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TRAUMATIC PATELLAR DISLOCATION IN CHILDHOOD – LATE EFFECTS ON KNEE FUNCTION AND CARTILAGE QUALITY

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Traumatic patellar dislocation in childhood – Late effects on knee function and cartilage quality

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my family

ABSTRACT

Background and aim: Acute patellar dislocation affects approximately 1:1000 healthy children 9-15 years of age, and up to 50% are at risk for recurrent dislocations. In adults the condition is associated with long-term complications, such as osteoarthritis and impairment of knee function. However, literature describing the outcome in a pediatric population is sparse. The aim of this thesis was to evaluate the long-term effects on knee function and cartilage quality after traumatic patellar dislocation in childhood, and also to evaluate the reliability of two clinical tests of medio-lateral knee position, in healthy children.

Patients and methods: In Study I, 246 healthy children were included to evaluate the Q-angle and the Single-limb mini squat test, reflecting static and dynamic medio-lateral knee position, respectively. In Study II, III and IV patients with a history of acute, unilateral, first-time traumatic patellar dislocation, 9-15 years of age at index injury, and with a follow-up time of ≥5 years were included. Recurrence rate and patient reported outcome were assessed. In Study II, n=52, the objective- and subjective knee function were evaluated in relation to type of obtained treatment. In Study III and IV the quality of the patellar cartilage was evaluated with quantitative MRI metrics, T2 mapping and delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC). In Study III 16 non-operatively treated patients with recurrent patellar dislocation, and in Study IV 17 patients surgically treated in childhood due to unilateral recurrent patellar dislocation, were evaluated.

Results: In Study I the reliability for the Single-limb mini squat test was determined moderate, the Q-angle measurement was found to have fair to moderate reliability. The Q-angle varied with age and sex; however, this finding may not be clinically relevant. Study II, III and IV reveal that the patients were affected KOOS *quality of life* and *sports and recreation*, with lower scores than normal for the age. 67% reported recurrence among the non-operatively treated patients. Despite regained stability in patients operated on due to recurrences, the subjective knee function was not restored. In both the non-operatively treated patients with recurrent patellar dislocations (Study III), and the surgically stabilized patients (Study IV), very early cartilage changes were detected in the patellar cartilage of the affected knee with dGEMRIC and T2 mapping. The shortening of T1(Gd) indicate loss of glycosaminoglycans. The localization of the findings were similar in Study III and IV, although, at different tissue depths; with changes in the superficial half of the cartilage in patients with recurrent dislocations (study III), and changes in the deep half in the operated patients (study IV). In Study III *shorter* T2 values were detected in superficial half of the cartilage in the peripheral parts of affected patella, whereas *longer* T2 was observed most medially in the deep cartilage of the operated group (Study IV).

Conclusion: The Single-limb mini squat test can be used to evaluate the medio-lateral knee position in a pediatric population, whereas the Q-angle only showed fair reliability.

Acute traumatic patellar dislocation in childhood has a negative long-term impact on quality of life and ability to participate in physical activities. Traditional surgical methods reduced the recurrence rate, but the knee function was not restored.

Recurrent patellar dislocation, and patellar stabilizing surgery, seem to have a negative effect on cartilage quality; most likely through different biological mechanisms and at different depths of the cartilage. The results from quantitative MRI of the patellar cartilage indicate changes in both GAG content and collagen structure. These new findings show that dGEMRIC, in combination with T2 mapping, are feasible methods to detect early degenerative changes in vivo in this condition.

LIST OF SCIENTIFIC PAPERS

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

I. **Reliability and reference values of two clinical measurements of dynamic and static knee position in healthy children**
Örtqvist M, Moström EB, Roos EM, Lundell P, Janarv PM, Werner S, Broström EW
Knee Surgery, Sports Traumatology, Arthroscopy. 2001; 19(12):2060-6

II. **Long-Term Follow-Up of Non operatively and Operatively Treated Acute Primary Patellar Dislocation in Skeletally Immature Patients**
Bengtsson Moström E, Mikkelsen C, Weidenhielm L, Janarv PM
The Scientific World Journal, vol. 2014, Article ID 473281, 8 pages, 2014. doi:10.1155/2014/473281

III. **Pre- and Postcontrast T1 and T2 Mapping of Patellar Cartilage in Young Adults with Recurrent Patellar Dislocation**
Bengtsson Moström E, Lammentausta E, Finnbogason T, Weidenhielm L, Janarv PM, Tiderius CJ
Magnetic Resonance in Medicine.2015;74(5):1363–1369

IV. **T2 mapping and Post-contrast T1 (dGEMRIC) of the patellar cartilage - long term follow-up after patellar stabilizing surgery in childhood**
Bengtsson Moström E, Lammentausta E, Finnbogason T, Weidenhielm L, Janarv PM, Tiderius CJ.
Manuscript

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LIST OF ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ASIS	Anterior Superior Iliac Spine
B_0	External magnetic field
BMI	Body Mass Index
CDI	Caton-Deschamps Index
CT	Computerized Tomography
dGEMRIC	delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage
GAG	Glycosaminoglycan
Gd-DTPA^{2-}	Gadolinium Diethylene Triamine Pentaacetic Acid (Contrast agent)
γ	Gyromagnetic constant
FCD	Fixed Charge Density
FID	Free Induction Decay
^{1}H	Hydrogen
HQ ratio	Hamstrings to Quadriceps ratio
Hz	Hertz
ICC	Intraclass Correlation Coefficient
LSI	Leg Symmetry Index
ω	Larmor frequency
M_0	Net magnetization
MPFL	Medial Patellofemoral Ligament
MRI	Magnetic Resonance Imaging
OA	Osteoarthritis
RF	Radio Frequency
ROI	Region of Interest
T1	T1 relaxation time
T1(Gd)	T1 relaxation time of cartilage after saturation with the contrast agent Gd-DTPA^{2-}
T2	T2 relaxation time
TTTG distance	Tibial Tuberosity Trochlear Groove distance
KOOS	Knee Injury and Osteoarthritis Outcome Score
PRO	Patient Reported Outcome
Q-angle	Quadriceps angle
ROM	Range of Motion
SD	Standard Deviation
SDC	Smallest Detectable Change
SEM	Standard Error of Measurement
VMO	Vastus Medialis Obliquus muscle

1 INTRODUCTION

Participation in sports and recreational activities is essential for most children. Being able to participate at one's own level of capability, and experience the sheer joy of movement is fundamental not only in organized forms but also in the daily life of a child.

In pediatric orthopedics sports-related injuries are common. According to a report from Socialstyrelsen, Sweden, in 2011, sports-related injuries account for 28% of the total number of casualties at emergency departments between 0 and17 years of age, and peak between 13 and 15 years. Up to the age of 15, there is no difference between girls and boys in this report. The knee is the second most common site of injury after the ankle[1].

Given the spectrum of diagnoses associated with knee trauma in children and to provide accurate treatment to potentially serious knee injuries, the importance of correct diagnosis in the acute phase cannot be overstressed. Even though acute traumatic patellar dislocation is a common problem in childhood the literature regarding long-term outcome and sequelae is sparse; oftentimes results from a mixed population of children, adolescents, and adults are presented. As the characteristics of the lower extremities and the knee function will differ according to age and skeletal maturity, using a mixed population carries the risk of presenting false conclusions. There is a great need for further knowledge in this discipline.

2 PATELLAR DISLOCATION

In children 9-15 years of age traumatic patellar dislocation is the most common cause of traumatic haemarthrosis in children, affecting 0.3-1.2: 1000; it is sports related in the majority of cases (30-70%)[2–5]. The relatively large span of reported incidence in the literature is most likely based on different inclusion criteria and age groups in the studies (see table 1)[2–5].

Author	Age group	Incidence
Nietosvaara 1994	< 16 years (9-15 years)	0.43:1000 (1.1:1000)
Fithian 2004	10-17 years	0.3:1000
Askenberger 2014	9-14 years 12-14 years	0.6:1000 1.2:1000
Waterman 2012	0-19	0.4-0.5:1000

Table 1. Reported incidence of acute patellar dislocation in children and adolescents[2–5].

