent on training and match exposure in the multivariate regression analysis.

Paper II: At the time of inclusion, male athletes who went on to develop jumper's knee had significantly better results in CMJ (38.0 ± 5.8 cm) compared to asymptomatic males (34.6 ± 5.5 cm, $p=0.03$), while no difference was detected in SJ. In a multivariate logistic regression analysis corrected for gender and previous volleyball training, the OR was 2.09 (1.03 to 4.25) per cm difference in CMJ at the time of inclusion. Our results did not reveal any significant differences in the change in jumping ability between the groups, although both groups improved their jumping performance.

Paper III: About half of the asymptomatic athletes who went on to develop jumper's knee (17 of 35 tendons) had hypoechoic areas when they started at TVN, while 10% of the tendons that remained asymptomatic (24 of 238 tendons) had the same changes. Neovascularisation was found in 4% (9 of 238 tendons) of asymptomatic tendons and in 48% (15 of 35 tendons) of those who later developed jumper's knee. In a multivariate logistic regression analysis, a baseline finding of a hypoechoic tendon area (OR 3.3, 95% CI 1.1 to 9.2) and neovascularisation (OR 2.7, 95% CI 1.1 to 6.5) increased the risk of developing jumper's knee. Patellar tendon thickness among healthy athletes did not change (Wilk's lambda, $p=0.07$) while quadriceps tendon thickness increased ($p=0.001$). The athletes reported a VISA score of 72 (SD 23) when first diagnosed, and knee function did not change during subsequent examinations and was 73 (SD 21) when they left TVN.

Conclusion

A high volume of volleyball training and match exposure were important risk factors for developing jumper's knee. Body composition or change in body composition were not associated with injury risk. Volleyball players with a natural ability for jumping high have an increased risk of developing jumper's knee, while change in jumping ability was not identified as a risk factor. Hypoechoic areas and neovascularisation at baseline were risk factors for developing jumper's knee. Quadriceps tendon thickness increased 7-11% among healthy athletes, while there was no change in patellar tendon thickness.

List of publications

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

- I. Visnes H, Bahr R. *Training volume and body composition as risk factors for developing jumper's knee among young elite volleyball players*. Scand J Med Sci Sports 2013, 23 (5), 607-13.
- II. Visnes H, Aandahl HÅ, Bahr R. *Jumper's knee paradox--jumping ability is a risk factor for developing jumper's knee: a 5-year prospective study*. Br J Sports Med 2013, 47 (8), 503-7.
- III. Visnes H, Tegnander A, Bahr R. *Ultrasound characteristics of the patellar and quadriceps tendons among young elite athletes*. Scand J Med Sci Sports 2014, online Feb 24. doi: 10.1111/sms.1219

Definitions

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 (Jozsa and Kannus 1997; Khan et al. 1998; Maffulli et al. 1998; Lian 2006; Hoksrud 2011) the following terminology is used in this thesis:

Tendinosis is histopathological intratendinous degeneration without clinical or histological signs of intratendinous inflammation. The term “tendinosis” is used regardless of clinical symptoms, as it can be both symptomatic and asymptomatic.

Tendinopathy is a condition characterized by a combination of tendon pain and tenderness to palpation verified by ultrasound or magnetic resonance imaging (MRI) findings demonstrating structural changes in the affected area.

Patellar tendinopathy means a lesion associated with pain and tenderness at the lower point of the patella and with structural changes in the affected area verified by ultrasound or MRI.

Jumper's knee is 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.

Abbreviations

ADAM	A disintegrin and metalloproteinase
ADAMTS	A disintegrin and metalloproteinase with thrombospondin
AGE	Advanced glycation end product
BMD	Body mass density
CGRP	Calcitonin generelated peptide
CI	Confidence interval
CMJ	Counter movement jump
COX-2	Cyclooxygenase-2
CSA	Cross-sectional area
ECM	Extracellular matrix
GAGs	Glucosaminoglycans
GLM	Global multivariable linear model
H&E	Hemotoxylin and eosin
IGF-1	Insuline like growth factor-1
IL-6	Inter leukin-6
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
NMDAR1	N-methyl-d-aspartate receptor 1
OR	Odds ratio
PDGF	Platelet derived growth factor
PDGFR	Platelet-derived growth factor receptor
PGE2	Prostaglandin E2
ROM	Range of motion
SD	Standard deviation
SJ	Standing jump
SLRP	Small leucine-rich proteoglycans
TGF- β	Transforming growth factor- β
TIMP	Tissue inhibitor of matrix metalloproteinase
TVN	Toppvolley Norway
UTC	Ultrasonographic tissue characterization
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VISA-P	Victorian institute of sport assessment score – patellar tendon

1. Introduction

1.1 Anatomy of patellar and quadriceps tendon

Tendons are anatomic structures interposed between muscles and bones transmitting the force created in the muscle to bone, and in this way, making joint movement possible. The anatomy of the patellar and quadriceps tendon is described in more detail by several other authors (Jozsa and Kannus 1997; Stäubli et al. 1999; Staubli et al. 1999; Kannus 2000; Basso et al. 2001). A healthy tendon is brilliant white in color and fibro-elastic in texture, showing great resistance to mechanical loads. 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. The patellar tendon width is approximately 3 to 3.5 cm, the thickness is about 4 to 5mm (Lian et al. 1996; Khan et al. 1998) and the length varies from 5 to 7.5 cm depending on the attachment on the patella and tibial tuberosity (Basso et al. 2001). A normal adult patellar tendon has a cross-sectional area (CSA) of 1 cm² (Hansen et al. 2006). The CSA of the patellar tendon increases distally (Seynnes et al. 2009). 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 more 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 quadriceps tendon is interposed between the myofascial junctions of the superficial layer of the rectus femoris muscle, the middle layers of the vastus medialis and vastus lateralis muscles, and the deep layer of the vastus intermedius muscle (Stäubli et al. 1999). The layers converge to the broad insertion of the quadriceps tendon at the base of the patella. The most anterior fibers of the quadriceps tendon blend over the anterior aspect of the patella as structural components of the vertical and horizontal tensile bracing system (Stäubli et al. 1999). Biomechanically, the quadriceps tendon and the patella are integral parts of the active

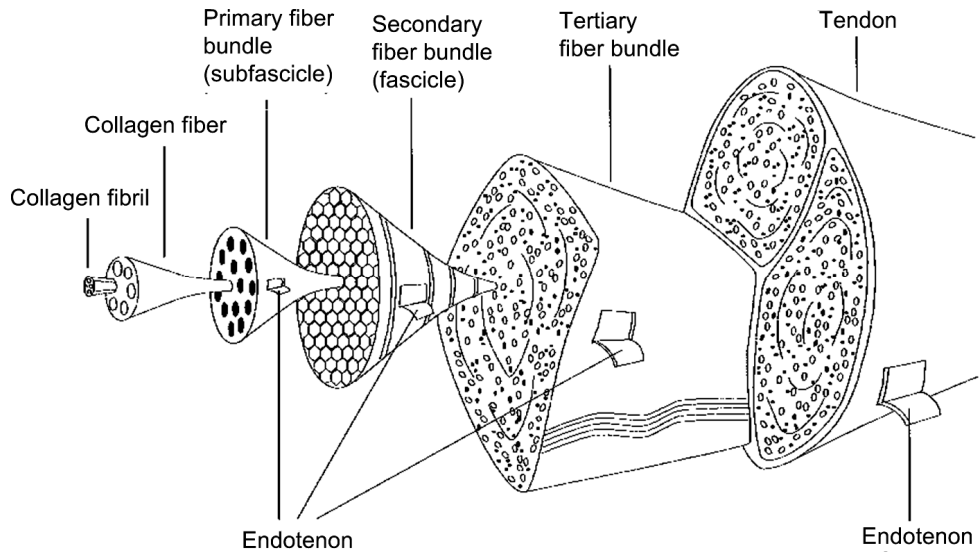
and passive extensor mechanisms of the knee joint. Quadriceps tendon thickness is measured to 7 ± 1 mm in women and 8 ± 1 mm in men (Staeubli et al. 1999).

In general, the blood supply of tendons is mainly from the muscle and is usually divided into three regions: (i) the musculotendinous junction; (ii) the length of the tendon; (iii) the tendon bone junction (O'Brien 1997). The patellar tendon receives its vascularisation from three main arterial pedicles (superior, middle and inferior) located on each side of the patellar tendon (Soldado et al. 2002; Pang et al. 2009). The vascular network inside the tendon consists of longitudinally arranged vessels localized in the endotenon septas together with veins, nerves and lymphatics. These small arterioles are oriented parallel to the collagen fibers in the endotenon (Aström and Rausing 1995; Khan et al. 1996). The blood supply of the quadriceps tendon arises from descending branches of the lateral circumflex femoral artery, by branches of the descending geniculate artery and by branches of the medial and lateral superior geniculate arteries. Blood vessels penetrate the tendon from the surrounding connective tissue and anastomose with a longitudinally orientated intraligamentous network. Compared to the surrounding synovial layer, the amount of vessels in the tendon substance is less (Petersen et al. 1999).

1.1.1 Elements of human tendons

Many of the tendons are surrounded by a loose connective tissue called paratenon. Paratenon functions as an elastic sleeve permitting free movement of the tendon against the surrounding tissues (Hess et al. 1989). The entire tendon is surrounded by a fine connective tissue sheath called epitenon. The epitenon is a relatively dense fibrillar network of collagen with strands of 8–10 nm in thickness. This network contains longitudinal, oblique, as well as transversal fibrils (Kannus 2000). The endotenon is a thin reticular network of connective tissue inside the tendon that has a well developed crisscross pattern of collagen fibrils (Kannus 2000). The endotenon fibrils invest tendon fibers and bind fibers together.

Figure 1: The hierarchical organization of tendon structure. (Reproduced with permission from Kannus 2000).



1.1.2 Extracellular matrix

Tendinous tissue is composed of tendon cells and almost exclusively extracellular matrix (ECM) (Kannus 2000). The load bearing elements of tendinous tissue are collagen fibrils that are embedded in a hydrated viscous proteoglycan-rich substance called ground substance. The dry mass of human tendons is approximately 30%, with water accounting for the remaining 70% of the tendon mass (Kirkendall and Garrett 1997; Kannus 2000).

Collagen is the abundant protein in tendons, accounting for 65-80% of the dry mass of the tendon (Jozsa et al. 1989). Tendons are predominantly made up of collagen type I and smaller amounts of other collagen types including type II, III, IV (Kadler et al. 1996; Bailey 2001). Collagen type I (~60%) is arranged in tensile-resistant fibers, and composed of two $\alpha 1$ - and one $\alpha 2$ -chains (Kjaer 2004). It is organized in a complex structure and the structure provides a good buffer capacity against longitudinal, transversal horizontal and rotational forces during movement (Jozsa et al. 1989). The collagen fiber is the basic force-transmitting unit of the tendon, and it determines the mechanical properties of the tendon; small fibrils increase the

elastic properties whereas larger fibrils increase the strength (Provenzano and Vanderby 2006).

Ground substance surrounds the collagen and elastin molecules and consists of polysaccharide chains called GAGs and small leucine-rich proteoglycans (SLRP) which are bound to the protein in the form of proteoglycans (O'Brien 1997; Kannus 2000). The large glycosaminoglycans have a high number of negatively charged GAGs attached to their core protein, which gives these proteoglycans the ability to attract and bind water (Fu et al. 2007). SLRP constitute about 80% of the total proteoglycan content in the tendon (Samiric et al. 2004). Their main function is to bind collagen fibrils and regulate fibrillogenesis and they are also important for the structure and function of the extracellular matrix (Scott et al. 1981; Danielson et al. 1997; Samiric et al. 2004). Any increase in size and concentration or negative charges of proteoglycans and GAGs may cause disruption of normal ECM architecture (Scott 1990). Although the role and function of many of these components are still poorly defined, the molecular architecture of the matrix is ideally suited primarily for the transmission of tensile load. Tendons also function to stabilize joints and absorb large shocks, protecting muscles from damage (Riley 2008). It is clear that the ECM of tendons would adapt to mechanical stimulus to make the tissue more damage resistant to ensure an optimal force transmission with muscular contractions (Kjaer 2004).

1.1.3 Tendon cells

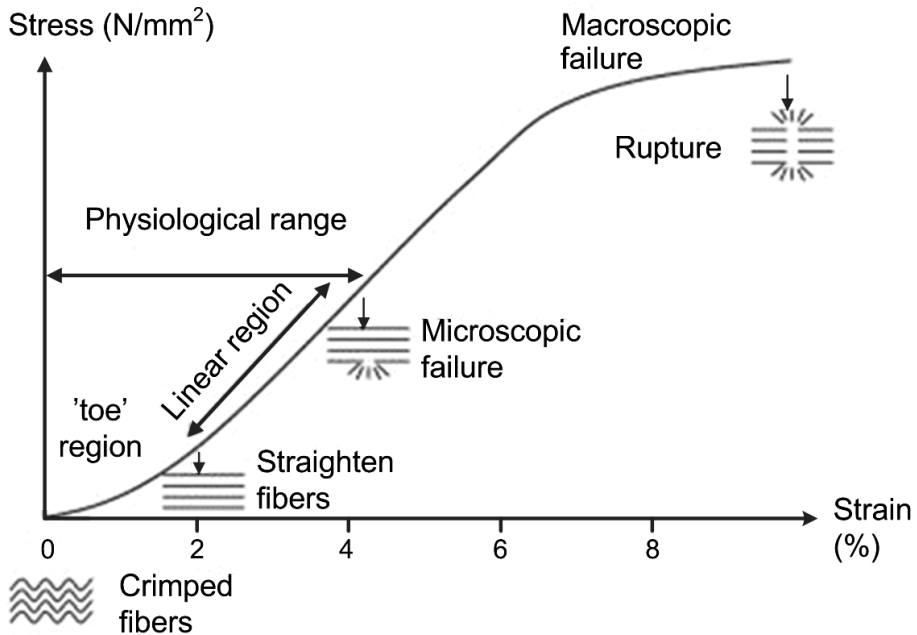
The normal tendon tissue has sparse distribution of cells and consists of approximately 95% of fibroblasts (tenoblasts and tenocytes) (Aström and Rausing 1995; Kannus 2000). Additional cells may include chondrocytes, synovial cells and endothelial cells (Jozsa and Kannus 1997). The tenocytes are elongated spindle-shaped fibroblasts placed between and in parallel with collagen fibrils (Kirkendall and Garrett 1997). In general, fibroblasts are attached to the ECM via integrins that span the cell membrane and connect the intracellular cytoskeleton with the surrounding matrix: fibroblasts are connected to each other by gap-junctions (Wang et al. 2006; Chiquet et al. 2009). These cells respond to mechanical stimulus by becoming deformed; they respond to changes in force by altering their function and composition (Khan and Scott 2009). The tendon fibroblasts synthesize and maintain the elements of extracellular matrix, and therefore the connection between fibroblasts and tendon

matrix permits the cells to sense and respond to mechanical stimuli and thus adapt to changed patterns of mechanical loading. (Heinemeier and Kjaer 2011).