2.1 ANATOMY

Due to the large inter-individual variation in skeletal maturation of the lower extremities in healthy children; age alone cannot determine the treatment, and evaluation of risk factors for patellar dislocation must be done in relation to maturity. Therefore, a brief presentation of the normal development of the lower extremities will follow.

2.1.1 Development of the lower extremities during childhood

The skeleton develops from a condensation of mesenchymal cells, which serves as precursors for membranous bone or cartilage[6]. The cartilaginous model for the patella start to develop in the deep layer of the patellar tendon during the 7th week of gestation, and the patella ossifies at 4–6 years of age [7]. Epiphyseal cartilage is responsible for shaping the ossified ends of bone and forming the shape of the trochlear groove[6,8]. Formation of the hyaline articular cartilage and the subchondral bone plate occurs in the end stage of the development of the epiphysis, but maturation of the cartilage continues throughout childhood[6,9–11].

Longitudinal growth of the axial skeleton is mediated by the physis, and according to Swedish normal reference values, the prepubertal growth is approximately 5 cm/year in boys and 5.5 cm/ year in girls[12]. The process of skeletal maturation follows a relatively consistent pattern; hands and feet are first to start and stop their growth spurt; when the growth plate is ossified the longitudinal growth stops; and at the knee, physeal closure occurs around 14 years in girls and around 16 years in boys[12,13].

Both the range of motion (ROM) and the alignment of the lower extremities are age dependent and changes over time. As a part of the normal and physiological development, there is a gradual change from bowlegs (genu varum) in the infant to knock knees (genu valgum) at 1-4 years of age[14]. Also, in 2-8 year olds a slight knee hyperextension is normal, but it reduces over time[15]. Confusing visual clues on clinical examination of the knee alignment may be related to the pelvis, hip, and femur. For example, an increased internal rotation of the femur might be related to the higher grade of femoral neck anteversion seen in young children. As the child grows, the femoral anteversion decrease from around 25˚ by 8 years of age, to the adult mean of 16˚ between the ages of 14-16 years, and a decrease in the internal rotation of the femur will follow[16,17]. Furthermore, despite similar limb segment growth and development, girls have an increased rate of generalized joint hyperlaxity at the onset of puberty, which boys do not have; this gender difference is not seen in prepubertal children[18]. Regarding knee laxity and gender differences, the literature is inconsistent[19,20].

These normal developmental changes in the lower extremities at growth stresses the importance of child specific evaluation tools and reference values when assessing knee problems, such as patellar dislocation in children.

2.1.2 The patellofemoral joint

The patella is a large sesamoid bone imbedded in the quadriceps tendon. It has the thickest cartilage in the human body (1-6 mm), and the patella increases the lever arm of the quadriceps muscle[21]. The patellofemoral joint is complex; a good stability and a high function depend on the conformity of osteoarticular structures, the articular geometry, and the soft tissues. A balanced interaction maintains the patellar stability through the entire range of motion. Patellar tracking is defined as the motion of the patella relative to the femur, or the femoral groove, on knee flexion and extension. Maltracking, or abnormalities of the patellofemoral joint, can be difficult to observe[22,23].

To describe the details of the patellofemoral joint kinematics, most studies have been conducted in vitro. In different settings, the kinematics of the normal patellofemoral joint, the patellar instability as well as the effect of surgical procedures on the biomechanics have been studied[23–26]. Patellar tracking has also been evaluated in vivo with kinematic magnetic resonance imaging (MRI) and computer tomography (CT) studies to exploit the dynamics of the patellofemoral joint by imaging at different degrees of knee flexion[27–29].
In a congruent patellofemoral joint, the patella moves slightly medial in early knee flexion. The patella articulates to the trochlear groove at approximately 20-30˚ of flexion with an initial loading of the medial cartilage. With increased flexion the patella will center in the trochlear groove, and at the end of flexion, it will move slightly laterally. The contact area on the patellar cartilage moves from inferior to proximal in flexion[23,26].

The soft tissues that stabilize the patellofemoral joint can be referred to as dynamic or static stabilizers. The dynamic, or active, stabilizer of the patella is the Quadriceps muscle. The Rectus Femoris muscle generates force acting directly along the femoral axis, whereas the oblique muscles, Vastus Medialis (VMO), and Vastus Lateralis, produce a transverse force vector[30,31]. In summary, this will result in a slight lateral force on the patella.

The static stabilizing soft tissues are the medial patellofemoral ligament (MPFL), the medial patellomeniscal and the medial patellotibial ligament, and the retinaculum. The MPFL is a thin facial band with fibers stretching from the medial femur epicondyle, the adductor tubercle, and the superficial medial collateral ligament; it passes deep to the distal part of the VMO and inserts at the proximal medial border of the patella[32]. In early knee flexion the MPFL is the major restraint to lateral patellar translation, contributing 60% of the restraining force; the medial patellomeniscal ligament contribute with 13%, whereas the medial retinaculum and the medial patellotibial ligament only contributes with 3% each. Also the lateral retinaculum plays a role as a passive stabilizer, contributing with 10% of the restraining force[33]. Injuries or imbalance between the above described structures may lead to conditions that affect the patellofemoral joint, such as subluxations, dislocations, and perhaps also contribute to pain and increased stress on the articular cartilage.

2.2 ASSESSMENT OF THE PATIENT WITH PATELLAR DISLOCATION

2.2.1 Assessment in the acute phase

At the time of an acute knee injury, diagnostics may be difficult; not only is the child in pain, but often the anamnestic information about the traumatic event may be misleading. In acute traumatic knee injuries, plain radiographs are often the first diagnostic tool. But several studies have found a high incidence of significant knee injuries despite normal plain radiographs in children with haemarthrosis after acute knee trauma[2,34,35]. Hence, further diagnostics are needed.

Throughout the years, concerns have been raised regarding the accuracy of MRI in the diagnostics of intraarticular injuries, mainly regarding meniscal and anterior cruciate ligament (ACL) tears in children[36,37]. When examining children, it should be pointed out that the anatomical structure of the menisci, with persisting vascularization, might mimic a lesion. Increased signal intensity (Grade I and II) is considered to be consistent with a normal meniscus in children[34,38]. Though, seeing that the MR technique, the imaging protocols, and the knowledge of interpretation of the images has improved, the sensitivity and the specificity is considered good[39].

At the acute patellar dislocation the MPFL can be distended or disrupted. In children, the site of injury is most often at the insertion at the patellar border (Type I); however the MPFL injury can also be a mid-substance injury (Type II), a tear at the femoral origin (Type III), or a combined injury (Type IV)[40,41]. There is no consensus regarding acute repair or reconstruction of the MPFL versus nonsurgical treatment[42–44]. Whether the site of injury influences the healing potential in children is not yet known.

When the patella dislocates, it is not only the MPFL injury that is of concern, there is also a significant risk of chondral and osteochondral lesions. The high risk of traumatic osteochondral injury in adolescence is most likely related to the immaturity of the cartilage[45,46]. Depending on the definition of osteochondral injuries, the incidence differ in the literature. Matelic et al. presented an arthroscopic study of children with traumatic haemarthrosis and reported osteochondral fractures in 67% of the cases; due to the location of the injuries on the medial facet of the patella and the lateral femur condyle, they suggested that the majority of the osteochondral fractures were related to patellar dislocation[47]. Nietosvaara et al. reported 39% osteochondral injuries in children with acute patellar dislocation[4]. Using MRI, Zaidi et al. reported similar findings; the authors detected osteochondral fragments in 42%, chondral injury to the patella in 38% and at the lateral femur condyle in 38%, of the children with traumatic patellar dislocation[48].

In general, osteochondral fragments > 1 cm^2 from weight-bearing joint surface are re-fixated, and often a patellar stabilizing procedure is performed at the same time to reduce the risk of recurrence. If treated early, the healing potential is considered to be good in children, although, the series were small and long-term evaluation of the cartilage quality and risk of post traumatic osteoarthritis after childhood injuries are unknown[49–51]. Thus, with the high rate of potentially serious joint surface injuries, it is essential to evaluate the cartilage by MRI (or arthroscopy) to give adequate treatment from the start.

2.2.2 Clinical evaluation tools

Several diagnostic tests to evaluate patellar instability are described for clinical practice. For example, *the Q-angle*, *the J-sign* and *the Apprehension test* are often mentioned tools that are aimed to evaluate different aspects of the condition. In what direction the Quadriceps muscle act on the patella may be estimated by measuring the quadriceps angel, or *the Q-angle*. The Q-angle is generated by measuring the angle between two lines: one line runs from the anterior superior iliac spine (ASIS) to the center of the patella, and the second line runs from the center of the patella to the tibial tubercle. If there is an increase in the Q-angle, the patella shifts laterally and rotates medially, following the quadriceps force in early flexion, but as the flexion angle increases the articular constraints within the trochlea limits the shift and rotation[25]. A positive *J-sign* is when the examiner observes an exaggerated lateral to medial translation of the patella into the trochlear groove in early flexion; this may suggest a tight lateral retinaculum. A positive *Apprehension test* is when the knee is held relaxed in 30° flexion, the examiner uses one hand to push the patella laterally, and the maneuver induces expression of anxiety and/or involuntary quadriceps muscle contraction in the patient. The sensitivity and specificity as well as reliability and validity of physical diagnostic tests for patellar instability are unclear or indefinite[52]. Despite that, a thorough examination of the knee and the alignment of the lower extremities, together with assessment of general risk factors (see next section), complement the radiological evaluation in decision making in clinical practice. The use of different outcome measures might increase chances to capture the consequences of patellar dislocations.

Performance based outcome measures, or functional tests, such as muscle strength measurements and hop tests are often applied to evaluate the outcome after knee disorders[53,54]. In functional tests, there may be difficulties for children to perform certain tasks, and the performance is variable at the same age. In a study of isokinetic muscle strength in children, 7-12 years of age, an increase was seen according to age, but no sex difference was seen up to age 11. Also, there was a large variability within the same age group[55]. Likewise, the normal muscle function in adults is variable. A comparison of the strength between the affected and non-affected leg (leg symmetry index, LSI) and a ratio of the flexor-to-extensor muscle strength (Hamstrings to Quadriceps ratio, HQ ratio) can be used to compare individuals. A LSI of >85% and HQ ratio of <0.6, respectively, are considered normal[56–59].

To intercept the patient's own perception of the knee function, different *patient reported outcome measures (PRO)* are used. PROs are often questionnaires designed to express symptoms, limitations in activities, and in the daily living. Often region-specific tools are used when evaluating long-term consequences of patellar dislocation such as anterior knee pain and osteoarthritis, and several instruments have good reliability and validity[60]. In 2013, "the Norwich Patellar Instability (NPI) score" was presented; the results indicated that the 19-item questionnaire was a suitable tool to assess patellar instability in adults[61]. Recently, this outcome measure has been validated to assess patellar instability symptoms in people conservatively treated after first-time patellar dislocation[62].

When evaluating children, it is important to recognize that all outcome measures for adults are not tested for reliability or validated in a pediatric population, and normal values are often lacking. The adult PRO questionnaires are not always well understood; in order to catch the child's perspective of the condition, the use of an adapted instrument is to be preferred. At what age adult questionnaires can be used is not just a concern of the reading skills but also whether the instrument is relevant for the daily living and the functional demands of the child[63].

2.2.3 Evaluation of the risk for recurrent patellar dislocation

The multifactorial etiology of recurrent patellar dislocation is a challenge. Contributing factors include bony variants of the patellofemoral joint and altered alignment in the lower extremities. In addition to these predisposing skeletal conditions, incompetent soft-tissue stabilizers might lead to loss of patellar stability and can place the patient at high risk of recurrent dislocation.

In the past, the stereotypical patient with recurrent patellar dislocation was often referred to as a sedentary, ligamentous lax and slightly overweight adolescent girl. However, this has been questioned in recent years. Whether females are at greater risk of persistent instability problems or not, the literature is inconsistent. Earlier studies report a female dominance, but in more recent reports there is an almost equal sex distribution[41,64–66]. Hypermobility, genu recurvatum, genu valgum, increased external tibial torsion and/or increased collum femoris anteversion are conditions often mentioned as "*general risk factors for patellar dislocation*" [67,68].

In the 1990s, Dejour et al. suggested four anatomic patellar instability factors and classified radiological signs of trochlear dysplasia[67].

- *Trochlear dysplasia;*
  A sulcus angel of >145º, a trochlear medial/ lateral facet asymmetry <40%, and a lateral trochlear inclination angle ≤ 11° are signs of trochlear dysplasia[67,69]. According to Dejour et al., the appearance of trochlear dysplasia can be classified in four types; Type A has a preserved but shallow trochlear morphology, Type B a flat trochlea, Type C a lateral convexity, and Type D a lateral convexity and medial hypoplasia with an additional vertical link[67,70]. The grading of trochlear dysplasia can also be defined as the following: no dysplasia, low grade (Type A) and high grade dysplasia (Type B, C or D), respectively. Merging the groups has shown better intra- and inter-observer agreement when evaluating later views on plain radiographs [71]. Assessment of trochlear dysplasia with CT or MR images, most likely provide a higher accuracy than plain radiographs only [69,71–73].

- *Patella alta;*
  An Insall Salvatio index >1.3. This index is defined by the ratio between the patellar tendon length (measured from apex patella to the insertion point for the patellar tendon on the tibial tuberosity) and the length of the patella [74]. A Caton-Deschamps index (CDI) >1.2. CDI is defined as the length from the anterior proximal corner of the tibia plateau to the most inferior point of the patella articular surface divided by the length of the patellar articular surface [75]. The CDI is higher in young patients as the ossification of the patella proceeds from proximal to distal; for example, in 6-7 year olds, a CDI of 1.27 (± 0.25) was measured in "normal" knees [76]. Therefore, there is a risk in diagnosing patella alta even if the patellar position is normal. In a study by Jaquith et al., CDI>1.45 was shown to be a significant risk factor for recurrence in children 8-18 years of age [77].

- *Increased tibial tuberosity trochlear groove (TTTG) distance;*
  This measurement is obtained by superimposing the MRI, or CT slide, which best represents the trochlea and the slide that passes through the tibial tuberosity. Two lines, one beginning at the bottom of the groove and another at the center of the tibial tuberosity, are then drawn perpendicular to the posterior condylar line; the distance between the two lines are measured in mm. The TTTG distance is the radiological equivalent to estimation of the quadriceps vector by the Q-angle. A TTTG distance of >20 mm in adults is regarded pathological[67,78,79]. Dejour et al. reported an increased TTTG-distance in 56% of patients with patellar instability problems[67]. The TTTG distance varies with age and height in children and adolescents; a one cm increase in height increases the TTTG by 0.12 mm[80]. Dickens et al. described that in healthy children without patellar instability the median distance was 9.1 mm (± 1.7) in the age 9-10 and 9.3 mm (± 0.6) in 15-16 year olds[81].

- *Patellar tilt;*
  According to Laurin, the patellofemoral angle is defined when one line is drawn between the margins of the anterior femoral condyles, and one line is drawn between the margins of the lateral facet of the patella on an axial view of the patella, and the angle between the two lines is measured. This patellofemoral angle is regarded pathological if the lines are parallel, or if the angle opens up medially[82] and it is then associated to patellar instability[67,82]. Several other methods to measure the patellar tilt angle have been suggested in the literature. For example, using a reference line connecting the edges of the patella, and a second line between the margins of the femoral condyles, and measuring the angle; it is considered pathological if the angle is > 20° [83].

In adults with patellar dislocation, it has been reported that in female patients, the trochlear dysplasia and the TTTG distance were more pronounced compared with males; this could lead to an increased risk of recurrent dislocation[84]. Balkarec et al. have suggested a patellar instability severity score based on six factors - age, bilateral instability, the severity of the trochlear dysplasia, patella alta, TTTG distance, and patellar tilt - to evaluate which patella that are likely to re-dislocate[85].Young age (<16years), a severe dysplastic trochlear groove, and a high patellar tilt were significantly associated with an early episode of patellar redislocation in their age mixed population (mean 19 years, range 9-51 years). Based on their previous described risk factors, the gender was also analyzed, but it was not associated to redislocation[84,85].