1.2 Tendon biomechanics and properties

Tendons must be able to transmit high muscle force to the skeleton for movement and the parallel arrangement of fiber bundles is quite efficient for this purpose. However, tendons have low resistance to shear forces. Thus, tendons are designed to transmit forces with minimal deformation and energy loss (Kirkendall and Garrett 1997). Tendon dimensions (length and cross-sectional area) affect the mechanical properties. Typical parameters describing the tendon mechanical properties of tendons were described by Heinemeier and Kjaer (2011). Tendon strain describes the elongation and deformation of the tendon relative to the normal length (figure 2), while tendon stress describes the tendon force relative to the tendon CSA. Thus, tendon stiffness describes the change in tendon length (deformation) in relation to the force applied to the tendon. This parameter is dependent on the CSA and length of the tendon. i.e. greater CSA and shorter length will lead to greater stiffness. Tendon modulus describes the relation between tendon stress and tendon strain. In other words, modulus represents the properties of the actual tendon material independently of the CSA. This makes it possible to compare structures with different dimensions. A high tendon modulus indicates a relatively stiff tissue. Tendon strength is related to tendon CSA but also the tensile quality of the tendinous tissue (i.e. intrafibrillar cross links and collagen type distribution) (Butler et al. 1978; Kirkendall and Garrett 1997). Therefore, the previously described stress/strain curve would depend on the tendon CSA. It is estimated that an increase in length of the tendon of more than 4% would lead to microscopic tendon rupture and a total rupture would appear at approximately 8-12% of strain (Butler et al. 1978; Wang 2006).

Figure 2: Stress-strain curve. The mechanical response of the tendon is defined by the stress-strain curve. (Reproduced with permission from Wang 2006).



1.2.1 Tendon adaptation to mechanical loading

How tendons adapt to mechanical loading is of great interest. Tendons of athletes have high demands and it is important to adapt to increasing training volumes. In spite of the relatively low occurrence of fibroblasts and rather limited vascularity, tendons have been shown to be metabolically responsive structures. The natural development of tendons from childhood to adulthood is not well investigated. Some data from animal studies indicate that tendons of immature animals are more likely to hypertrophy than tendons of mature animals (Elliott 1965; Smith et al. 2002). Since studies among children and adolescents are needed, the current knowledge is therefore based on the effect of exercise on adult tendons.

Investigating tendon adaptation to mechanical loading is challenging. It is suggested that endon tissue is protected from rapid changes in tissue mass, while muscle tissue, which is known to act as protein store for the organism, is subject to substantial and fast changes in the

tissue (Kjaer et al. 2009). The level of collagen synthesis seems to be quite uniform and relatively independent of the magnitude of exercises (Kjaer et al. 2009). Change in collagen synthesis or structure can be studied in different ways. Animal models have used indirect enzymes involved in the formation and processing of collagen, and data suggest that increased loading could increase collagen synthesis (Kovanen 1989). Microdialysis technique on human tendons using catheters placed near the loaded tendon, found that tendons responded to loading. Markers of collagen synthesis are increased in peritendinous tissue for 2–3 days after an acute training bout and remain elevated with prolonged training (Langberg et al. 1999; Langberg et al. 2001). Increased collagen synthesis has also been documented by percutaneous biopsies. The mechanism linking mechanical loading of tendon tissue to the apparent increase in collagen synthesis is still unknown (Heinemeier and Kjaer 2011) as well as the precise link between the tendon metabolic response to increased loading and changes observed at macroscopic level. Changes in mechanical properties (CSA, modulus and tendon stiffness) have been investigated with ultrasound-based techniques and MRI. As previously described, the increase in tendon stiffness could be linked to either changes in material properties or increased CSA. Table 1 presents studies investigating changes in tendon thickness and CSA as well as tendon stiffness and modulus.

Table 1: Effect of mechanical load on tendon thickness and CSA, stiffness and modulus among healthy athletes.

Author	Design	Study population	N	Study period	Training program	Tendon	Results
Kubo et al. (2001)	Cohort study	Healthy men	8	12 week	4 days per week: knee extension at 70% of maximal voluntary contraction (MVC)	Quadriceps	No change in tendon CSA, but increased muscle volume
Kubo et al. (2002)	Cohort study	Healthy men	8	8 weeks	4 days per week: resistance training; unilateral plantar flexion at 70 % of one repetition maximum	Achilles	No change in CSA , but increased stiffness
Roager et al. (2002)	Case-control study	Runners & controls	10	--	--	Achilles	The Achilles tendon CSA was markedly larger in runners than non-runners
Reeves et al. (2003)	RCT	Training group & controls, (mean age 75yrs)	18	14 weeks	2 times per week. Two series of 10 repetitions at 80 % of five-repetition maximum	Patellar	No change in CSA, but tendon stiffness increased 65 % and modulus increased by 69 %
Hansen et al. (2003)	Cohort	Untrained	11	9 months	Running (70–80 training sessions over 9-month period)	Achilles	No change in CSA or mechanical properties
Magnusson and Kjær, (2003)	Cross-sectional study	Runners and non-runners	12	--	--	Achilles	Runners CSA (36%) >non-runners at the most distal part of the tendon
Kongsgaard et al. (2005)	Case-control study/Cross-sectional study	Runners, volleyball players, kayakers	25	--	--	Achilles	Achilles tendon CSA in runners and volleyball players > kayakers

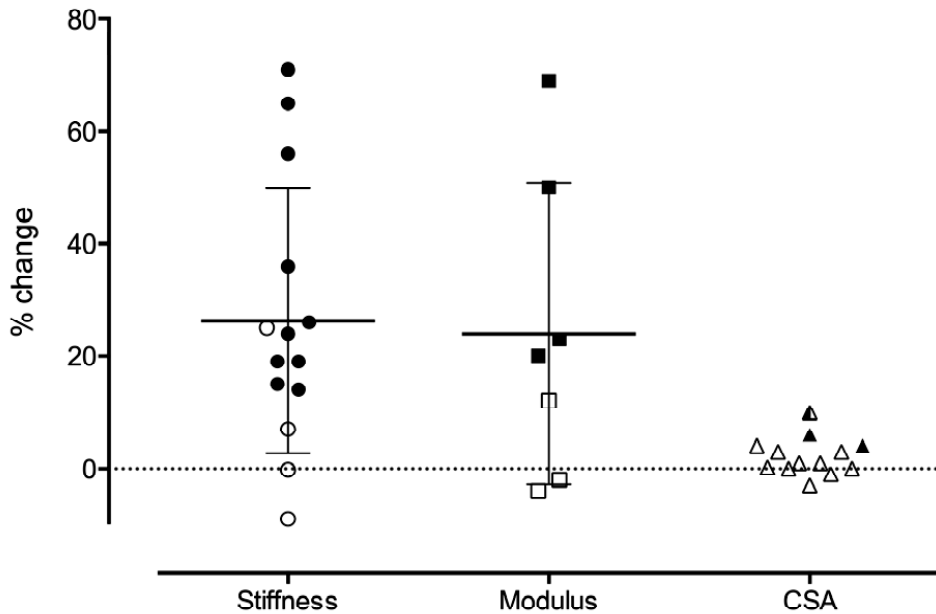
Author	Design	Study population	N	Study period	Training program	Tendon	Results
Kubo et al. (2006)	Case-control study	Healthy males & controls	14	12 weeks	4 times per week, isometric squat training	Vastus lateralis + patellar	Increased stiffness in vastus lateralis tendon– aponeurosis complex but not in patellar tendon
Arampatzis et al. (2007)	Case-control study	Healthy adults & controls	21	14 weeks	4 times per week: isometric plantar flexion contractions	Achilles	Increased CSA, tendon stiffness and tendon modulus
Kongsgaard et al. (2007)	Cohort study	Untrained men	12	12 weeks	Training 3 times per week, leg extension machine	Patellar	Increased proximal tendon CSA, but unchanged for mid tendon
Urlando and Hawkins, (2007)	Cohort Study	Untrained men	10	8 weeks	3 times per week, isometric plantar flexion	Achilles	No change in CSA
Coupe et al. (2008)	Cross-sectional study	Elite fencers and badminton	7	--	--	Patellar	CSA in lead extremity was (20-28%) greater. The lead extremity displayed greater tendon stiffness with no difference in modulus.
Seynnes et al. (2009)	Cohort study	University students	15	9 weeks	3 times per week, heavy resistance training in leg extension machine.	Patellar	CSA proximal increased
Kubo et al. (2009)	Cohort study	Healthy men	10	12 weeks	4 times per week. Isometric knee extension.	Patellar	No change in CSA

Author	Design	Study population	N	Study period	Training program	Tendon	Results
Aramatzis et al. (2010)	Cohort study	Male adults	11	14 weeks	4 times per week, isometric plantar flexion contractions	Achilles	No change in CSA, some changes in strain, stiffness and modulus
Foure et al. (2010)	RCT	Training group & controls	19	14 weeks	2 times per week, different jump exercises (1 hour/(200-600 jumps)	Achilles	No change in CSA, but increased tendon stiffness
Kubo et al. (2010)	RCT	Training group & controls	14	6 months	Isometric knee extension	Patellar	No change in CSA or patellar tendon thickness
Foure et al. (2013)	RCT	Training group & controls	24	14 weeks	Eccentric training, 34 sessions of 1hour	Achilles	No change in CSA, but some changes in stiffness
Malliaras et al. (2013)	RCT	4 groups	38	12 weeks	Eccentric and concentric training in a leg extension machine	Patellar	No change in CSA, but increased stiffness and modulus especially in high load eccentric group

1.2.2 Short term training effects

The evidence from short-term training studies on tendon size is conflicting (Kongsgaard et al. 2007; Kubo et al. 2009; Seynnes et al. 2009; Kubo et al. 2010; Malliaras et al. 2013). Kongsgaard et al. (2007) enrolled 12 untrained 25-yr old men in 12 weeks of resistance training 3 times per week, comparing one-leg training with heavy loads (10 sets of 8 repetitions at 70% of one repetition maximum) in a leg extension machine to the contralateral leg training with light loads (10 sets of 36 repetitions with a load equaling the amount of work to the work performed by the heavy leg). They concluded that proximal tendon CSA increased in both groups. Seynnes et al. (2009) recruited 15 20-yr old university students, who at baseline were involved in recreational training 1-2 times/week. After 9 weeks of heavy resistance training, patellar tendon cross-sectional area increased by 3.7%. In contrast to these findings, Kubo et al. (2009; 2010) have published two studies where they did not find any change of CSA. First, they followed a cohort consisting of 10 healthy males for 12 weeks (Kubo et al. 2009). The program was isometric knee extension training (4 times per week, at 70% of maximal voluntary strength with 10 contractions of 15 s duration), and they observed no change in CSA or patellar tendon thickness. In the second study they randomized 14 athletes to a training group using the same training program or to a control group (Kubo et al. 2010). Training increased muscle strength and they suggested that adaptation of tendon properties is slower compared to muscle function. In a recent paper, Malliaras et al. (2013) randomized a group of healthy men into 4 different groups (no training, concentric training, eccentric training (normal load) and eccentric training (heavy load)). After 12 weeks of training they did not find any change in patellar CSA. However, they found modulus to increase in all exercise groups but only high load eccentric group had significantly higher force, stiffness and modulus compared to the control group. At the 8th International Conference on Strength Training in Oslo, Norway in 2012, Seynnes summarized the studies available on changes in stiffness, modulus and CSA in response to short-term resistance training in the patellar and Achilles tendons. In figure 3 each point represents different studies (Kubo et al. 2001; Kubo et al. 2002; Kubo et al. 2003; Reeves et al. 2003; Kubo et al. 2006; Kongsgaard et al. 2007; Kubo et al. 2009; Seynnes et al. 2009; Foure et al. 2010). The results from previous studies indicate that newly synthesized collagen is deposited into fibrillar structure, making tendons stiffer and stronger but that the effect on tendon CSA is not unambiguous.

Figure 3: Studies available on the effects of short-term resistance training on patellar and Achilles tendon stiffness, modulus and CSA. Significant (filled symbols) and non-significant (empty symbols) changes observed after 8 to 15 weeks of resistive exercise. Half-filled symbol denotes estimated mean change. (Reproduced with permission from Seynnes 2012).



1.2.3 Long-term training effects

There are strong indications of tendon adaptation in cross-sectional studies in athletes performing long-term load bearing sports. Male runners were found to have ~30% larger Achilles tendon CSA than non-runners (Rosager et al. 2002; Magnusson and Kjaer 2003), and in a similar study weight-bearing sport athletes had thicker tendons (~20 %) compared to athletes in non-weight bearing sports (Kongsgaard et al. 2005). Another research approach used to address this question is to study athletes with asymmetric loading patterns of the lower extremities, e.g. where the leading leg is consistently subjected to higher loads. Seven fencers and badminton players, participating at the elite level for >5 yrs, displayed a side-to-side isometric knee extensor strength difference of more than 15%, in favor of their lead extremity (Couppé et al. 2008). Tendon CSA in lead extremity was also significantly greater

(20-28%) proximally and distally. Furthermore, the lead extremity displayed greater tendon stiffness with no difference in modulus, suggesting that the change in mechanical properties was largely the result of the increase observed in CSA. There is no long-term randomized study on this topic. The only “long-term” training study identified was Hansen et al. (2003), who made 11 untrained adults run 70–80 training sessions over a 9-month period without detecting any change in Achilles tendon CSA or tendon properties.

To summarize, tendon material properties (modulus) as well as CSA appear to increase in response to long-term loading. However, so far there exists no clear dose-response relationship between mechanical load and changes in tendon properties. As described in chapter 1.2.2, the common belief is that newly synthesized collagen is deposited into fibrillar structure, collagen packing density is increased, making tendons stiffer and stronger and, eventually, increasing their cross-sectional area. In Paper III we wanted to examine the medium-term effects of intensive loading on tendon thickness among adolescent athletes.