The majority of the anatomical risk factors presented for adults may also be important for children[86,87]. Balkarec et al. found approximately the same measurements of the trochlear depth and the sulcus angle in children, adolescents, and adults[88], while Düppe et al. found a significant difference according to age when evaluating sulcus angle, sulcus depth, and cartilage thickness of the lateral condyle in skeletally immature children. Furthermore, both the osseous and cartilaginous sulcus angles were age dependent, and the development differed between a normal and an unstable cohort[87].

Based on retrospective evaluation of radiographs or MRI, anatomic predictors for recurrent patellar dislocation in children have been suggested. Lewallen et al. reported that for a patient with open physes *and* trochlear dysplasia, the risk of recurrent instability was increased by a factor of 3.3, whereas in patients with closed physes and trochlear dysplasia, the risk was increased by a factor of 2.2. Among the patients with immature physes and trochlear dysplasia, 68.8% of the 48 patients had recurrent instability events[89].

Similar results were presented in a recent study by Jaquith et al., where the risk of recurrence was 56% in patients with open physes and trochlear dysplasia. The authors evaluated the risk of recurrence based on four risk factors: skeletal immaturity, trochlear dysplasia, patella alta, and contralateral dislocation. With all four risk factors present, the predicted risk of recurrence was as high as 88%; among the four factors trochlear dysplasia, and history of a contralateral patellar dislocation had the highest predicted risk of recurrence[77]. The retrospective design and relatively short follow up times (1.3 years (range 0-7.9 for Jaquit et al. and 3.1 years (range, 3 days - 12.5 years) for Lewallen et al.) are of course limitations in the studies. An exact risk of recurrence might be difficult to predict, and both anatomical and general risk factors must be considered in the clinical setting to provide the best possible information for the patient.

2.3 TREATMENT

In the absence of a significant osteochondral injury, the general opinion is that non-surgical treatment is advocated in first-time acute traumatic patellar dislocation[90–96]. However, Nwachukwu et al. presented a meta-analysis of surgical compared to non-surgical treatment of children with acute patellar dislocation. Based on the meta-analysis of 11 studies, the authors concluded that acute surgical treatment was associated with a lower risk of recurrent dislocation and provided higher health-related quality of life and sporting outcome[44].

Non-operative treatment of first-time traumatic patellar dislocation typically includes a brief period of immobilization, possible bracing, and physiotherapy. Regarding conservative treatment, the study designs vary and it is difficult to directly compare outcomes. Regimens range from immediate mobilization without a brace to cast immobilization in extension[97–99]. Physiotherapy focuses on establishing optimal lower extremity balance, strength, and function. Although, to the best of my knowledge there are no available outcome studies for either type of immobilization, or the efficacy of physiotherapy after patellar dislocation in childhood.

It is well known that after non-surgical treatment of acute patellar dislocation the recurrence rate is high. Approximately 50 % of children are at risk of recurrence, and it seems that the risk of recurrence is higher in younger children[4,65,95]. The high recurrence rate is of major concern. Surgical treatments for patellar instability are numerous and include both procedures aimed at reconstruction of the soft-tissue stabilizers, and procedures aimed to correct malalignment and dysplasia through modifications of the bone[100–104]. In skeletally immature patients, the tibial tubercle apophysis should be preserved; disruption of this apophysis by distal realignment procedures might lead to genu recurvatum. Also, the distal femoral and proximal tibial physes must be avoided to prevent the risk of asymmetric and premature physeal closure.

Historically, in recurrent patellar dislocations the surgical methods of choice for skeletally immature patients have been the following: proximal realignment (i.e., medial reefing, vastus medialis muscle advancement, and lateral release in cases with patellar tilt), combined with a distal realignment procedure (Roux-Goldthwait in the most skeletally immature patients or Roux-Elmslie-Trillat) in patients with an increased Q-angle (>20˚)[102,103]. The proximal realignment procedures mentioned above mainly addressed the dynamic stabilizer, the VMO, and not the primary soft-tissue restraint, the MPFL.

In 1992, Ellera Gomes proposed that surgical MPFL reconstruction was preferred over correction of other predisposing conditions when treating recurrent patellar dislocation in patients with closed physes[105]. To strive for a more anatomical approach, and to optimize the stabilizing procedure, several techniques to reconstruct the MPFL have since then been presented. The results are promising regarding recurrence rate and patient reported outcome and MPFL reconstruction is an option when treating children with recurrent patellar dislocation[43,86,100,106,107]. However this approach also has pitfalls and may alter the biomechanics pressure on the patellar cartilage[107–109].

Surgical procedures to correct predisposing anatomical risk factors, is sometimes used in combination with soft tissue procedures to reconstruct the MPFL, though, to address trochlear dysplasia most surgeons await physeal closure at skeletal maturity. Also, in growing children the possibility to address unfavorable alignment in the lower extremities by guided growth, i.e. temporary epiphyseodesis, should not be forgotten as a complement to the treatment regimen of recurrent patellar dislocation.

2.3.1 Long-term outcome

In a description of the natural history of 100 non-operatively treated patients with a median age at injury of 23 years (10-64), only 37% of the patients reported no complaints, all the remaining patients experienced instability or pain at follow up 13 years after the first patellar dislocation[110]. Unfortunately, several studies of the long-term outcome after surgical stabilization in adults indicate that despite regained stability, there is a risk of cartilage degeneration and future osteoarthritis[111–113]. Reduced participation in sports and increased pain are described[112,114], and reduced thigh muscle volume[115] are also reported among operated patients.

It is clear that attention must be given to children and adolescents with patellar dislocation. Palmu et al. randomized 62 children with acute patellar dislocation to non-operative treatment and primary repair, respectively, and found similar results in redislocation rate and Kujala score between the groups[95]. Comparing the results after 6 years, to the results after 14 years, the redislocation rate increased in both groups. In the non-operative group redislocation rate increased from 54% to 71%, and in the operated group from 50% to 67%. At the latest follow-up the Kujala score was 84 in the non-operated patients and in the operated group it was 83. Furthermore, the patients were asked to grade their knee function as excellent, good, fair or poor[95]. In the group of operated patients, the proportion of participants who reported “excellent or good” knee function increased from 58% to 66%;

despite a very high rate of recurrences, and lower Kujala scores compared to normal. Perhaps this is an expression of adaptation to the condition over time.

In summary, there might be a risk of cartilage degeneration and symptoms from the patellofemoral joint, impaired knee-function and limitations in activities after patellar dislocation in childhood; but, further evaluation of these effects are needed.

2.4 ARTICULAR CARTILAGE

A healthy joint relies on the interplay between cartilage biology, mechanics and structure. The articular cartilage is a highly specialized avascular tissue. It provides a low friction surface to the joint, and evenly distributes the load to the underlying bone. The composition of the hyaline cartilage covering the joint surfaces is unique and adjusted to the requirements of the specific joint. At the inner lining of the joint capsule, the synovial cells secret viscous synovial fluid, which is rich in water and acts like a lubricant, containing proteins, electrolytes, and nutrients for the chondrocytes[116].

The major constituents of the hyaline cartilage are proteoglycans (3-10% of cartilage wet weight), collagen type II (10-30 % of cartilage wet weight), chondrocytes (approximately 10% of wet weight), water, and dissolved electrolytes (60-85%)[117]. Oftentimes the cartilage is referred to as a tissue with a fluid phase (water) and a solid phase (collagen, proteoglycans and proteins). The mechanical properties and the viscoelastic behavior of the tissue is sensitive to changes in the structure or composition of either the fluid phase or the solid phase, and the cartilage depends on the interactions of its constituents to function optimally[118].

In children, the chondrocytes and the collagen structure will gradually be arranged according to the loading and the demands of the joint[11,119]. Eventually, at skeletal maturity, the articular cartilage will be organized in three characteristic zones: the superficial-, the transitional- and the radial zone (Figure 1). Histologically, in the deepest part of the radial zone, the tidemark delineates the boundary between the deep cartilage and the calcified cartilage. This is a mark of increase in stiffness that is seen in adults but not in children. Bellow the calcified zone is the subchondral plate.

In the extracellular matrix of articular cartilage, the type II collagen fibers form a well-organized network. In the superficial zone the fibers run parallel to the surface, in the transitional zone the fibers are less organized but will curve down towards the radial zone. In the radial zone, the collagen II fibers are perpendicular to the cartilage surface. Through the tidemark and the calcified cartilage the collagen fibers are anchored to the subchondral bone.

The chondrocytes in the superficial zone have an oval shape, while in the deeper part of the cartilage they have a round appearance. In the radial zone, the chondrocytes have roughly twice the volume of the superficial cells[120]. In the radial zones the chondrocytes are up to ten times more active than the superficial cells in synthesizing extracellular matrix, but there is also a gradient of which type of molecules predominantly synthesized at different tissue depths. For example the chondrocytes in the superficial zone mainly secrete collagen and less proteoglycans, whereas in the deeper part the production of aggrecan increases[120–122].

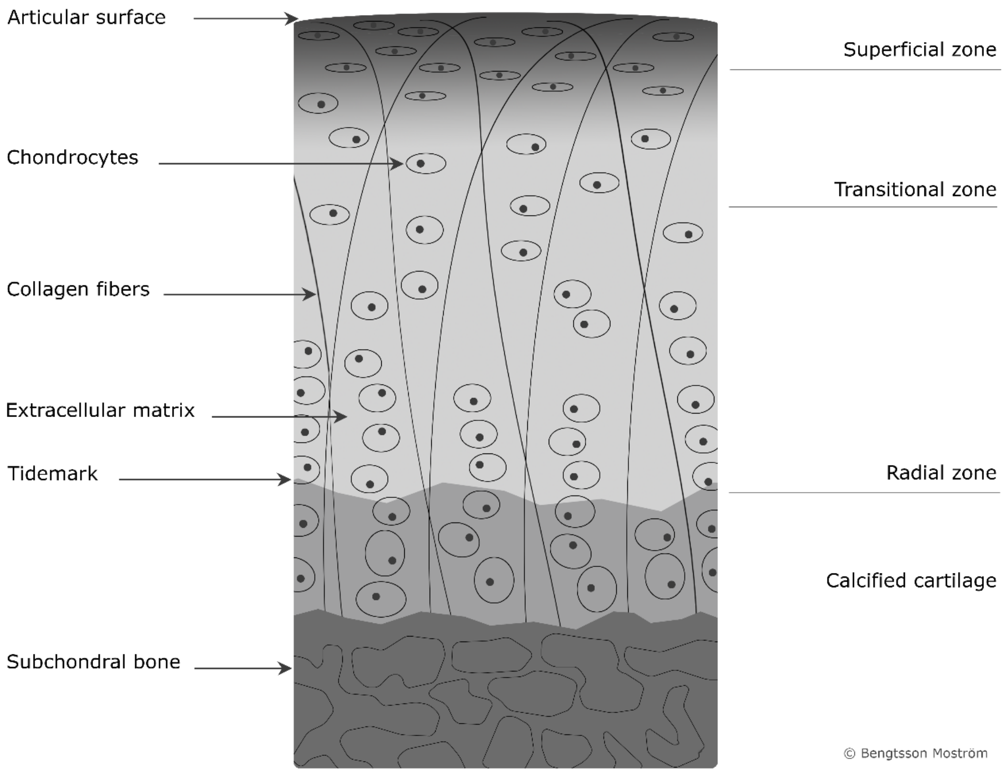

Figure 1. Schematic presentation of the articular cartilage.

Articular cartilage contains two major classes of proteoglycans: large aggregating proteoglycan monomers (aggrecans), and small proteoglycans. The proteoglycans are composed of a central core protein to which one or more negatively charged side chains, glycosaminoglycans (GAG), are attached. GAG chains are long unbranched polysaccharide chains, consisting of repeating disaccharides that contain an amino sugar[123,124]. Each of the disaccharide units has at least one negatively charged carboxylate or sulfate group. GAG in cartilage include hyaluronic acid, chonroitin sulfate, and keratin sulfate. The proteoglycans and small link proteins bind to, or are entrapped in, the collagenous network of the extracellular matrix. Aggrecan fill most of the interfibrillar space in the extracellular matrix, contributing to 90% of the proteoglycan mass[124].

As the proteoglycans with their negatively charged GAG side chains are immobilized in the extracellular matrix, they repel other negatively charged molecules and attract cations. This will contribute to a negative charge called the fixed charge density (FCD) that draws cations into the tissue. Since every negative fixed charge requires a mobile cation to maintain electro-neutrality, and as the synovial fluid is rich in Na^{+}, this cation will be drawn into the cartilage to maintain the electro-neutrality in the tissue [125]. The Na^{+} concentration will yield a pressure difference and in turn will draw water into the tissue. Hence, the amount of interstitial water depends on the FCD (created mainly by the negative proteoglycans), the organization of the collagen network, and the interaction of collagen with the proteoglycans[126]. In the superficial zone, there will be a high fraction of water and a relatively low concentration of proteoglycans; the water fraction decreases, whereas the proteoglycan content increases towards the deeper cartilage zone[127–129].

Maintaining a balance between syntheses and degradation of matrix molecules is important for the integrity and the viscoelastic properties of the tissue throughout life. An imbalance in the regulatory mechanisms may lead to cartilage degeneration and osteoarthritis[130].

The biosynthetic processes of the chondrocytes require nutrients and regulatory substances such as cytokines and growth factors. Metabolic waste products must also be transported out. As the cartilage is an avascular tissue, the transport of solutes occurs through diffusion in the aqueous phase of the extracellular matrix, and it is therefore dependent on the water content and the pressure applied to the cartilage[131]. Mechanical loading, or tissue compression, not only affect the flow and the diffusion, it is also associated with alterations of the cell-mediated matrix turn over[132]. Compression of the chondrocytes and their nuclei will occur in the direction of the loading, and the changes will differ according to depth, anisotrophy, inhomogeneity, and age[120]. In general, static compression is associated with decreased metabolic rate, while low amplitude dynamic compression is associated with increased cell activity[133–135]. However, the response to dynamic compression is dependent on the frequency and amplitude. Over time, there may be fatigue; a decrease in the enzymes needed for glycosylation and sulfatation, and a longer time needed for the recovery of the aggrecan synthesis with increased duration of the compression[132].

Shear stress to the cartilage surface in patellar dislocation might harm the superficial cartilage layer. Removal of the superficial zone, whose structure is adjusted to withstand and resist shear forces and contribute to the compressive behavior of the cartilage, may increase the permeability of the tissue and probably increase loading of the macromolecular framework during compression[118,122,136], potentially affecting the cartilage in the long run.

Normally, the cartilage serves as an attenuating layer that redistributes contact stresses over a greater area and thereby protects the more rigid underlying bone from mechanical damage. The junction between cartilage and bone is of importance in distributing the load. In vitro studies report that the anchoring of the cartilage to the subchondral bone differs according to skeletal maturity, and this will affect the type of injury acquired at trauma[137]. In adolescents, the articular cartilage is anchored through interdigitating fingers of uncalcified cartilage penetrating into the subchondral bone, whereas in the mature joint, it is anchored subchondrally via the calcified cartilage layer[137]. The interdigiting cartilage fingers penetrate deep into the subchondral boneplate to create a relatively strong bond. If a shear force is applied, the failure will occur at this level, resulting in an osteochondral injury in the immature joint. As the adolescent cartilage matures, there is a gradual transit to the adult cartilage structure. At maturity, failure often occurs along the tidemark, and a chondral separation occurs[46].