1.3 Pathology

1.3.1 Jumper’s knee diagnosis

Jumper’s knee is 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. This terminology was first used by Blazina et al. (1973), but the original definition also included the tibial attachment of the patellar tendon. The most common site is the proximal part of the patellar tendon (80-95%), even if some have reported that up to 25% of cases of jumper’s knee were located in the distal insertion of the quadriceps tendon (Fredberg and Bolvig 1999; Hak et al. 2010). On the other hand, all 137 new cases of jumper’s knee affected the patellar tendon in a large European study among elite football clubs (Hägglund et al. 2011), and only one of 87 athletes with jumper’s knee had pain localization in the quadriceps tendon in a Norwegian cross sectional study among 613 athletes (Lian et al. 2005). Symptoms typically increase gradually and there is often no clear cut-off for when to diagnose jumper’s knee. Even if jumper’s knee can be defined as a clinical diagnosis, ultrasound or MRI imaging of the painful tendon will reveal morphological abnormalities in many (but not all) painful tendons. Warden et al.

(2007) used ultrasound and MRI to verify 30 athletes with clinical diagnosis with jumpers' knee and a group of 33 activity-matched, asymptomatic controls. They found that tendons clinically diagnosed with jumper's knee had pathological findings evaluated by MRI in 56% of the cases and with grey-scale ultrasound in 87% of cases. Hoksrud et al. (2008) examined 63 patients with 79 symptomatic patellar tendons and did not find any structural changes on ultrasound examination in 14% of cases. It is therefore important to note that a study population based on a clinical diagnosis of jumper's knee alone compared to patellar tendinopathy verified by ultrasound or MRI, would not include the same patients.

Evaluation of symptoms

Blazina et al. (1973) developed the first grading scale for jumper's knee. This scale was later modified by Roels et al. (1978) and Lian et al. (1996). This 5-grade clinical grading system is based on the clinical severity of the problem, but is not suited to assess treatment outcomes.

Table 2: Blazina's clinical grading scale (1973), modified by Roels et al. (1978) and Lian et al. (1996).

Grade	Classification
Grade I	Pain at the infrapatellar or suprapatellar region after practice or after an event
Grade II	Pain at the beginning of the activity, disappearing after warm-up and reappearing after completion of activity
Grade IIIa	Pain during and after activity, but the patient is able to participate in sports at the same level
Grade 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

VISA-P score

The Victorian Institute of Sport Assessment (VISA) score was designed specifically to quantify knee function in subjects with patellar tendinopathy and has also been shown to be a reliable and valid measure (Cook et al. 1998; Visentini et al. 1998; Khan et al. 1999). It was originally designed to be an index of severity of symptoms in patients with jumper's knee but today there is also a version for the Achilles tendon (VISA-A) (Robinson et al. 2001). Therefore, the knee score has been denoted to VISA-P to avoid

confusion. This self-recording questionnaire is designed specifically to quantify knee function in subjects with patellar tendinopathy, and assesses symptoms, simple tests of function, and the ability to play sports. Six out of eight questions are scored on a scale from 0 to 10 with 10 representing optimal health. The maximal VISA-P score for an asymptomatic, fully performing individual is 100 points and the theoretical minimum is 0. Symptoms reported by adult, elite volleyball players with jumper's knee are 60 to 80 points in patients enrolled in non-operative clinical trials (Lian et al. 2005; Visnes et al. 2005; Hoksrud and Bahr 2011; Zwerver et al. 2011; Zwerver et al. 2011), and candidates for surgery typically have VISA-P score ranging from 30 to 50 points (Bahr et al. 2006; Hoksrud and Bahr 2011; Pascarella et al. 2011; Maier et al. 2013). The VISA score appears to be the simplest and most reliable questionnaire available today for monitoring clinical and functional changes over time with minimal investigator's influence (Marcheggiani Muccioli et al. 2013). VISA is well suited to evaluate progression of symptoms and also evaluate outcome after treatment (Visentini et al. 1998; Robinson et al. 2001).

Visual analogue scale (VAS)

A 100 mm VAS has been used widely as outcome measure for pain. VAS has been shown to be reliable and valid (Price et al. 1983), and it is commonly used to evaluate the effect of different treatment regimes. The limitation with VAS is that it does not take into account the activity level and change of activity level in athletes, especially since these symptoms in these cases are clearly related to activity. To compensate, pain might be recorded more specifically i.e. pain under activity or average pain during day. Still, this makes comparisons between different treatment studies difficult.

1.3.2 Epidemiology of jumper's knee

The prevalence of jumper's knee is high, up to 40-50%, in sports characterized by high demands on leg extensor speed and power, such as volleyball, basketball, football and athletics (Ferretti et al. 1990; Lian et al. 2005). Volleyball players are more susceptible for jumper's knee compared to other athletes (Lian et al. 2005; Zwerver et al. 2011). Lian et al. (2005) published a cross-sectional study among 9 different elite sports and 613 athletes in Norway. They found 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 his or her athletic career. The prevalence varied from no cases in cycling and orienteering to 45% with current symptoms in male volleyball. Zwerver et al. (2011) investigated non-elite athletes in 7 different sports in the Netherlands. They found that the prevalence of jumper's knee varied between 2.5% (football) and 14.4% (volleyball), and the overall prevalence in the survey was 8.5%. The main limitation of these two studies is that the athletes with the most serious problems, those who could not participate in training or competition, were not included in the study. Thus, the samples represent the survivors especially at the elite level, and the true career prevalence is higher than reported. Prevalence data among adolescents are limited. Among elite junior volleyball players in Sweden, age 17 yrs, , the prevalence was reported as 14% (Gisslen et al. 2005). This prevalence was higher than the 7% Cook et al. reported in a group of 14–18 yrs male and female basketball players (Cook et al. 2000). Incidence data of jumper's knee is not notably evident, since it is not always clear when the injury occurs. In a retrospective study of 100 athletes with jumper's knee who presented to a sports medicine clinic 56% had developed symptoms before the age of 20 (Cook et al. 1997). Data from European elite football clubs on 2229 male athletes found an incidence of 0.12 injuries per 1000 hours of total exposure and an overall prevalence of 2-3% (Hägglund et al. 2011). However, this study only registered time loss injuries and therefore the definition of injury is different. They also reported a high recurrence rate (12%-27%) and this probably reflects the chronic and recurrent character of the condition. On the other hand, studies from Danish elite male football show that 7% of players (3% to 7% of patellar tendons) developed symptomatic jumper's knee during a season (Fredberg and Bolvig 2002; Fredberg et al. 2008). Interestingly, as many as 6% of players (3% of patellar tendons) reported time loss attributable to jumper's knee (Fredberg et al. 2008), indicating that over the season a majority of players with jumper's knee developed symptoms severe enough to limit performance and lead to missed training or match exposure. Table 3 summarizes the data on the prevalence, incidence and severity of jumper's knee.

Table 3. Prevalence, incidence and severity of jumper's knee

Author, Year	Study design	Population	Number	Prevalence	Incidence	Severity
Ferreti et al. (1984)	Cross-sectional study	Competitive volleyball players	407 (93 PT, 314 controls)	23%	--	--
Lian et al. (1996)	Cross-sectional study	High level volleyball players	47 (m)	36%	--	--
Lian et al. (1996)	Cross-sectional/ case-control study	Well trained volleyball players	141 (males)	39%	--	--
Cook et al. (1998)	Cross-sectional/ cohort study	Elite basketball, cricket, Australian football	200	20%	--	--
Cook et al. (2000)	Prospective study	Elite junior basketball players	26 (8m/18f)	--	12% pr 16 months	--
Cook et al. (2000)	Cross-sectional study	Junior basketball players & swimmers	163 (82 m/ 81f)	Basketball -7%, Swimming -0%	--	--
Fredberg & Bolvig (2002)	Longitudinal study	Elite soccer club players	54 (males)	9% at baseline	3% per year	--
Kettunen et al. (2002)	Case- control	Athlete & control after 15 years	36	--	--	Jumper's knee- 53% quit sport, controls- 7%

Author, Year	Study design	Population	Number	Prevalence	Incidence	Severity
Lian et al. (2003)	Cross-sectional study	Volleyball players	47 (males)	51%	--	--
Bahr and Reeser, (2003)	Cohort study	Professional beach volleyball players	178 (92m/ 86f)	12%	--	38% had received medical attention during a 7-week period
Giisslen et al. (2005)	Case-control study	Junior elite volleyball student & non active controls	112	Volleyball -21% Non-active – 0%	--	--
Lian et al. (2005)	Cross-sectional study	Elite athletes from 9 different sports	613 (506m/107F)	Volleyball -45%, basketball- 32%	--	Duration of symptoms:32 months, Mean VISA-score: 64
Fredberg et al, (2008)	RCT, (prophylactic training or not)	Professional elite soccer players	209 (males)	--	7% per year	--
Zwerver et al. (2011)	Cross-sectional study	Non-elite athletes, 7 different sports.	891 (502m/ 389f)	2.5% (soccer) – 14.4% volleyball)	--	Duration of symptoms: 18.9 months, Mean VISA-score: 71
Hagglund et al. (2011)	Cohort study	51 European elite soccer clubs	2229 (males)	2.3%-2.6%	0.12 injuries/ 1000 hours	--

The severity of jumper's knee is difficult to quantify. Overuse injuries are difficult to record in epidemiological studies, especially when standard methods of injury registration are used, typically relying on a "time-loss" injury (Bahr 2009). Jumper's knee symptoms such as pain or functional limitation most often appear gradually and may be transient in nature. Therefore it is likely that athletes will continue to train and compete despite the presence of overuse conditions, at least in the early phase. Thus, it is likely that few overuse injuries lead to time-loss from sport (Clarsen et al. 2013). Overuse problems should therefore be expressed using prevalence and severity measures, rather than as the incidence of time-loss injuries (Bahr 2009; Clarsen et al. 2013). In volleyball and beach volleyball the prevalence and severity of overuse injuries such as jumper's knee is high, while the number of time-loss injuries is low (Bahr and Reeser 2003; Bahr 2009; Clarsen et al. 2013). The mean duration of jumper's knee symptoms varied in two cross-sectional studies between 19-32 months and the mean VISA score in the same studies was 64-71 (Lian et al. 2005; Zwerver et al. 2011). Long duration of symptoms has been described by other studies (Willberg et al. 2011; Hoksrud et al. 2012; van der Worp et al. 2013) and has previously been reported as high as up to 72 months (Visnes et al. 2005). Despite the high prevalence in cross sectional studies among top athletes, the number of athletes retiring from sports because of their problems with jumper's knee is unknown. To investigate the long-term prognosis of jumper's knee, Kettunen et al. (2002) followed 36 athletes from a previous case-control study for 15 years. They found that as many as 53% of athletes with jumper's knee were forced into retirement. However, 15 years later jumper's knee caused mild pain during daily activities. However, there was no difference in work ability or current physical leisure time activity between the athletes with or without previous jumper's knee.

1.3.3 Imaging of pathological tendons

Ultrasound and MRI visualize anatomic structures of the tendon very well, and demonstrate structural changes in tendinopathic tendons. Ultrasound changes described in tendinopathic tendons typically include localized tendon thickening with hypoechoic areas and increased vascularity (Khan et al. 1996; Lian et al. 1996; Cook et al. 1998; Cook et al. 2000; Cook et al. 2001; Cook et al. 2004; Malliaras et al. 2006; Comin et al. 2013). Ultrasound changes are usually seen in the deep proximal part of the tendon. The pathological tendon is thicker compared to the normal tendon. The increased thickness and hypoechoic areas may be

explained by increased extracellular matrix synthesis, disorganisation of matrix and increased water content. However, as early as in 1996, cross-sectional studies by Khan et al. (1996) and Lian et al. (1996) revealed no one-to-one relationship exists between pain and structural changes. They observed that not only were there symptomatic tendons with normal tendon morphology on ultrasound examination, but also that asymptomatic tendons with tendon thickening and hypoechoic areas were not uncommon. Khan et al. (1996) found that all 28 symptomatic tendon had hypoechoic areas while 4 of 22 tendons in athletes who had never reported any problems had these changes. Lian et al. (1996) examined Norwegian elite volleyball players. They found that 7 of the 30 knees with a clinical of jumper's knee diagnosis in the patellar tendon had normal ultrasound findings, and whereas 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. These findings have also been reproduced in subsequent cross-sectional studies (Cook et al. 1998; Cook et al. 2000; Warden et al. 2007).

Modern ultrasound-based imaging technology (color Doppler sonography) showed that chronic painful Achilles tendons include increased blood flow and perfusion (called neovascularization) intratendinously, peritendinously, or both (Öhberg et al. 2001). Normal tendon and osseotendinous junction display a low blood flow, evidenced by minimal colour Doppler activity, whereas tendinopathic tendon displays increased colour Doppler activity and up to three times the number of intratendinous microvessels. (Öhberg et al. 2001; Scott et al. 2008). Weinberg et al (1998) were the first to describe their experience with color Doppler ultrasound in the evaluation of patellar tendinosis. They found that in 20 symptomatic tendons from 14 patients, 11 had a proximal hypoechoic area, 12 had a thickened proximal patellar tendon and all but 1 of 25 these exhibited increased blood flow. Öhberg et al. (2001) examined 28 Achilles tendons (21 patients) with a painful mid-portion condition as well as 20 normal (pain-free) tendons, and these were examined with grey-scale ultrasonography combined with color Doppler examination. In all painful tendons, but not in any of the normal pain-free tendons, neovascularisation was seen in the area with tendon changes (localised widening of the tendon with focal hypoechoic areas). These findings have later been described in the patellar tendon as well (Cook et al. 2004; Alfredson and Öhberg 2005; Gisslen and Alfredson 2005; Hoksrud et al. 2006). It is difficult to know if this neovascularisation represents genuine neoangiogenesis; however, in histological studies of chronic tendinopathy angiogenesis is a

common finding (Rees et al. 2013). Still, the relation between the color Doppler findings and clinical severity is unclear (de Vos et al. 2007; Hoksrud et al. 2008; Tol et al. 2012).

It is not clear whether the presence of ultrasound changes in asymptomatic tendons precede (and predict) future tendon problems, and longitudinal studies have conflicting results (Cook et al. 2001; Fredberg and Bolvig 2002; Gisslen and Alfredson 2005; Gisslen et al. 2005). In Paper III, we therefore wanted to investigate whether hypoechoic areas and neovascularisation represented risk factors for jumper's knee in a large cohort of elite adolescent volleyball players and also to investigate the correlation between tendon pain and ultrasound findings.

1.3.4 Histopathological findings

The histopathological findings in biopsies from tendinopathy tendons are consistent, and the pathological changes in patellar, Achilles and supraspinatus tendinopathy have been shown to be similar (Khan et al. 1999; Maffulli et al. 2004). As shown in light microscopy, tendon from patients with chronic patellar tendinopathy differs from normal tendon in several key ways. The changes in ECM composition, including increased ECM synthesis, disorganisation of matrix and increased water content are supported by most authors even though some have found conflicting results. Puddu et al. (1976) first documented that the pathology in tendons clinically known as "Achilles tendonitis" was characterized by an absence of inflammatory cells in or around the lesion but instead a separation and fragmentation of collagen, which he labeled "tendinosis". The tendons display a loss of collagen continuity and appear amorphous and disorganized with collagen replaced by degenerative and necrotic tissue (Khan et al. 1998).