2.4.1 Development of osteoarthritis

Osteoarthritis (OA) is an imbalance between biosynthesis and degradation of cartilage matrix, where the degradation finally surpasses the attempt of cartilage repair. Over time, this eventually lead to destruction of the articular cartilage. Histological signs of the degenerative process of OA was described and categorized in the 1970s by Mankin et al.[138]. In the earlier stages there is increased degradation of aggrecan, disruption if the collagen network and swelling; as the disease progress there will be clefts in the cartilage, further loss of structure and hypocellularity[128,138].

Radiological signs of OA includes subchondral sclerosis, joint space narrowing, osteophyte formation, and deformation, and it takes years to develop[139,140]. The correlation between the radiological signs and the clinical signs of OA are limited[141,142]. Pain, locking, stiffness, and swelling of the affected joint may well be present without advanced stage OA on conventional radiographs. Aging exponentially increases the incidence of OA, but in this thesis the post traumatic OA will predominantly be discussed.

It has been suggested to classify OA into different groups according to the causation, if the OA is primary of congenital or acquired type, and if the principal mechanism is biological or biomechanical. The acquired-biomechanical type is the largest group and contains for example development of OA after chondral or osteochondral injury, or after anterior cruciate ligament injury[143]. Repeated trauma to the joint surface as seen in recurrent patellar dislocation is a potential risk factor for degenerative cartilage changes and future post traumatic osteoarthritis (acquired-biomechanical cause of OA). Different processes might be triggered and may occur simultaneously in the development of OA in patients with patellar dislocation. For example, *malalignment* may shift the center of pressure and may increase the local pressure, *ligament instability* may lead to increased shear stress but also to a shift in pressure, *cartilage lesions* may result in increased pressure at the rim of the lesion and exposure of the subchondral bone, and the *traumatic* event may induce cartilage damage per se due to increased metabolic and oxidative stress of chondrocytes[144,145].

In a prospective cohort study of 1321 former medical students (91% male, mean age at injury 16 years, median follow up time 36 years), the mean cumulative risk of OA at 65 years of age was 13.9% among those who had a knee injury in adolescence, compared to 6% in those who did not; this represents nearly a three-fold increase in risk of development of OA (relative risk 2.95 (CI 1.35-6.45)[146]. Even though this was an unsorted population regarding type of traumatic event, it puts emphasis on the long-term risk of joint injury in childhood.

In studies of OA after anterior cruciate ligament injury, 51% of women (mean age 31 years (range 26-40) had radiological signs of OA 12 years after the injury[147]. In men of similar ages (mean age 38 (range 30-56 years)) 41% had radiological signs of OA 14 years after the ACL injury[148]. Even if ACL surgery was successful with respect to increased stability, it did not decrease the risk of future OA[149]. The literature indicates that most likely the process of developing OA is both a biological/inflammatory response already at the time of injury with haemarthrosis and subchondral reactions as well as biomechanical responses[150]. Other traumatic events to the knee (e.g. patellar dislocations) may follow the same path of degeneration.

An arthroscopic follow up of adults with recurrent patellar dislocations describe that macroscopic signs of cartilage injury were observed in 73% of the cases. Fibrillation and/or cracking of the patellar cartilage were predominantly localized on the medial facet and on the central dome. The mean age at the initial dislocation was 14.6 years (range 7-26)[151]. Even though the study presents patients at a wide range of skeletal maturity, presumably with different cartilage healing capacity at the initial dislocation, it indicates a progress in cartilage degeneration over time in patients with recurrent patellar dislocations. Furthermore, in a study of 37 adult patients (mean age of 37 years, range 29-43 years), 78% had full thickness cartilage lesions on the medial patellar facet when assessed with MRI (1.0T scanner) 12 years (range 10-21 years) after patellar stabilizing operation. This indicates a progressive disease despite surgical stabilization[111]. Additionally, a two- to four-fold increased risk of disability has been reported in those with isolated symptomatic patellofemoral OA compared to age-gender matched controls and patellofemoral OA seem to be more associated to pain than tibiofemoral OA[152,153].

Studies on the long-term effects on the cartilage quality in children and adolescents with patellar dislocation have been lacking. Most studies that evaluate the risk of OA after patellar dislocation present results from a very wide age range; hence, the cartilage biology and the inherent possibilities for regeneration after trauma will differ in the cohort. No matter what the cause of onset is, there is currently no cure for OA. In order to improve the knowledge of OA and to find potential prevention strategies for the patients in the future, there is a need to detect early stages of cartilage degeneration, sometimes referred to as “the pre-arthritic stage”, before macroscopic loss of cartilage occur[143,150]. To detect early degenerative changes, conventional radiographs are insufficient, and other modalities must be developed and used in the clinic.

3 MRI

The basic principles of magnetic resonance was discovered and described by Isaac Rabi in the 1940s; and his research was awarded with the Nobel Prize in Physics in 1944. In the 1970s, it was proposed that magnetic resonance could be used to create images, and in 2003 the work of Professors Paul C Lauterbur and Sir Peter Mansfield were awarded with the Nobel Prize in Physiology or Medicine for their contribution to the development of magnetic resonance imaging (MRI). Today, MRI is a widely used tool to visualize internal organs and applications for MRI are continuously evolving. The basic principles of MRI presented in this section of the thesis is only a brief summary; the underlying theories are presented in rich detail in textbooks and in literature reviews[154–156].

MRI is based on the interactions between static and dynamic external magnetic fields and nuclei of the specimen to be imaged. The number of protons and neutrons will determine if the nucleus itself will have a nonzero spin or not. Only nuclei with an odd number of protons and/or neutrons possess a nonzero magnetic moment for the nucleus as a whole. Without the presence of an external magnetic field, the spins of the different nuclei are randomly oriented, and thus the magnetic moment arisen from the spins is canceled out.

Hydrogen (^1H) consists of a single proton, and is sometimes referred to as “proton”. This single proton in ^1H results in a net magnetic moment; it acts as a dipole that can be modeled as a miniature compass needle. The dipolar property and the large quantity of ^1H in the body make it a suitable nucleus for imaging.

The dipole is affected by an external magnetic field (B_0). The nuclei will experience a torque from the B_0, and start to wobble and rotate around the field lines of the external field; this is called precession. B_0 interacts with the spin of the protons causing them to line up as small compass needles parallel or anti-parallel to the direction of the magnetic field (z-direction). Energy is required to cause a transition from a parallel (lower energy state) to an anti-parallel orientation of the magnetic dipole moment. The randomly oriented transverse vectors are canceled out. In a bulk matter, the number of protons with parallel magnetic moments is slightly higher than those with anti-parallel magnetic moments, this creates a net magnetization (M_0) in the same direction as the main field (z-direction).

Due to the spin of the nuclei, the process of alignment with the external field occurs in circular movements. At what speed the nucleus precesses depends on its unique gyromagnetic constant (γ) and the external field strength. The rotation frequency is called the Larmor frequency (ω), which is measured in cycles per second or Hertz (Hz).

$$\omega = \gamma \cdot B_0$$

For example, the gyromagnetic constant for ^1H is 42.58 MHz/T, and when calculating with a field strength of 1.5T (the field strength of the MR scanner used in this thesis), the Larmor frequency will be 63.87 MHZ.

In order to generate a detectable MR signal the protons in the state of equilibrium with B_0 must be put out of balance; the spins are then excited, and the magnetization is tipped away from the direction of B_0. This is done by briefly applying a radio frequency (RF) pulse perpendicular to the main magnetic field. Only RF waves of the Larmor frequency will transfer energy by resonance to the spins of the nuclei and flip the magnetic vector. When the RF pulse is turned off, the excited nuclei return to their initial equilibrium state (M_0). This relaxation generates a time signal from the scanned body part, the Free Induction Decay (FID), which is picked up by a receiver coil placed around the examined part of the body. As for transmission of the RF pulse, the signal is detected and received perpendicular to B_0.

The relaxation is comprised of two independent processes, T1 and T2. T1 is always longer than T2. The T1 relaxation reflects nuclei falling from the high to low energy state ("The spin-lattice relaxation"). The time T1 is defined as the time for 63% recovery of the longitudinal magnetization (i.e., return to equilibrium in the direction of B_0). Simultaneously relaxation in the transverse plane occurs. T2 reflects the decay of transverse magnetization due to loss of phase coherence among the precessing nuclei ("The spin-spin relaxation"); T2 denotes the time at which the transverse magnetization has decayed to 37% of its maximum strength in the transverse plane.