Parkinson et al. (2010) compared normal human tendon tissue obtained from patients undergoing ACL reconstruction using a patellar tendon graft with abnormal tendon tissue obtained from patients undergoing a surgical procedure for patellar tendinopathy. They found that the rate of synthesis of proteoglycans is 25-fold greater in abnormal patellar tendons than in normal tissue. This was due to the significant increase in the synthesis of the large proteoglycans aggrecan and versican in abnormal tissue, whereas negligible levels of these proteoglycans were synthesized in normal tissue. Normal tissue predominantly synthesized SLRP. The increase in the synthesis of large proteoglycans by abnormal tissue was reflected in greater tissue levels of large proteoglycans in the matrix of tendons in human patellar

tendinopathy. Scott et al. (2008) had tendon biopsies from 21 patients with documented patellar tendinosis and from 10 control participants with healthy tendons operated with intramedullary nailing for low-energy tibia fractures. The major finding was that elevations in versican levels contribute to the increased ECM volume in symptomatic patellar tendinosis. This is consistent with the results of previous studies showing increased levels of large proteoglycans associated with overuse tendinopathy. Samiric et al. (2009) had similar findings when they examined 25 pathological tendons and 23 normal tendons and found increased water content and GAGs levels in patellar tendinopathy compared to normal tissue. Nerve sprouting and change in the distribution and type of nerves have also been reported in tendinopathic tissue (Lian et al. 2006; Danielson 2009). Lian et al. (2006) had biopsies from the patellar tendon in 10 patients with patellar tendinopathy and 10 from a control group without any previous or current knee symptoms compatible with patellar tendinopathy. They found an increased occurrence of sprouting nonvascular sensory substance P-positive nerve fibers and a decreased occurrence of vascular sympathetic nerve fibers, positive to tyroxin hydroxylase, a marker for noradrenaline. Their conclusion was that altered sensory-sympathetic innervation suggests a role in the pathophysiology of tendinopathy, and that ingrowth of sprouting substance P fibers presumably reflects a nociceptive and maybe a proliferative role. Lian et al. (2007) also found that there was a significantly higher number of apoptotic cells per unit area and a significantly higher apoptotic index in biopsy specimens from the patellar tendons in patients with patellar tendinopathy compared with controls. The role of apoptotic cells is unclear and need further research.

1.3.5 Molecular findings

Biochemical and molecular studies of chronic tendinopathy during the last 15-20 years have increased our understanding of underlying pathology, focusing in changes in factors regulating ECM, enzymes and cytokines and signalling factors. In order to maintain homeostasis, the ECM is regulated by a number of complex enzyme systems.

These have been investigated in animal studies like Samiric et al. (2004), where they examined tendons from 1- to 2-year-old steer. They found the continual process of matrix remodeling is a constitutive (albeit slow) activity in normal tendons, affecting proteoglycans in addition to collagen, and is thought to be primarily mediated by metalloproteinases acting in the extracellular environment, such as matrix metalloproteinases (MMPs) and a disintegrin

and metalloproteinase with thrombospondin motifs (ADAMTS). Briefly, there are 23 MMPs in humans, which have a wide range of matrix substrates and several of these enzymes have activity against fibrillar collagen. Studies from human tissue found that increased levels of different MMPs and ADAMTS are likely to be responsible for the breakdown and disorganization in ECM (collagen and proteoglycans) in tendinopathic tendons (Jones and Riley 2005; Nagase et al. 2006). Proteoglycans are primarily degraded by enzymes of the ADAMTS family known as "aggrecanases", but precisely which enzyme is involved in the turnover of tendon proteoglycan is currently unknown. Jones et al. (2006) sampled normal tendons from 32 men where 11 tendons were normal, 9 painful, and 12 ruptured Achilles tendons and found that almost all of the 23 MMP and 19 ADAMTS family members were detectable in normal tendon, although levels of expression varied widely. They also examined the mRNA profile from these samples and different mRNA characteristic profiles between the groups. They were also able to identify a number of genes worthy of further study. Fu et al. (2002) compared 11 patellar tendons from patients operated for patellar tendinopathy with 12 controls operated undergoing ACL reconstruction using a healthy patellar tendon as an autograft indicating that collagen disturbances in human patellar tendinosis may be related to augmented collagenolysis and a high MMP1 expression. MMP1, ubiquitous in soft tissues, is one of the collagenases with proteolytic activity in type I collagen, the most abundant collagen in tendons. The same authors published from the same material (Fu et al. 2002) that in tendinosis samples immunopositive cells for cyclooxygenase-2 (COX-2) and transforming growth factor-beta1 were significantly higher than those of the control subjects. Tendinosis fibroblast culture also produced more prostaglandin E2 and active transforming growth factor-beta1. These findings indicate the involvement of prostaglandins and cytokines that may explain the clinical symptoms and nonhealing features of tendinosis.

Different cytokines and signalling factors like increased level of transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF) and COX-2 are signalling factors also stimulating synthesis of the ECM (Fu et al. 2002; Fu et al. 2002; Riley 2008). Other signal factors stimulating general cell proliferation (tenocyte proliferation, angiogenesis and nerve sprouting) have been demonstrated in tendinopathic tendons (glutamate, substance P, insulin growth factor-1, vascular endothelial growth factor (VEGF), mast cell tryptase (Fu et al. 2002; Lian et al. 2006; Riley 2008; Scott et al. 2008). Scott et al. (2008) and Lian et al. (2006), as previously described, found elevations in versican levels contributing to the increased extracellular matrix volume in symptomatic patellar tendinosis. Up-regulation of

glutamate and its receptor NMDAR1 in the tendinopathic tendons has also been demonstrated (Alfredson et al. 2000; Alfredson et al. 2001; Schizas et al. 2012). Alfredson et al. (2000; 2001) used microdialysis technique in two small case-control studies (extensor carpi radialis brevis, n=8, and patellar tendon, n=10), and found that tendinopathic tendons had higher concentrations of the excitatory neurotransmitter glutamate, but not prostaglandin E2. A cornerstone in the degenerative model of tendinopathy is therefore the absence of inflammatory cells.

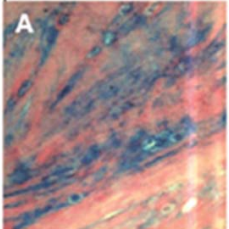
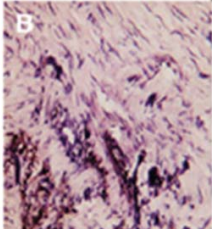
Schizas et al. (2012) had biopsies from 10 patellar tendons and 8 controls and concluded that tendinopathic tendons had up-regulation and activation of glutamate receptors in painful tendinosis. The increased level of glutamate is suggested to give cell proliferative effects seen as angiogenesis, tenocyte transformation and nerve sprouting and thereby stimulating neovascularisation in tendinopathic tendons (Alfredson and Lorentzon 2003). Glutamate is also a potent modulator for pain and is suggested to be implicated in tendinopathic pain. Substance P is another modulator for pain by transmitting nociceptive information and the level is increased in these tendons (Lian et al. 2006; Scott and Bahr 2009). In addition, substance P may play a role in healing the tendon by its stimulation of fibroblast proliferation and angiogenesis, but also activate mast cells and release histamine and thereby stimulate nerve endings and cause a process called neurogenic inflammation (Lian et al. 2006; Scott and Bahr 2009).

Riley (2008) has summarized this complex regulation and remodelling of the tendon matrix (fig.4). Enzymes like MMP have a key role in the regulation of the activity of tendon cells and matrix remodelling in both normal and pathologic tendon. In a pathological tendon the excessive or inappropriate activity of enzymes, cytokines and signalling factors and destructive matrix-degrading enzymes lead to tendinopathy.

Figure 4. Major molecular changes that have been identified by gene-expression studies, protein analysis or both are summarized (Riley 2008). Molecules for which expression levels are increased are denoted by an upwards arrow, molecules for which expression levels are decreased are denoted by a downwards arrow and molecules for which expression levels remain unchanged are denoted by a horizontal arrow. Photomicrograph (A) is an alcian blue/H&E-stained section of supraspinatus tendinopathy, showing proteoglycans stained blue. Photomicrograph (B) is an H&E-stained section of Achilles tendinopathy, showing increased cellularity and proliferation of blood vessels. Abbreviations: ADAM, a disintegrin

and metalloproteinase; ADAMTS, ADAM with thrombospondin motifs; AGE, advanced glycation end product; COX2, cyclooxygenase 2; H&E, hemotoxylin and eosin; IGF-I, insulin-like growth factor 1; MMP, matrix metalloproteinase; NMDAR, N-methyl-D-aspartate receptor; PDGFR, platelet-derived growth factor receptor; PGE2, prostaglandin E2; TGF- β , transforming growth factor β ; TGF- β R1, TGF- β type 1 receptor; VEGF, vascular endothelial growth factor. Reproduced with permission from Riley 2000).

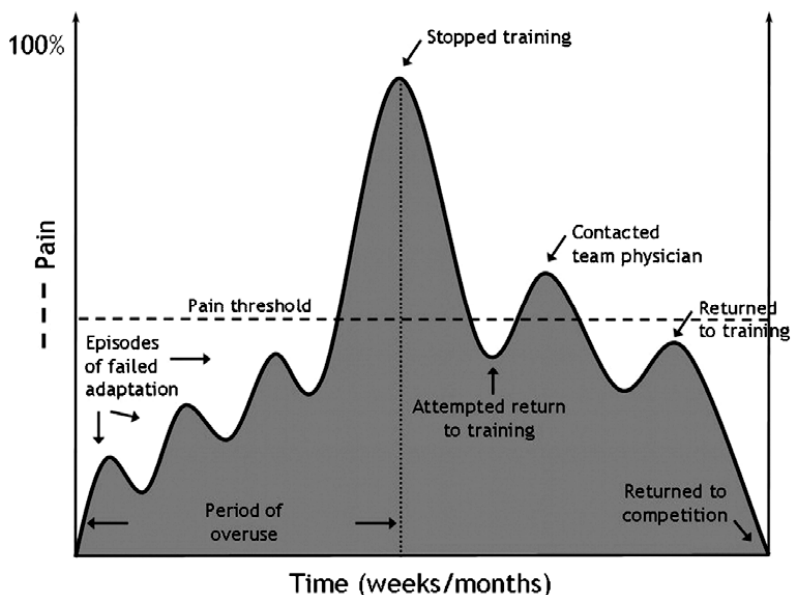
Matrix	Cytokines and signaling factors		Enzymes
Collagen type I \uparrow	TGF- β \uparrow	COX2 \uparrow	MMP1 \uparrow
Collagen type III \uparrow	IGF-I \uparrow	Glutamate \uparrow	MMP2 \uparrow
Fibronectin \uparrow	PDGFR \uparrow	Substance P \uparrow	MMP23 \uparrow
Tenascin C \uparrow	VEGF \uparrow	NMDAR \uparrow	ADAM12 \uparrow
Aggrecan \uparrow	PGE ₂ \leftrightarrow	TGF- β R1 \downarrow	ADAMTS2 \uparrow
Biglycan \uparrow			ADAMTS3 \uparrow
Versican \leftrightarrow			MMP3 \downarrow
Decorin \leftrightarrow			MMP10 \downarrow
Dermatan sulfate \downarrow			MMP12 \downarrow
Pentosidine			MMP27 \downarrow
(AGE cross-link) \downarrow			ADAMTS5 \downarrow

1.3.6 Models of tendinopathy

Synthesizing the data available on the histopathological and biological changes observed in tendinopathic tendons into a model explaining how and why tendinopathy develops, is not an easy task. In 1992, Leadbetter (1992) suggested that tendons develop tendinosis because of a “failed tendon healing response”. He proposed that inadequate adaptation (i.e. microtrauma) to tendon load preceded the moment of conscious injury. With continued overexertion and the accumulation of repetitive scar adhesions, degenerative change, and adverse effects of chronic microtrauma recovery from this problem will be slow. Khan et al (1998) and Bahr (2009) have used this model to point out that with overuse injuries the pathological process is often under way for a period of time before the athletes notices the symptom. Figure 5 presents a hypothetical overview of the time course of onset of tissue injury and pain in a typical overuse injury (Khan et al. 1998; Bahr 2009).

Figure 5: Pain profile of typical of overuse tendon injury". (Reproduced with permission from Bahr 2009)



In 2009, Cook and Purdam (2009) presented their continuum model of tendinopathy. This model suggests that the pathological process can be described in three stages: reactive tendinopathy, tendon dysrepair (failed healing) and degenerative tendinopathy. Stage one is a non-inflammatory proliferative response in the cell and matrix, occurring with acute overload. This results in a short-term adaptive and relatively homogeneous thickening of a portion of the tendon that will either reduce stress (force/unit area) by increasing the cross-sectional area or allow adaptation to compression. There is ECM change due to an increase in bound water. Collagen integrity is mostly maintained, and the authors speculate that these initial changes in ground substance in reactive tendinopathy occur because quick adaptation is necessary until longer-term change in either structure or mechanical properties (true adaptation) happens. Tendon dysrepair is stage two and describes the attempt at tendon healing, similar to reactive tendinopathy but with greater matrix breakdown. The increase in proteoglycans results in separation of the collagen and disorganization of the matrix. The changes are somewhat more focal and matrix changes more varied than in the reactive stage. There may also be an increase in vascularity and associated neuronal ingrowth. Degenerative tendinopathy is thought to represent stage three, with progression of both matrix and cell changes as seen in histopathological studies. Areas of cell death due to apoptosis, trauma or tenocyte exhaustion

are apparent. Large areas of the matrix are disordered and filled with vessels, matrix breakdown products and little collagen. According to Cook and Purdam (2009), there is little capacity for reversibility of pathological changes at this stage.

Recently, Rees et al. (2013) suggested that there may be a need to revisit the role of inflammation in the development of tendinopathy. They argue that the “tendinosis” paradigm oversimplifies our understanding of the pathological process. Even if inflammatory cells is not the dominant pathology in established tendinopathy, they suggest that it is likely that elements of the inflammatory response play a role in the progression or continuation of tendon dysrepair. Since mechanical overload is likely to be the dominant factor at least at one point, some of the damage is mediated through a process that involves elements of the inflammatory process, according to their hypothesis.

To summarize, current knowledge of why and how tendinopathy develops is incomplete. Too much load of the tendon is probably an important factor that may initiate a cascade of events, still there is no model of tendinopathy describing the complete process from a healthy tendon to tendinopathy. The process is often gradual and bilateral, and the pathological changes are thought to occur before tendons become symptomatic.

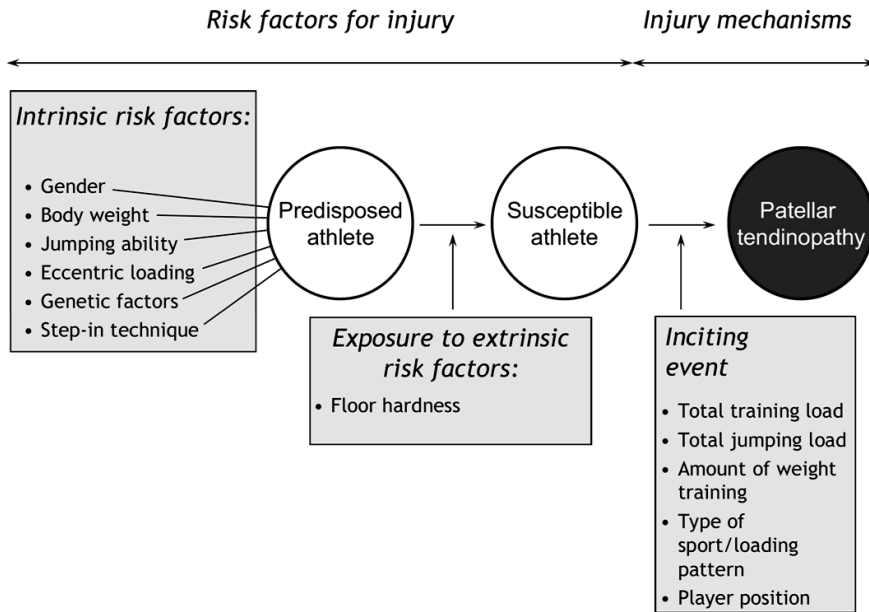
The main limitation with our current evidence is that little research has been conducted in early-stage tendinopathy -therefore the complex interactions between the cell and matrix and systemic and local factors in the transition from healthy to end-stage tendinopathy need further investigation. So far, no high-quality animal model has been developed, and future research is needed to develop a model where tendinopathy may be induced and investigated in all phases. Repetitive biopsies or imaging studies from an asymptomatic tendon until tendinopathy have not been done, for obvious reasons. Previous case-control studies and cross-sectional studies on humans have been based merely on static histopathology in chronic tendons scheduled for surgery. Tendon pain is another difficult topic which is not properly explained in any model of tendinopathy (Khan and Cook 2000; Khan et al. 2006). Although molecular research has identified changed levels of enzymes, cytokines and signaling factors (i.e. substance P and glutamate) in end-stage tendinopathy (Lian et al. 2006) many tendons with histopathological findings of tendinosis are pain free (Kannus and Jozsa 1991).

1.4 Injury prevention

An injury prevention research model has been described by van Mechelen (1992) as a four-step sequence. Firstly, the magnitude of the problem must be identified and described in terms of its incidence and severity. Secondly, the risk factors and injury mechanisms that play a part in the occurrence must be identified. In practical term this means establishing the causes of injury. The third step is to introduce measures that are likely to reduce the future risk and/or severity. Such measures should be based on information on the aetiological factors and the injury mechanisms as identified in the second step. Finally, the effect of the measures must be evaluated by repeating the first step, which can be achieved by time trend analysis of injury patterns or, preferably, by means of a randomised clinical trial (Bahr and Krosshaug 2005).

The magnitude i.e. prevalence of the problem of jumper's knee, was presented in chapter 1.3.2. The etiology of tendinopathy, as described in chapter 1.3.4-1.3.6, is complex and far from well understood. However, even if the underlying pathophysiology is poorly understood, it may be possible to point out some important etiological factors. Meeuwisse (1994) introduced a model to understand the multifactorial causation of sport injuries, where he proposed that intrinsic risk factors are predisposing factors that may be necessary, but seldom sufficient, to provoke an injury. The intrinsic and extrinsic risk factors contribute towards athlete susceptibility to injuries, but are usually distant from the time of injury and rarely sufficient as a cause of injury alone. It is the sum of, as well as the interactions between, these factors that cause the athlete to be injured. Lian (2006) applied the model of Meeuwisse (1994) Bahr and Krosshaug (2005) to the case jumper's knee. In figure 6 the most important potential risk factors are summarized. The role of inciting event is unclear, but in the etiology of jumper's knee, there is not a single event but the sum of events that might cause the athlete to be injured.

Figure 6. A dynamic, multifactorial model of the etiology of jumper's knee (Reproduced with permission from Lian 2006)



1.5 Risk factors for jumper's knee

The results of the literature search until the start of the study in 2006 on the risk factors for jumper's knee are presented in table 4. The following text summarizes the main findings.

Table 4. Risk factors prior to 2006 for jumper's knee (statistically significant risk factors are denoted in bold)

Author, year	Design	Study period	Study population	N	Risk factors investigated
Ferretti et al. (1984)	Cross-sectional study	--	Competitive volleyball players	407 (93 PT, 314 controls)	Age, sex, years of play, frequency of play, playing surface , strength training
Kujala et al. (1986)	Case-control study	--	Competitive athletes (volleyball, running, basketball, other sports)	40 (20 patellar apicitis, 20 controls)	Weight, height-to-weight ratio, leg-length inequality , knee laxity, Q-angle displacement, maximal knee hyperextension
Kujala et al. (1987)	Case-control study	--	Athletes	141 (121 with "knee exertion injuries", and 20 controls)	Leg length inequality (P < 0.001) and patella alta (P < 0.05)
Lian et al. (1996)	Cross-sectional/ca se-control	--	High level volleyball players	141 (55 PT, 86 controls)	Age, height, weight, Number of seasons played, number of volleyball training sessions/week , strength training, jump training , warming up, stretching, jump performance
Cook et al. (2000)	Cohort study	16 months	Basketball players	26	Hypochoic areas appears to confer a four times greater risk to develop jumper's knee
Cook et al. (2001)	Cohort study/longitudinal study	48 months	Football, basketball and cricket players	23 (23m)	No statistically relationship between ultrasonographic patellar tendon abnormalities and clinical outcome
Witvrouw et al. (2001)	Cohort study	24 months	Students (physical education)	138 (19 PT, 119 controls)	Age, height, weight, Q-angle, leg-length difference and medial tibial intercondylar distance, quadriceps flexibility, hamstring flexibility , quadriceps & hamstring strength

Author, year	Design	Study period	Study population	N	Risk factors investigated
Schmid et al. (2002)	Case-control study	--	Patients from a orthopaedic clinic	51 (19 PT and 32 controls)	No difference in patella position
Fredberg and Bolvig, (2002)	Longitudinal study	11 months	Professional soccer players	54 (54m)	Hypochoic regions were associated with development of symptoms
Richards et al. (2002)	Cross-sectional study	--	National volleyball players	10 (3 jumper's knee)	Biomechanical analysis of jump: inversion moment during the landing of the spike jump
Lian et al. (2003)	Cross-sectional study	--	High level volleyball players	44 (24 PT, 20 controls)	Age, height, weight , years of volleyball, training h/week, jump training, stretching, strength training, jump performance
Cook et al. (2004)	Cross-sectional study	--	Junior elite basketball players (age 14-18)	135 (49 with abnormal ultrasound, 86 normal tendons)	Height, weight, skinfolds, arm span/height Sit and reach agility, speed, endurance, vertical jump height (f)
Gaida et al. (2004)	Cross-sectional study	--	Elite basketball players	39	Height, weight, tibial length to stature ratio, waist-to-hip ratio, training volume , Sit-and-reach test, concentric strength, eccentric strength, jump height
Malliaras et al. (2006)	Cross-sectional study	--	Competitive volleyball players	113 (groups: pain/image abnormal, no pain/image abnormal, no pain and image normal)	Years of volleyball, weekly activity, ankle dorsiflexion range , sit-and-reach test, jump height, ankle flexion strength

1.5.1 Training volume & match exposure

There are three studies showing an association with the amount of training and playing (Ferretti et al. 1984; Lian et al. 1996; Gaida et al. 2004) and two with no association to the risk of developing jumper's knee (Lian et al. 2003; Malliaras et al. 2006). Ferretti et al. (1984) studied a sample of 407 volleyball players chosen randomly from different levels of the Italian leagues. As many as 93 of 407 (23%) were suffering or had suffered from jumper's knee. They found a close relationship between the number of weekly training sessions and jumper's knee. Prevalence among players who trained more than 4 times a week was over 40%. Lian et al. (1996) examined 141 well-trained volleyball players, of which 55 (39%) satisfied the diagnostic criteria for jumper's knee. They found that athletes with jumper's knee trained a significant higher number of volleyball sessions per week (4.4 ± 1.0) than athletes without symptoms (3.9 ± 1.0). Gaida et al. (2004) investigated 39 elite female basketball players with patellar tendinopathy. The 24 asymptomatic controls trained significantly less during the last 6 months (9 ± 3 h/week) compared to athletes with patellar tendinopathy symptoms (12 ± 5 h/week). On the other hand, Lian et al. (2003) examined 47 athletes in a high-level volleyball tournament and found 24 with current symptoms (55%) and 20 without any symptoms and three with previous symptoms. In this study they did not find any difference in volleyball training per week or career length. However, they found a difference in the weekly volume of weight training (jumper' knee: 4.5 ± 2.8 , controls: 2.3 ± 2.3). Malliaras et al. (2006) found no difference in weekly activity level and number of years of volleyball competition in 113 male and female volleyball players. The volume of strength training was not associated with jumper's knee in two studies (Ferretti et al. 1984; Lian et al. 1996), whereas in another study (Lian et al. 2003), doing more strength training was associated with jumper's knee. Two studies found no association between the amount of jump training and jumper's knee (Lian et al. 1996; Lian et al. 2003). It has been hypothesized that a sudden change and increase in the volume of training when young, promising players are promoted from the junior to the senior level can increase the risk of jumper's knee (Reeser et al. 2006). Perhaps athletes that increase their training volume the most also have the highest risk of developing jumper's knee (Lian et al. 2003; Reeser et al. 2006). Early sports specialization is a contentious issue (Malina 2010; Capranica and Millard-Stafford 2011; Moesch et al. 2011). One question is whether varied sports participation during adolescence can protect against overuse injuries, because relatively little evidence exists regarding the

long-term medical effects of rigorous training and competitive schedules on children in specific sports.

Most of the data available on the relationship between training/competition load are from cross-sectional or case-control studies. These research question needs to be addressed in prospective studies. Therefore in Paper I we wanted to investigate whether training volume and match exposure were risk factors for developing jumper's knee.

1.5.2 Body composition

A cross-sectional study among volleyball players showed that athletes that had developed jumper's knee had higher body mass compared to asymptomatic controls (Lian et al. 1996). In this study there was no data on body composition (fat mass vs muscle mass), but the participants were described as well trained athletes. The higher body mass was therefore assumed to represents higher muscle mass, perhaps causing tendinopathy through higher load on the patellar tendon. Lian et al. (2003) found the same association in another cross-sectional study, where subjects with jumper's knee were on average heavier than subjects without jumper's knee. None of these two studies (Lian et al. 1996; Lian et al. 2003) found an association between body height and jumper's knee. Cook et al. (2004) found no difference in height, weight, skinfolds, or arm span/height between 135 junior elite basketball players with and without jumper's knee. Gaida et al. (2004) found that athletes with unilateral patellar tendinopathy had a higher waist to hip ratio than controls in their cross-sectional study among female basketball players. This indicates a larger abdominal fat distribution relative to gluteofemoral fat deposits. Human fat distribution is controlled by a complex interaction of hormones and is particularly influenced by the female sex hormones (oestrogen and progesterone), but the mechanisms whereby hormones control this fat distribution are unclear. Why there were no detectable differences between the bilateral group and controls in any of the measured variables is not explained, and only subjects in the unilateral group were distinguished from the control group. In the general population previous studies have found a correlation of tendinopathy and body composition (Wendelboe et al. 2004; Werner et al. 2005). Wendelboe et al. (2004) compared three hundred and eleven patients who underwent shoulder surgery with 933 age and frequency-matched controls. They found that individuals who are obese are at increased risk for "rotator cuff tendinitis" and rotator cuff-related surgery, but it is important that most of these cases had a body mass index (BMI) higher than

30. Werner et al. (2005) found similar results in their cohort including 501 active workers followed for an average of 5 years.

We therefore do not know if fat mass and body composition represents a risk factor in well-trained athletes. In Paper I, we wanted to investigate if body composition or change of body composition was a risk factor for developing jumper's knee in a cohort of adolescents athletes.

1.5.3 Gender

Ferretti et al. (1984) concluded that there was no difference between the incidence of jumper's knee in males and females, and the slightly higher rate in males could be attributed in part to more training in males. Witvrouw et al. (2001) followed a cohort of 138 athletes. During the 2-year study period of the study "patellar tendinitis" was diagnosed in 19 (13.8%) of the 138 students. Of the 99 boys, 11 developed "patellar tendinitis", as did 8 of the 39 girls. Statistical analysis showed no significant sex difference in the incidence of "patellar tendinitis" in this study ($p=0.36$). In contrast, Lian et al. (2005) examined 613 male and female athletes at the national elite level from different sports (athletics, basketball, ice hockey, volleyball, orienteering, road cycling, wrestling) but football and team handball were the only sports where both gender were investigated. They found male gender to be 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.

Prior to 2006 there is limited epidemiological evidence to substantiate the claim for a gender difference. Still, some hypotheses have been postulated to explain potential gender differences. A biomechanical approach would be that women have less quadriceps strength and inferior jumping capacity, so the patellar tendon is exposed to lower forces. However, thickness and CSA of the tendon is smaller in female and therefore the tendon stiffness, which is dependent on the CSA, might not be different between the genders. So far it is unknown if jump height is a more important determinant of patellar tendon loading than sex. If different hormone concentrations might influence susceptibility to tendinopathy between gender is another approach (Gaida et al. 2004). There is no obvious hormonal explanation for males having a higher prevalence than females, since studies indicate that estrogen inhibits exercise induced collagen synthesis and then leads to a lower rate of tendon tissue repair. Miller et al. (2007) investigated the tendon collagen fractional synthesis rate in healthy male

and females and concluded that both in the resting state and after exercise, tendon collagen synthesis was lower in women than in men. Hansen et al. (2009) investigated users of oral estradiol replacement therapy and controls (nonusers), and found that collagen turnover in the resting state, and collagen responses to exercise were negatively associated with s-estradiol. Therefore, in Paper I we wanted to investigate whether male had higher risk of developing jumper's knee compared to females in a cohort of adolescent athletes.