To create a spatial encoding for an MR image, there are three main steps; slice selection, frequency- and phase encoding, respectively. With the use of dedicated coils, gradient fields are applied in three planes (x, y and z) within the external magnetic field (B_0). The gradient coils in the x, y and z plane are utilized in combination of each other, and the field strength may be increased in any desired direction; this enables slice positioning.
Only the protons in the selected slice of the scanned body part are excited by an RF pulse. An applied gradient will give faster or slower precession of the protons depending on the position within the selected slice. This position-dependent change in frequency is termed frequency encoding. The final step is the phase encoding, which is accomplished by applying yet another gradient, perpendicular to the frequency encoding direction. By this a phase shift is induced to the slice. The phase encoding is repeated several times at different amplitudes, but with the same orientation all the time. The MR signal originating from different positions along the phase encoding direction, will have different phases. The signals emitted from the selected slice are picked up by a receiver coil and a grid of raw data is created (k-space). In the dataset each point corresponds to a unique combination of frequency and phase, and contain information about the entire image. The data is thereafter reconstructed into an image (through inverse Fourier transformation).

A key to the contrast in MR images is that the T1 and T2 relaxation times differ among various tissues in the human body. The macromolecular environment and the magnetic field strength influence the relaxation time. In general, the greater the percentage of free water the longer T1 and T2 relaxation times, but T1 is always longer than T2. Manipulation of the net magnetization can be done in many ways to generate data; different pulse sequences and imaging protocols are used to optimally visualize the contrast differences between tissues in different body parts. Furthermore the presence of contrast agents may enhance the contrast. In this thesis the paramagnetic properties of Gadolinium (Gd^{3+}), in the form of Gd-$DTPA^{2-}$ (Magnevist®), is used. The paramagnetic ion shortens the T1 relaxation time. In this thesis, T1 in the presence of Gd-$DTPA^{2-}$ will be referred to as (T1(Gd)).

3.1 QUANTITATIVE MRI OF CARTILAGE

Most available data of cartilage biology is based on in vitro studies from experimental research and animal models, but several imaging techniques have evolved to examine the human cartilage quality in vivo. As the integrity of the cartilage is based on the interactions of its components, changes in both the GAG content and in the collagen fiber network are of interest when evaluating the cartilage quality[157]. In this thesis T2 mapping (without contrast) and measurements of T1 relaxation times (without and with the presence of Gd-DTPA^{2-}) are used. Both T2 mapping and dGEMRIC are good predictive tools for better understanding the mechanical properties of the cartilage[157,158].

3.1.1 T2 mapping

There is a significant relation between T2 relaxation and the collagen content of articular cartilage[159,160]. Hence, processes affecting the collagen may be evaluated by measuring T2 relaxation. The sensitivity of T2 to collagen has been attributed to the dipolar coupling of the spins of the collagen associated water, which provides an extra source of T2 relaxation in cartilage[161,162]. The strength of this dipolar interaction is orientation-dependent and the interaction is at its minimum at 54.7°relative to B_0, i.e. at “the magic angle”. At the magic angle there will be an augmentation of the signal intensity indicating increased T2 relaxation time[162,163].

Depending on the orientation of the collagen fibers in relation to the static magnetic field (B_0), the dipolar interactions will vary between the different zones of the articular cartilage. T2 will have a depth-wise pattern sensitive to the integrity and the three-dimensional arrangement of the collagen network[159,160,163]. This spatial variation is seen in normal cartilage[164,165]. Cartilage T2 rises from approximately 10 ms near the bone to approximately 60 ms near the articular surface[166].

In addition to collagen, the T2 may also be influenced by the GAG and water content[166–168]. For example, even though the GAG content itself does not correlate to T2, the GAGs may affect the packing and orientation of the of collagen fibers. Therefore, loss of GAG alters the water content in the cartilage and affects T2[167,169].

Since spontaneous cartilage degeneration involves progressive disruption of the collagen network, T2 mapping is suitable when studying cartilage quality[159,168,170–172]. Generally, there is an elevation of T2 in early osteoarthritis[173,174]. Furthermore, a correlation between long T2 values and future degenerative cartilage changes indicates a prognostic value of T2 mapping regarding OA development[175]. T2 mapping has also been used in studies of cartilage repair where shortening of T2 has been found after micro-fracturing and in fibrous healing of cartilage defects[176,177].

3.1.2 delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC)

Analysis of T1 in the presence of a paramagnetic contrast agent is used in dGEMRIC to estimate the GAG content of the cartilage in vivo. The method was introduced in the late 1990’s by Bashir, Burstein and Gray[178,179]. Bashir et al. found a strong correlation between the GAG concentration and T1(Gd) in vitro[178]. Studies have validated the dGEMRIC technique both in vitro and in vivo[173,180–182]. The intra- and inter observer variability is low, and the repeatability is high[183,184]. With dGEMRIC, it has been possible to detect reduced cartilage quality in different patient groups, for example, after ACL injury and after partial meniscectomy[185,186]. In 2009 Watanabe et al. described that dGEMRIC could be a useful method to detect degenerative cartilage changes in adults with recurrent patellar dislocation[187]. The T1Gd values generated from the use of dGEMRIC has also been shown to predict the development of knee osteoarthritis in patients with arthroscopic cartilage aberrations[188].

In dGEMRIC, a negatively charged contrast agent containing gadolinium, namely Gd-DTPA^{2-} (Magnevist®), is injected intravenously and distributes into the cartilage by diffusion. As the diffusion takes time, a time period is needed between the injection of the contrast agent and the scanning; for that reason the letter “d” for delayed is used in the name of the method. Furthermore, it has been shown that approximately 5-15 minutes of joint movement after contrast injection is necessary in order to achieve adequate diffusion of the contrast medium into the cartilage[179,189–191].

Gd-DTPA^{2-} has a double negative charge and will distribute inversely proportional to the negatively charged GAGs in the cartilage. Healthy cartilage rich in negatively charged GAG repel the Gd-DTPA^{2-}. According to the principle of electro-neutrality, the concentration of Gd-DTPA^{2-} will be relatively low in healthy cartilage with a high FCD, and high in cartilage with less GAG. Gd-DTPA^{2-} provides a local magnetic moment that will shorten the T1 relaxation time and the difference between T1 without contrast (T1pre) and with contrast present (T1(Gd)) can be used to estimate the GAG content in the cartilage. T1(Gd) serves as a surrogate marker for the GAG concentration.