1.5.4 Jumping ability

Jumping plays an essential role in volleyball; key skills like spiking, blocking, serving and even setting involve jumping. These jumps are often maximal and, depending on their playing position, athletes could jump up to 300 times during a 5-game match (Hasegawa et al. 2002; Forthomme et al. 2005; Sheppard et al. 2007). Middle blockers tend to suffer from jumper's knee more than players in other positions (Bahr and Reeser 2003). Jumping ability is an important criterion when selecting players. Studies show that players on a high level have higher vertical jump height compared to players at lower levels (Smith et al. 1992; Hasegawa et al. 2002). Forthomme et al. (2005) examined 19 male volleyball players from the two highest Belgian national divisions, and they underwent a jumping capacity test. They also compared first-division and second-division player data and found that counter movement jump (CMJ) was 10% higher among male first division than second division players. The first division players were older and trained more "muscular" training per week. Such differences could be a consequence of not just selection and genetics, but also training could obviously make a difference. Lian et al. (1996) had 12 athletes with jumper's knee and 12 controls selected from a population of 141 well-trained male Norwegian volleyball players, of which 55 (39%) satisfied the diagnostic criteria for jumper's knee. Their testing program consisted of different types of jumps: standing jump (SJ), CMJ, 5-second rebound jump test, standing jump with a 20-kg load, and standing jump with a load corresponding to one-half of the subject's body weight. The test results of the patient group were significantly higher than those of the control group for the countermovement jump (15% increase), power during rebound jump (41%), work done in standing jump (12%) and countermovement jump (22%), and the difference between countermovement jump and standing jump (effect of adding eccentric component). Thus, in this case-control study athletes with jumper's knee demonstrated better performance in jump tests than uninjured athletes, particularly in ballistic

jumps involving eccentric force generation. Lian et al. (2003) did a similar study among 47 elite volleyball players where 24 (51.0%) were diagnosed with current jumper's knee. They used the same jump tests but were unable to reproduce the same results as in 1996. Still, they concluded that the results from the jump-testing program showed an increased overall performance ability of the leg extensors among players with a current diagnosis of jumper's knee compared with players without a history of jumper's knee. In contrast, Malliaras et al. (2006) found no differences in jump height in a cross-sectional study of 113 participants in athletes between the three outcome groups; athletes with pain and image abnormal, no pain and image abnormal and no pain and image normal. Tendons with pain and normal imaging were excluded.

The jumper's knee paradox, where symptomatic athletes in case-control studies seems to have performed substantially better in a counter movement jump compared to asymptomatic controls has never been explained properly. We do not know if athletes who naturally jump well have a higher risk of developing jumper's knee or if their jumping skills are the result of higher training loads. Therefore, this issue was investigated in Paper II.

1.5.5 Ultrasound changes

As previously described, most tendons with symptoms of jumper's knee do reveal pathological abnormalities when examined by ultrasound. However, the relationship between structural tendon changes and pain remains to be fully elucidated. Present knowledge is not clear on whether the presence of ultrasound changes in asymptomatic tendons precedes (and predicts) future tendon problems. Previous longitudinal studies on the patellar tendon have yielded conflicting evidence. Cook et al. (2000) followed 26 young asymptomatic basketball players (14-18 yrs) for 16 months. At baseline, 10 of 52 patellar tendons had hypoechoic areas and 3 of them went on to develop jumper's knee compared to 3 of the 42 normal tendons. The authors concluded that a hypoechoic area represented a risk factor for developing jumper's knee, but also that structural changes were not necessarily associated with symptoms. However, the same research group also followed 23 asymptomatic football, basketball and cricket players (age: 30 yrs) for 4 years (Cook et al. 2001). In this small prospective study on adult athletes, ultrasound changes did not predict future tendon problems. At baseline, 18 of 46 tendons had hypoechoic changes. During the 4-yr study period, 6 tendons developed clinical symptoms; of these, 4 had hypoechoic changes at

baseline and 2 were normal. Fredberg & Bolvig (2002) followed 54 adult professional soccer players for one season. They concluded that hypoechoic regions were associated with development of symptoms, even if only 3 of 18 with hypoechoic areas at baseline became symptomatic. Notably, 9 tendons were still hypoechoic but asymptomatic and 6 tendons normalized. Also, 6 normal tendons developed hypoechoic areas but no symptoms after 11 months.

Hypoechoic changes are observed in 10-30% of asymptomatic tendons, and hypoechoic areas can resolve, remain unchanged, or expand (Lian et al. 1996; Khan et al. 1997; Cook et al. 2000; Fredberg and Bolvig 2002). It can be hypothesized that the presence of ultrasound findings in the tendon may increase the risk of developing tendon pain. This effect may be somewhat more pronounced in younger athletes than among adults. Paper III aimed to investigate the relationship between the development of ultrasound changes in the patellar and quadriceps tendons and symptoms of jumper's knee.

1.5.6 Genetics

Involvement of genetics in tendon injury was originally proposed because of an association between the blood group O and Achilles tendon ruptures or chronic Achilles tendinopathy evident in Hungarian and Finnish populations (Jozsa et al. 1989; Kujala et al. 1992; Kannus and Natri 1997). The gene for ABO on chromosome 9q34 encode for transferases which, apart from determining the structure of glycoprotein antigens on red blood cells, may also determine the structure of some proteins of the extracellular matrix of tendons (Jozsa et al. 1989). Sequence variants within genes that encode for several tendon and/or ligament extracellular matrix proteins have been shown to be associated with specific musculoskeletal soft tissues injuries (Mokone et al. 2005; Mokone et al. 2006; Collins and Raleigh 2009). Variants within the TNC, COL5A1 and MMP3 genes co-segregate with chronic Achilles tendinopathy. The variant within the TNC gene also appears to co-segregate with Achilles tendon ruptures, while sequence variants within the COL1A1 and COL5A1 genes have been shown to be associated with cruciate ligament ruptures and/or shoulder dislocations. The COL5A1 gene, which is in close proximity to the ABO genes on chromosome 9q34 (Caridi et al. 1992), encodes for a structural component of type V collagen which forms heterotypic fibres with type I collagen in tendons and possibly plays an important role in regulating fibrillogenesis and, therefore, tendon strength (Silver et al. 2003; Riley 2004). Still it is

unclear whether or not COL5A1 and TNC genes are the ideal markers of tendinopathy (Magra and Maffulli 2008). The relationship between genetics and tendinopathy has mainly been investigated in Achilles tendon but also in studies in supraspinatus tendon, anterior cruciate ligament (ACL) rupture, superficial digital flexor and posterior tibial tendon. The role of these genes in the pathogenesis of tendinopathy needs further investigation, as does their association with patellar tendinopathy.

1.5.7 Anthropometry and biomechanics

Several studies have investigated the association between leg-length differences and jumper's knee. Kujala et al. (1986) reported a larger leg-length difference in subjects with jumper's knee in a case-control study with 20 patients with patellar "apicitis" (jumper's knee) and 20 controls. The study of Witvrouw et al. (2001), however, found no association with leg-length difference in their cohort between the 19 athletes developing jumper's knee compared to 119 that remained asymptomatic after having been followed for two years. A longer tibia length relative to stature was found by Gaida et al. (2004) in subjects with unilateral jumper's knee. Kujala et al. (1986) found no difference between controls and subjects with jumper's knee in Q-angle displacement during knee flexion. Similar results were found by Witvrouw et al. (2001) with no difference in Q-angle at rest and no difference in the medial tibial intercondylar distance. One study that investigated the arm span to height ratio found no association between this ratio and jumper's knee (Cook et al. 2004). Malliaras et al. (2006) examined 113 competitive volleyball players in a cross-sectional study. They concluded that there was a reduced range of ankle dorsiflexion in the jumper's knee group. Having less than 45° of ankle dorsiflexion range increased the risk of patellar tendinopathy by 1.8 to 2.8 times. Schmid et al. (2002) investigated 19 patients from an orthopedic clinic with jumper's knee with 32 asymptomatic controls. They found no differences between the groups regarding patellar impingement when examined with dynamic MRI. The biomechanical aspects of jumping and landing have not been investigated properly. There are some indications that large external tibial torsional moments combined with deep knee flexion angles during a jump and landing increases the risk of jumper's knee (Richards et al. 2002). These results are from a small cross-sectional study of 10 members of the Canadian Men's National Volleyball Team where 3 of the 10 players had jumper's knee at the time of the study. Landing surface may be

important and beach volleyball players have a lower prevalence of jumper's knee compared to indoor volleyball players (Ferretti et al. 1984; Bahr and Reeser 2003).

1.6 Aim of the thesis

Based on this literature review the aims of this thesis were:

1. To investigate total training and competition load as risk factors for developing jumper's knee (Paper I).
2. To investigate whether body composition or change of body composition represents a risk factor for developing jumper's knee (Paper I).
3. To investigate jumping ability and change of jumping ability as risk factors for developing jumper's knee (Paper II).
4. To investigate the relationship between the development of ultrasound changes in the patellar and quadriceps tendons and symptoms of jumper's knee (Paper III).
5. To examine the medium-term effects of intensive training on tendon thickness among adolescent athletes (Paper III).

2. Methods

2.1 Study design

Paper I- III were based on a prospective cohort study with a total data collection period of 5 years. All participants were recruited from the same cohort, but the time and duration of inclusion were differed between participants. Data collection for Paper I & II started year 1 (2006) while data collection for Paper III started year 2 (2007).

2.2 Patient recruitment

All participants (Paper I-III) were recruited among players entering the Toppvolley Norway (TVN) program. TVN is located in Sand, Norway and combines an elite volleyball training program with a three-year senior high school boarding school program. The students started at the age of 15-16 years, and they were expected to complete three years for a college-entry baccalaureate degree. Some students entered the program in the second or third school year. TVN aimed to recruit the most talented junior volleyball players in Norway, and the athletes represented the school in the Norwegian national leagues at various levels. However, players could also play tournaments and league matches for their home clubs. Many of the players also qualified for different junior national team programs.

The recruitment process began when school started every autumn with an information meeting. Potential participants were also informed in writing before their written consent was obtained, and also that of their parents if the athlete was younger than 18 years old. The flowcharts from Paper I-III, depicting how participants entered and left the study are not identical. In Paper II some students could not be included because no data were recorded and some could not be included because a technical problem caused loss of data from testing during year 2.

2.3 Inclusion criteria

All students at TVN were eligible for this study. In Paper I & II only athletes without jumper's knee at baseline were included, while Paper III also included athletes with pre-existing jumper's knee.

2.4 Diagnosis

Jumper's knee is a clinical diagnosis. The following diagnostic criteria were used (Lian et al. 1996; Lian et al. 1996; Lian et al. 2003; Lian et al. 2005; Visnes et al. 2005; Hoksrud et al. 2008):

1. A history of pain in the quadriceps or patellar tendons at their patellar insertions in connection with training or competition
2. Tenderness to palpation corresponding to the painful area.
3. Symptoms had been present for a minimum of 12 weeks.

In addition, all symptomatic athletes underwent a standard knee examination to exclude other diagnoses like patellofemoral pain syndrome, inflammatory joint conditions, or degenerative conditions.

2.5 Patient evaluation

2.5.1 VISA score

Knee function was self-reported using VISA score (Paper II & III).

2.6 Body composition

Body composition was assessed by measuring height and weight, waist circumference and through skin fold caliper tests. Waist circumference (nearest mm) was measured with anthropometric tape around the umbilicus at the end of a normal expiration (Steene-Johannessen et al. 2010). Four skinfold thickness measurements (triceps, biceps, subscapular and suprailiac) were taken using a Harpenden skinfold caliper (John Bull, British Indicators Ltd., West Sussex, England) on the non-dominant side of the body according to the criteria described by Lohman et al. (Lohman et al. 1991). These examinations were repeated twice a year as long as participants remained in the cohort, and were presented in Paper I.

2.7 Training volume & match exposure

Training volume was recorded prospectively on a weekly basis (Paper I-III). We organized the registration on an individual basis through a web-based weekly training diary, with six questions about the number of hours of volleyball, beach volleyball, strength, jump training and other training. The number of sets played in matches during the last week were also recorded. An individual registration was necessary because not all training was organized and the athletes played matches for their home clubs and junior national teams, as well. In case data were incomplete, we interviewed the player and their coach to estimate exposure as precisely as possible. In Paper II-III. match exposure were not recorded. We only collected data during the 10-month school year. Information was also collected about their previous training volume in volleyball, strength training and other training during the last year before attending TVN.

2.8 Jump test (Paper II)

Two types of jumps were tested. Both SJ and CMJ are tests commonly used for testing elite athletes in different sports in Norway. SJ were performed with the subject starting from a stationary semisquatting position with 90° of knee flexion and with both hands kept fixed on the hips. No counter movement was allowed with any body segment and the computer measured these movements and did not accept such attempts. In the CMJ the subject started the movement from a stationary erect position with knees fully extended, and was allowed to bend down to approximately 90° of knee flexion before starting the upward motion of the jump. This jump is a ballistic movement with rapid eccentric muscle action immediately followed by a maximal concentric contraction. Both hands were kept fixed on the hips. (Lian et al. 2003) The best out of three technically correct jumps was used for the final calculations.

Figure 7. Starting position for a CMJ and SJ.



Jump tests were done on a portable force plate (Musclelab 4000, Ergotest Innovation a.s., Porsgrunn, Norway) to estimate vertical jump height. The portable force plate has demonstrated to be a valid measure of vertical jumping ability (Buckthorpe et al. 2012). These tests were performed two times per year, first at the start of the school year (August/September) and then 6 months later at the end of the volleyball season (March/April).

2.9 Ultrasound examination (Paper III)

An ultrasound examination were done within the first weeks and then again every 6 months for as long as students remained at TVN. An experienced orthopaedic surgeon with extensive musculoskeletal ultrasound training (AT), who was blinded to the clinical history carried out all ultrasound examinations during 4 year of the study period. Two ultrasound machines with similar specifications were used for all examinations over the study period (GE Logiq e, 12L-RS probe and GE Logic Book XP, 12L-RS probe, GE Vingmed ultrasound AS, Horten, Norway). Recent studies have shown that intratendinous flow can be increased during exercise (Malliaras et al. 2008; Koenig et al. 2010), and none of the athletes came straight from training, but we did not collect information about their activity during the previous 24 hours. Ultrasound examination of both the patellar and quadriceps tendon was carried out with the patient supine, with the knee in slight flexion (20°). The quadriceps muscles were relaxed to avoid underestimating color Doppler flow (Koenig et al. 2007). Tendon thickness was measured in the proximal, middle and distal part of the tendon. Any pathologic changes in the tendons were registered on a standard form. All clearly defined hypoechoic areas seen in both longitudinal and transverse ultrasound scans were registered as pathologic, regardless of the size of the area. Color Doppler was used to diagnose increased blood flow within the tendon, which has been termed neovascularisation (Öhberg et al. 2001). The color Doppler gain was set just below the level that produced random noise in the image (Boesen et al. 2012), and the Doppler settings were the same for all examinations. To our knowledge, no technology existed to reliably quantify flow in the tendon when the study started. Therefore, we used the same semiquantitative method that has been used in previous studies (no flow = 0; flow outside the tendon = 1; one or two vessels inside the tendon = 2; and multiple vessels inside the tendon = 3) (Hoksrud et al. 2006; Gisslen et al. 2007). For subsequent data analyses, we defined neovascularisation as the presence of vessels inside the tendon (2 and 3).

Figure 8. Ultrasound examination in athletes



2.10 Statistics

In Paper I-III: Training volume was calculated as the mean number of hours per week and match exposure as the mean number of sets per week for the period included. All potential risk factors were compared using unpaired *t*-tests examined in univariate analyses and those with a *P*-value <0.20 were investigated further in a multivariate regression model. Different logistic regression models were run to compare the strengths of association between injury and exposure of training and matches. Model prognostic indexes were also used to compare predictive ability between the different models by receiver operating characteristic analysis. In the multivariate analyses, we have combined data on present and previous training and match exposure with gender; but because of limitations in statistical power, we could only include two or three factors at the time. Also, as there was a strong correlation between total training volume and the other training forms, these factors could not be included in the same model. Odds ratio (OR) are reported with 95% confidence limits and *P*-values of <0.05 were considered statistically significant..

In Paper II: The results from the jump tests are presented as the height of rise of the center of gravity (in cm), and we calculated the change in jump height the same way for asymptomatic and symptomatic athletes in two ways: 1) From baseline until 6 months after enrolment, and 2) from baseline to graduation. Odds ratios for increased risk of jumper's knee are reported per cm difference in jump test results. We report Pearson coefficients for the correlation between training volume and change in jumping ability.

In Paper III: Changes in tendon thickness per site were analysed using paired *t*-tests. Since right and left tendons are coupled and not independent, a global multivariable linear model (GLM) on both sides and for the proximal, midportion and distal part of the tendon was fitted

to test the hypothesis that all changes in the tendon variables were equal to zero simultaneously. This test creates a vector of changes per tendon where change in measurements from proximal, mid and distal were three components in the vector account the within-person correlation of the components in the vector. This was done by the Wilks-Lambda method. Analyses were adjusted for gender. Similarly, total changes in tendon thickness were also tested against zero using the same method. The multivariable gender differences in changes (of tendon variables) were tested by Hotelling's T-squared statistics. Associations between training volume and changes in tendon thickness were assessed by multiple linear regression analyses. Odds ratios for hypoechoic areas and neovascularisation at baseline were analyzed with a logistic regression analysis model adjusted for gender.

3. Results and Discussion

3.1 Recruitment and patient characteristics

3.1.1 Results

Altogether, 192 students were registered in the school record at TVN during the 5-year study period, but some left school before they could be informed about and included in the study. Paper I and II are based on data collection from 2006, while data collection for Paper III started in 2007. In table 5, the three cohorts included in Papers I-III are summarized.

Table 5. Description of the inclusion and follow-up of subjects during the 5-year study period.

	Paper I	Paper II	Paper III
Study period	4 yrs	5 yrs	4 yrs
Total number of athletes in school	164	189	158
Athletes included	141 (69m/72f)	150 (68m/82f)	158 (84m/74f)
Mean observation period (years)	1.8±0.8	1.7±0.8	1.7±0.7
Developed jumper's knee (#)	28 (22m/6f)	28 (22m/6f)	22 (18m/4f) (35 tendons)
Time until diagnosis (years)	0.9	0.8	0.9

In most cases, their symptoms stemmed from the proximal patellar tendon (n=25); only 3 cases (2 males/1 female) were located in the distal quadriceps tendon (Paper I-II). The data and the athletes included in Paper I and II are similar but not identical (Paper I: years 1-4, Paper II: years 2-5). A total of 17 of 158 students (6 females, 11 males) had pre-existing jumper's knee when enrolling at TVN (Paper III). In most of these cases (n=14, 19 tendons), their symptoms stemmed from the proximal patellar tendon, while in 3 cases (1 female, 2 males, 4 tendons) symptoms were from the distal quadriceps tendon. Of the 22 athletes with new problems, all had symptoms from the proximal patellar tendon, and 13 (3 females, 10

males) developed bilateral symptoms. Therefore, a total of 35 tendons developed jumper's knee.

Prognosis (Paper III)

A total of 39 athletes with jumper's knee (22 new cases of jumper's knee and 17 with pre-existing symptoms) were followed for an average of 1.0 (SD 0.7) year and with 2.0 (SD 1.4) ultrasound examinations after diagnosis. They reported a VISA score of 72 (SD 23) when first diagnosed, which did not change during subsequent examinations and was 73 (SD 21) when they left TVN.

3.1.2 Discussion

Nearly one in three boys (32%) developed jumper's knee during their time at TVN (Paper I). Since only one out of 28 cases in Paper I debuted during the final year it seems as if a player is able to tolerate the high volume of training and matches the first 1-2 year, the risk of developing jumper's knee is much lower and that the at-risk players have been affected by the condition by then. However, we do not know if the asymptomatic group represented a more resistant group of players that will also avoid developing symptoms later in their career. Starting at TVN represents a high-risk situation for promising players and adolescents athletes may have more pronounced risk compared to adults. Cook et al. (1997) found that 56% of 100 athletes with jumper's knee had developed symptoms before the age of 20.

Prevalence is previously described around 40-50% among adult male volleyball players (Lian et al. 1996; Lian et al. 1996) while among elite junior volleyball players prevalence has been reported as 14% (Gisslen et al. 2005). In Paper III, the prevalence of jumper's knee among athletes leaving TVN was 25% (male 39%, female 8%). Thus, unfortunately males graduating from TVN have a prevalence of jumper's knee similar to that as previous found among adult elite volleyball players in Norway.

The jumper's knee diagnosis was based on clinical examination alone. Jumper's knee is a difficult diagnosis, but patellar tendon palpation is a reliable examination for a single examiner (Cook et al. 2001). Imaging like ultrasound or MRI was not required to make the diagnosis, and at the time of diagnosis 6 of 35 had no ultrasound findings like hypochoic areas and neovascularisation. These results are similar to previous studies, and it is therefore important to note that a study population based on a clinical diagnosis of jumper's knee

compared to patellar tendinopathy verified by ultrasound or MRI, would not include the same patients (Warden et al. 2007; Hoksrud et al. 2008).

The proximal patellar tendon was the dominant location of symptoms (92%) compared to the distal quadriceps tendon (8%). The majority of the athletes in this cohort had bilateral symptoms. Lian et al. (2005) found that 37 of 87 athletes with current symptoms had bilateral symptoms, and these are similar to findings in Paper III where 13 of 22 had bilateral symptoms. Development of jumper's knee seems to be a bilateral process where both tendons are affected.

Prognosis

The athletes were followed as long as they were students at TVN. We did not record treatment systematically. The general principles organized by school physiotherapist were reduced tendon load (less volleyball and less jumping), alternative training (swimming), training treatment (eccentric training or heavy slow resistance training) and shock wave therapy. Despite this symptoms remained the same during the observation period. Even though some athletes are able to participate in sport despite their problems, a cross-sectional study where athletes who had attended a sports medicine clinic were recruited, found that 33% of the 100 athletes had been kept out of sport for over six months because of symptoms of jumper's knee (Cook et al. 1997). The medium or long-term consequences of jumper's knee is poorly characterized; athletes may have retired early, 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. Kettunen et al. (2002) followed 36 athletes from a previous case-control study for 15 years. They found that as many as 53% of athletes with jumper's knee were forced into retirement. However, 15 years later jumper's knee caused mild during daily activities. However, there was no difference in work ability or current leisure time physical activity between the athletes with or without previous jumper's. This study included no data about reduced training volume, reduced training intensity or how many of the athletes left school because of the jumper's knee.

Treating these athletes is challenging and the best treatment regime is unknown. However, our data suggest that the prognosis is poor for complete rehabilitation of young athletes with jumper's knee as long as they remain students at an elite sport school.

3.2 Training volume & match exposure

3.2.1 Results

Athletes developing jumper's knee had higher total training volume and tendon load compared to those who remained asymptomatic. A significant difference was observed for indoor volleyball training (jumper's knee: 14.9 ± 2.8 h/week vs asymptomatic athletes: 12.0 ± 3.7 h/week, $p=0.001$), while we did not see any differences for beach volleyball training, strength training or other training. The number of sets played in matches was also higher in the jumper's knee group. These trends were similar for males and females. Previous training history was recorded and the jumper's knee group did significantly more volleyball training (10.5 ± 6.2 h/week) before entering the TVN program compared to the asymptomatic group (7.6 ± 4.6 , $p=0.01$). We found no difference in previous strength training, while the asymptomatic group did more training in other sports (1.5 ± 2.2 h/week) compared to the jumper's knee group (0.5 ± 0.9 h/week, $p=0.03$). In a multivariate regression analysis, corrected for gender, the analyses showed that match exposure was the strongest sports-related predictor for developing jumper's knee with an OR of 3.88 (95% CI 1.80 to 8.40) for every extra set played per week. Volleyball training had an OR 1.72, (95% CI 1.18 to 2.53) when combined with match exposure and gender. As we only had information about previous training volume in 124 out of 141 athletes, this factor had to be analyzed separately. We found that a high volume of previous volleyball training increased the risk of jumper's knee (OR 2.22 per hour of training, 95% CI 1.20 to 4.11).

3.2.2 Discussion

This is the first prospective cohort study to identify volume of training and match exposure as risk factors for jumper's knee. Volleyball training accounted for nearly all of the difference between the group that developed jumper's knee and the group that remained asymptomatic. As the daily volleyball training schedule on weekdays was organized by the school, these group differences were somewhat surprising. However, a closer look at the data revealed that some athletes in periods could train up to 30 h per week in different training camps with national teams or home clubs compared to those who went home to their families to relax. Based on the literature, athletes that increased their training volume the most were also expected to have the highest risk (Lian et al. 2003; Reeser et al. 2006). It was therefore

surprising that the jumper's knee group had trained significantly more volleyball the year before they started at TVN, about 3 h more per week. Since both groups increased their volume with approximately 5 h more volleyball per week, an increase of 42% for the jumper's knee group and 66% for the asymptomatic players were found. These numbers indicate that the total volume of training over a period is maybe as more important as the relative increase in training exposure from one year to the next. If the risk of jumper's knee increasing linearly in response to load, or if there is a threshold volume of training where the risk increases more, needs further study.

Match exposure, i.e. the number of sets played per week, was the strongest sports-related predictor for developing jumper's knee in the multivariate analysis. These athletes played matches for their home clubs as well as the school teams, and many of the league matches are organized as weekend tournaments. An obvious explanation may be that the players affected are the best players, and the player and their school, club and national team coach had the same interest in their playing as much as possible, without much thought of the consequences for injury.

Early sport specialization is a contentious issue. One question is whether varied sports participation during adolescence can protect against overuse injuries. Repetitive volleyball-specific training alone could overload the patellar tendon, in contrast to a more varied training program which includes other sports. Our data show that athletes and especially boys in the jumper's knee group hardly played any other sports during the final year before joining the intensive volleyball program at TVN. The group that remained healthy previously had trained more in other sport like football, handball or skiing. However, these numbers were small and should be interpreted with caution.

3.3 Body composition (Paper I)

3.3.1 Results

We did not detect any significant differences in body composition at the time of inclusion or change of body composition during the study period between players who developed jumper's knee and those who did not developed jumper's knee.

3.3.2 Discussion

It is important to note that the volleyball players studied represent a selected group of relatively tall and lean athletes, and therefore not comparable with previous studies, showing a correlation between tendinopathy and body composition in the general population (Wendelboe et al., 2004; Werner et al., 2005). A systematic review on the relationship between adiposity and tendinopathy (Gaida et al. 2009) identified only one study among young athletes (Cook et al., 2004). This cross-sectional study among elite junior basketball players found no differences in height, weight, or skinfold thickness between players with ultrasound abnormalities and players with normal tendons (Cook et al., 2004). Lian et al. identified body mass as a risk factor in two previous studies (Lian et al. 1996; Lian et al. 2003). In these studies there was no data on body composition, but the participants were described as well trained athletes. Crossley et al. (2007) found that a higher body mass index (BMI) was associated with jumper's knee. This finding concurs with a study by Malliaras et al. (2006), who also found an association between a higher BMI and jumper's knee, albeit only in men. Waist girth and hip girth were associated with jumper's knee in men in one study (hip girth only in men with bilateral jumper's knee) (Malliaras et al. 2007), but not in another study that only included women (Gaida et al. 2004). In a study among basketball players, hip-waist ratio had the highest odd ratio (21.6) for jumper's knee (van der Worp et al. 2012). Higher body mass could cause higher load on the patellar tendon. However, several studies have not identified body mass as a risk factor (Kujala et al. 1986; Lian et al. 1996; Witvrouw et al. 2001; Cook et al. 2004; Gaida et al. 2004). In other words, there is no evidence for a link between body composition and the risk of jumper's knee among young, well-trained athletes.

3.4 Gender (Paper I)

3.4.1 Results

Males had three to four times higher risk for developing jumper's knee compared to females, independent of training and match exposure in a multivariate regression analysis. Nearly one in three boys developed jumper's knee during their time at TVN (32%) compared to only 8% of the girls.

3.4.2 Discussion

Three to four times higher risk for men is somewhat higher compared to previous cross-sectional studies (Lian et al. 2005; Zwerver et al. 2011; van der Worp et al. 2012). Lian et al. (2005) found the prevalence of current symptoms of jumper's knee was lower among women in team handball and soccer with 5.6 % compared to a combined prevalence of 13.5 % in the corresponding male sports. Van der Worp et al. (2012) invited all basketball and volleyball players in the Netherlands to an online survey and found among the 2363 responded that males had around 2 times higher risk compared to females. Zwerver et al. (2011) interviewed 891 male and female nonelite athletes from 7 popular sports in the Netherlands, and male athletes had a significantly higher prevalence (10.2%) than in female athletes (6.4%). This gender difference may be caused by the difference in the force-generating capacity of the quadriceps between men and women. The gender effect seems more pronounced in volleyball, probably because the sport includes a lot of jumping. It is well documented that the jumping ability and force-generating capacity is lower among women than men (Lian 2006). So, even if the number of 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. Janssen et al. (2014) investigated landing technique and patellar tendon loading of 20 male and 20 female volleyball players performing a lateral stop-jump block movement. Male volleyball players were taller and heavier, landed from a higher height, displayed differences in landing kinematics, generated a significantly greater knee extensor moment, and experienced higher patellar tendon loading than female players. However, when participants were matched on jump height, they generated similar patellar tendon loading, irrespective of their sex. They conclude that jump height is a more important determinant of patellar tendon loading than sex. On the other hand, the CSA of the tendon is smaller in women, and since tendon stress describes the tendon force relative to the tendon CSA, the mechanisms underpinning the gender difference observed are not fully understood.

3.5 Jumping ability (Paper II)

3.5.1 Results

At the time of inclusion, healthy male athletes who went on to develop jumper's knee had significantly better results in CMJ (38.0 ± 5.8 cm vs 34.6 ± 5.5 cm) compared to asymptomatic

males, while no difference was detected in SJ (30.3 ± 7.4 cm vs 28.1 ± 6.1). Among females, there was no difference in SJ (jumper's knee: 22.1 ± 3.2 cm vs healthy: 21.7 ± 4.6 cm) or CMJ (jumper's knee: 27.2 ± 5.4 cm vs healthy: 24.8 ± 4.6 cm) at inclusion. In a multivariate logistic regression analysis corrected for gender and previous volleyball training, the OR for developing jumper's knee was 2.09 (95% CI 1.03 to 4.25) per cm difference in CMJ at the time of inclusion.

No difference in the change in jumping ability between the jumper's knee group and healthy group were detected. Compared to baseline, healthy males and females improved their jumping ability in both tests after 6 months and at the end of their period at TVN. In the jumper's knee group, only males improved their CMJ results compared to baseline, while females did not improve.

Among athletes that remained healthy there was a weak correlation between the volume of volleyball training and change in jumping ability for CMJ from baseline until their last test at TVN ($r^2=0.15$, $p<0.001$). We found no correlation for SJ (final test) in this group, nor was there any correlation between training volume and change in jumping ability in the group of athletes who developed jumper's knee.

3.5.2 Discussion

The jumper's knee paradox, where symptomatic athletes appear to perform better in a CMJ compared to asymptomatic controls in previous case-control studies, is poorly understood. This is the first prospective cohort study available, where jump performance was assessed before players developed symptoms of jumper's knee, documenting an association between the jumping ability and the risk for developing jumper's knee. An obvious explanation for this finding could be that players who jump well subject their tendons to higher load and therefore have higher risk. We only found this difference in the dynamic CMJ test, not in the more static SJ. It may be that these athletes are better at utilizing the eccentric prestretch component of the ballistic motion to increase their jumping height. It seems reasonable to suggest that their talent for jumping high, which results in higher tendon strain, amplifies the risk of tendon problems when subjected to an intensive program of training and competition such as that at TVN.

Another hypothesis was that not only baseline jumping ability, but also the rate of improvement in jumping ability could be a risk factor, i.e. that players who increase their

jumping ability rapidly would be at higher risk because their capacity for loading the tendon is not matched by a simultaneous improvement in tendon properties. Our results did not reveal any significant differences in the change in jumping ability between the group that developed jumper's knee and those who remained asymptomatic, although both groups improved their CMJ performance. The athletes developing jumper's knee increased their jumping performance continuously despite having developed symptoms. The exception was the few girls that developed jumper's knee, who decreased their jumping performance for CMJ. There is no obvious reason for girls to be more limited by pain and the numbers are small.

The main findings in Paper II support the hypothesis that there is an association between the talent for jumping high and the risk for developing jumper's knee. This sheds light on the jumper's knee paradox where athletes with tendon pain have performed substantially better in jump tests compared to asymptomatic controls. Our data support the theory that jumping ability is not affected by the pain associated with jumper's knee.

3.6 Ultrasound: Relationship between structural changes and symptoms (Paper III)

3.6.1 Results

About half of the asymptomatic athletes who went on to develop jumper's knee (17 of 35 tendons) had hypoechoic areas when they started at TVN, while 10% of the tendons that remained asymptomatic (24 of 238 tendons) had the same changes. Neovascularisation was found in 4% (9 of 238 tendons) of asymptomatic tendons and in 48% (15 of 35 tendons) of those who later developed jumper's knee. In a multivariate logistic regression analysis, a baseline finding of a hypoechoic tendon area (OR 3.3, 95% CI 1.1 to 9.2) and neovascularisation (OR 2.7, 95% CI 1.1 to 6.5) increased the risk of developing jumper's knee. At the time when the clinical diagnosis of jumper's knee had been made, 83% (29 of 35 tendons) of the tendons revealed hypoechoic areas and 74% (26 of 35 tendons) neovascularisation. The prevalence of ultrasound changes among the athletes who developed jumper's knee remained the same from the time of diagnosis until they left school. The asymptomatic tendons had the same prevalence during the whole study period (hypoechoic: 10%, neovascularisation: 3-4%).

In asymptomatic quadriceps tendons, the prevalence of hypoechoic areas (4-7 %) and neovascularisation (3-4%) was lower compared to asymptomatic patellar tendons.

3.6.2 Discussion

Our study, which is one of the largest to date on the patellar tendon, shows that the presence of hypoechoic areas and neovascularisation among asymptomatic athletes at baseline represented a risk factor for developing tendon pain. In the same time period as this study, others have investigated the same issue. Gisslén et al. (2007) monitored a population comparable to TVN, 22 adolescent volleyball players (16 yrs at inclusion), for 3 years. Of the 36 tendons which were asymptomatic at baseline, 3 of 9 with structural changes did develop symptoms, while only 2 of the 27 structurally normal tendons later developed jumper's knee. Fredberg et al. (2008) randomized 209 professional soccer players to either a control group or to an intervention group who was given a prophylactic eccentric training program for the Achilles and patellar tendons during one soccer season. At inclusion 28% had "severely abnormal" patellar tendons. They found that players had a relative risk of 2.2 (P=.09) for developing symptoms during the season if severe ultrasonographic abnormalities in the patellar tendons were detected before the start of the season. Two more recent studies have also identified ultrasound changes as a risk factor (Comin et al. 2013; Giombini et al. 2013). Comin et al. (2013) surveyed 79 professional ballet dancers (158 patellar tendons) in a 24-month longitudinal study. A total of 7 tendons developed disabling symptoms, 3 of these were among the 19 which had hypoechoic changes at baseline and only 4 of 139 with normal tendons developed symptoms. Giombini et al. (2013) followed 37 elite fencers training for the Olympics (age: 27 yrs) for 36 months. Since 2 of 8 tendons with abnormal ultrasound findings at baseline developed symptoms and none of 66 normal tendons did, they concluded that ultrasound imaging may be predictive for development of future symptoms in patients with patellar tendinopathy.

Whether color Doppler may contribute additional information to grey-scale ultrasound is unknown. Boesen et al. (2012) used color Doppler in their study among semi-professional badminton players. They concluded that intratendinous blood flow did not predict injury and that the level of intratendinous blood flow more likely represents a physiological response. Some studies have also shown that there is some degree of color Doppler activity in the healthy tendon after exercise (Boesen et al. 2006; Malliaras et al. 2008; Koenig et al. 2010)

and so far the role of these blood vessels in a painful tendon is unknown. It remains an important research question to distinguish between possible physiological intratendinous flow and possible pathological activity (Koenig et al. 2010).

The prevalence of hypoechoic areas is lower in asymptomatic quadriceps tendons compared to patellar tendons. Giombini et al. (2013) found abnormalities in 3 (4%) of 74 asymptomatic quadriceps tendons and this is similar to our results. There is no obvious explanation for why the prevalence of ultrasound changes is higher in patellar tendon compared to the quadriceps tendon.

Evidently there is not a one-to-one relationship between pain and structural changes, since 17% of those with a clinical diagnosis had no ultrasound changes and at any given time 11% of asymptomatic tendons displayed ultrasound changes. We cannot recommend instituting routine ultrasound screening programs to prevent jumper's knee when two-thirds of patients with hypoechoic areas on their baseline ultrasound examination did not develop symptoms during two seasons of intensive training on average. Perhaps improved technology can change this recommendation. More advanced ultrasound modalities such as ultrasonographic tissue characterization (UTC) may be promising (van Schie et al. 2010).

3.7 Ultrasound: Tendon adaptation among asymptomatic tendons (Paper III)

3.7.1 Results

Quadriceps tendon thickness increased 7-11% among healthy athletes, while there was no change in patellar tendon thickness during a mean observation period of 1.7 years. The increase in quadriceps tendon thickness among athletes developing jumper's knee in their patellar tendon was similar in magnitude to that observed in asymptomatic athletes.

3.7.2 Discussion

This is the first study to examine whether tendons hypertrophy in response to intensive training during adolescence. The results were somewhat surprising, since an adaptation and increase in thickness in both tendons would have been expected considering the large volume of training for two seasons. The only longitudinal studies available to date on the patellar tendon are on mature athletes and with a much shorter observation period (Kongsgaard et al. 2007; Kubo et al. 2009; Seynnes et al. 2009; Kubo et al. 2010; Malliaras et al. 2013). Normal structural changes from childhood to adulthood are not well characterized and there is a need for prospective studies to investigate if the increase in quadriceps tendon thickness is the result of intensive training or a consequence of growth and maturation. Mersmann et al. (2013) compared a group of adolescent athletes with former top volleyball players. They found that even if there was no strength difference in the knee extensors, the adolescent athletes featured a smaller tendon CSA. A tendon with larger CSA will have reduced mean stress for a given load and therefore, it is possible that differences in tendon dimension may play a role in developing tendinopathy. The quadriceps tendon was approximately 50% thicker than the patellar tendon and it may be speculated that this difference can provide clues as to why the patellar tendon is more susceptible to tendinopathy than the quadriceps tendon.

This study did not investigate tendon properties and therefore mechanical and material properties at baseline were unknown. Helland et al. (2013) found in their case-control study based on these athletes, that symptomatic tendons had lower stiffness and Young's modulus. These findings are in contrast to previous findings on the patellar tendon (Kongsgaard et al. 2009; Kongsgaard et al. 2010; Couppe et al. 2013), but in line with findings in the Achilles tendon (Arya and Kulig 2010; Wang et al. 2012). Future prospective studies are needed to monitor mechanical properties and their relationship to tendinopathy.

3.8 Prevention strategy

The balance between training hard to achieve results but not so much as to cause an overuse injury is difficult. The complex process from a healthy tendon to a symptomatic tendon is not fully understood, and more basal research is needed. Based on the evidence presented in chapter 1.5 and the results from the current study the major volleyball-specific risk factors of developing jumper's knee are presented in table 6.

Table 6. Volleyball-specific risk factors for jumper's knee, the level of evidence is estimated as strong, medium, weak or unknown.

Risk factor	Description	Level of evidence
Gender	Males > females	Strong (OR: 3-4)
Tendon load		
Match exposure	Per extra set played per week	Strong (OR: 3-4)
Volleyball training (previous and present)	Per hour extra training per week	Strong (OR: 2)
Jumping ability	Per cm difference in CMJ at the time of inclusion	Strong (OR: 2)
Ultrasound findings		
Hypoechoic areas	If hypoechoic areas is present	Medium (OR: 3)
Neovascularisation	If neovascularisation is present	Medium (OR: 3)
Court surface	Concrete > parquet > sand	Strong
Body composition	Body mass/BMI among adults - not adolescents	Weak
Genetics	Different candidate genes	Unknown
Biomechanics		
ROM	Low range of ankle dorsiflexion	Weak
Landing strategy	Knee position when landing	Unknown

Data from the current study suggest that one of the key elements in preventing jumper's knee is to load the tendon appropriately. We found that athletes developing jumper's knee trained more volleyball and played more matches than asymptomatic controls (Paper I). The most

talented boys stand out with a particular risk. Match exposure, i.e. the number of sets played per week, was the strongest sports-related predictor for developing jumper's knee in this study. Therefore, one lesson learned from this study is that there needs to be a focus on how many different teams youth players should represent during the season and how many matches they should play. This issue is unlikely to be raised by the player; this is the responsibility of the coaching staff. Jumping ability is another important risk factor (Paper II). An obvious explanation for this finding could be that players who jump well subject their tendons to higher load with each jump/landing and therefore have higher risk. Athletes could jump up to 300 times during a five-game match, while the number of jumps during a regular training week is unknown. Reducing the number of jumps may be a controversial strategy, but future guidelines might include "jump counts" among adolescent athletes. In baseball, safety recommendations have been developed for pitchers, limiting the number of pitches per game and number of months played per year from age 14 through 20 years. In volleyball, there is currently not enough evidence to introduce jump counts, nor do we know what the optimal number of jumps would be.

We have also investigated if we are able to identify athletes at higher risk by ultrasound examinations (Paper III). Even if hypoechoic areas and neovascularization were risk factors for developing jumper's knee, we cannot recommend instituting routine ultrasound screening programs to prevent jumper's knee.

Another approach would be to add "tendon strength training" to make tendons strong enough to better tolerate the sport-specific activity. Normal tendon adaptation to load is slow compared to muscles, especially when athletes rapidly increase the volume of training (Kjaer et al. 2009). Imbalances between muscle strength and tendon loading capacity in adolescent athletes might increase the risk of tendon injury. Structured warm-up programs, e.g. "the 11+" have reduced the risk of lower limb injury (Soligard et al. 2008), including the risk of overuse injuries. Other studies also indicate an effect on overuse injuries (Junge et al. 2002; Kraemer and Knobloch 2009). Such programs typically combine strength training, stretching, balance training, core stability and correct landing strategy after jumps. However, Fredberg et al. (2008) found that prophylactic eccentric training increased the risk of patellar tendinopathy. So far, the effect of and the potential mechanism behind structured warm-up programs in the prevention of overuse injuries like jumper's knee is unclear. Today there are no guidelines on how to make tendons stronger and how to improve tendon properties in a safe manner.

To summarize, based on the results of this study a potential prevention strategy would be to gradually “develop” athletes rather than to start with too much volleyball-specific training too soon. Even though a prevention program should not interfere with the development of the sports-specific skills, restrictions on the number of jumps and matches among adolescent athletes would probably reduce the risk of jumper’s knee. The problem is that we do not know where these limits should be set, and there is insufficient data to adapt programs to the risk profile of each athlete.

4. Conclusions

1. A high volume of volleyball training and match exposure were important risk factors for developing jumper's knee.
2. Body composition or change of body composition was not a risk factor for developing jumper's knee among young well-trained athletes.
3. Volleyball players with a natural ability for jumping high have an increased risk of developing jumper's knee, while the change of jumping ability was not identified as a risk factor.
4. Hypoechoic areas and neovascularisation at baseline were risk factors for developing jumper's knee.
5. Quadriceps tendon thickness increased 7-11% among healthy athletes, while there was no change in patellar tendon thickness during a mean observation period of 1.7 years (two volleyball seasons).

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