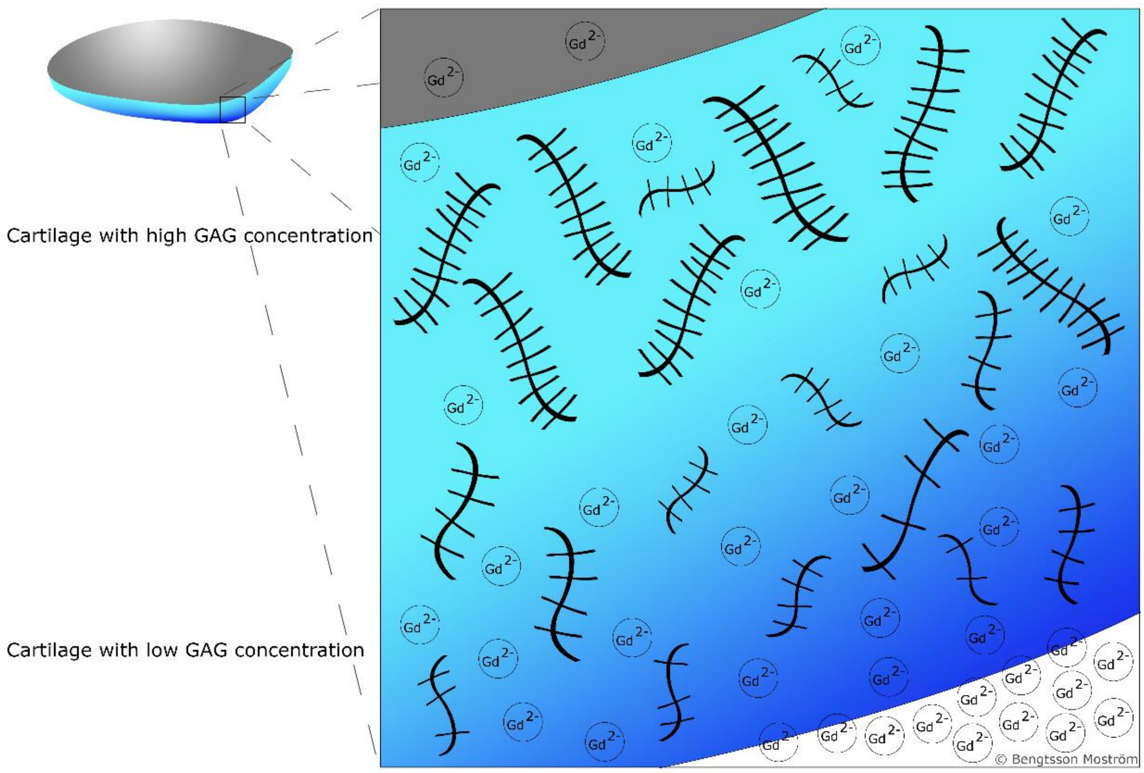

Figure 2. In dGEMRIC the distribution of Gd-DTPA^{2-} is inversely proportional to the concentration of negatively charged glycosaminoglycans (GAG). Cartilage regions with less GAG will be richer in Gd-DTPA^{2-} and this will shorten the T1(Gd).

4 AIMS OF THE THESIS

The overall aim of this thesis is to evaluate the long-term effects after traumatic patellar dislocation in childhood

- To evaluate two measurements of medio-lateral knee position, the Single-limb mini squat test (reliability), and the Q-angle (reliability and reference values), in healthy children

- To describe the long-term results regarding recurrence rate, and objective- and subjective knee function after first-time traumatic patellar dislocation

- To study the quality, and risk of degenerative changes, in the patellar cartilage after non-operatively and operatively treated recurrent patellar dislocations

5 METHODS

5.1 PARTICIPANTS AND DATA COLLECTION (STUDY I-IV)

Study I
A total of 253 healthy children were recruited from three schools in Stockholm, Sweden. Seven children were excluded due to self-reported earlier surgical treatment to the lower extremities, leaving 246 healthy children (9-16 years) included in the final analysis. All children were tested twice or by two examiners in the reliability analysis (intra-/inter-rater reliability for the Q-angle n =37/85 and for Single limb mini squat test n=33/28). During analysis, subjects were divided into groups depending on age and sex (9-11, 12-14, and 15-16). The legs were tested bilaterally for both tests; however, only data collected from the dominant leg were used for reliability analyses.

Data collection took place in conjunction with the children´s physical education classes at school. They were assessed approximately one week apart. Evaluation of dynamic medio-lateral knee position was conducted during the single limb mini squat test. The static medio-lateral knee position was measured by the Q-angle. Two physiotherapists assessed the Single limb mini squat test, and one physiotherapist and one orthopedic surgeon measured the Q-angle. Examiners were blinded to each other's measurements during the two tests. An interrater training session of measurements was performed for both measurements prior to data collection. The evaluation time lasted approximately 5-10 minutes per session for each subject.

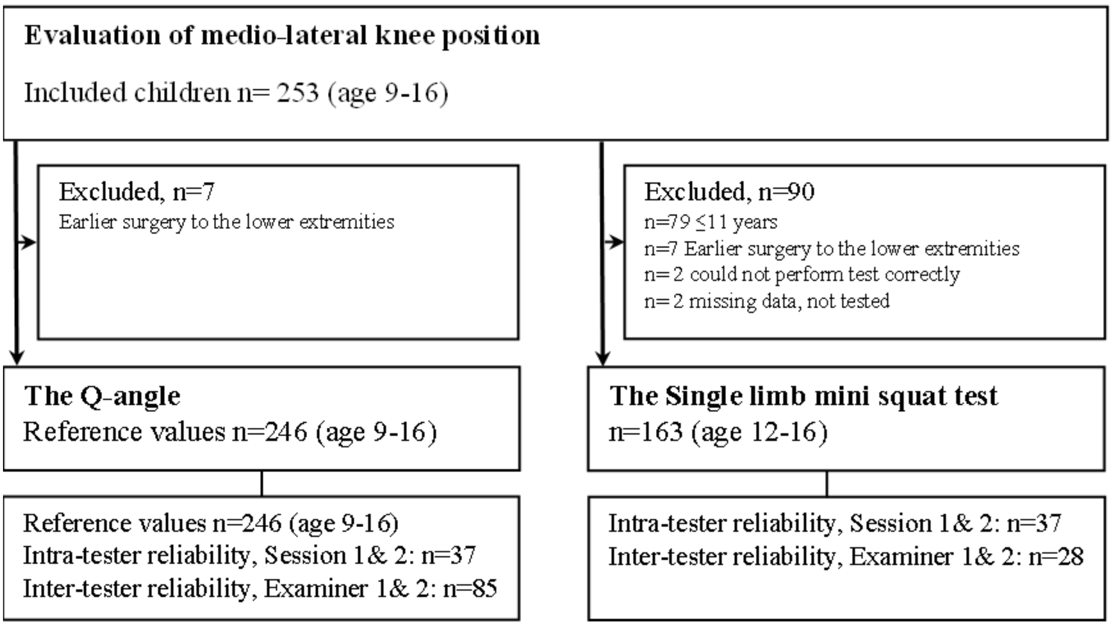

Figure 3. Participants in study I.

Study II

We retrospectively retrieved 83 consecutive patients, 9-14 years old, at index dislocation with primary traumatic patellar dislocation admitted to the emergency unit at Astrid Lindgren Children´s Hospital between 1998 and 2004. Seventy-two (87%) patients participated in the study. There was bilateral involvement in 21 cases (29%). The patients with bilateral involvement were excluded from further analysis because several of the patients were unable to provide reliable information regarding the recurrence rate for the left and right knee separately. Thus, the study group consists of 51 patients with unilateral patellar dislocation, open or partially open physes around the knee at the time of injury and with no previous history of knee injuries or other medical conditions that could influence knee function. The follow-up time was ≥ 5 years.

The patients were divided into subgroups according to obtained treatment from index dislocation to follow-up, and the results were compared between the groups:
(i) Group A: non-operatively treated.
(ii) Group B: operated in the acute phase due to osteochondral fragment ≥1 cm^2 from weight-bearing joint surface.
(iii) Group C: operatively treated due to recurrence.

Study III

Participants were recruited from the non-operatively treated group in study II (group A); twenty-two of the non-operatively treated patients reported recurrent patellar dislocations at follow up, and were invited to participate in study III. Three patients declined participation. One patient could not perform the MRI examination due to claustrophobia, and two patients were excluded due to motion artefacts. Thus, the study group consists of 16 non-operatively treated patients (32 knees) with more than two dislocations after the index injury. All patients participated in regular physical activities (with a workout rate of 1-3 times a week), but no one participated in sports at an elite level. The non-injured knee served as a control. The minimum follow-up time was set to ≥5 years after the first patellar dislocation.

Study IV

By searching the medical charts from 1998-2008 at Astrid Lindgrens Children`s Hospital, we identified 49 cases who met the following inclusion criteria: a unilateral first-time traumatic patellar dislocation before 15 years of age, with open or partially open physes around the knee at the time of the index injury, and operated at 9-16 years of age due to recurrence after a trial of non-surgical treatment, and no other reported knee injuries. We could establish contact with 23 of the 49 patients; 18 accepted participation. Three of the patients included had also participated in study II (group C). One patient was excluded from the analysis due to motion artefacts in the MR images. Thus, the study group consists of 17 unilaterally operated patients. The non-injured knee served as a control. The minimum follow-up time was set to ≥5 years after the patellar stabilizing surgery.

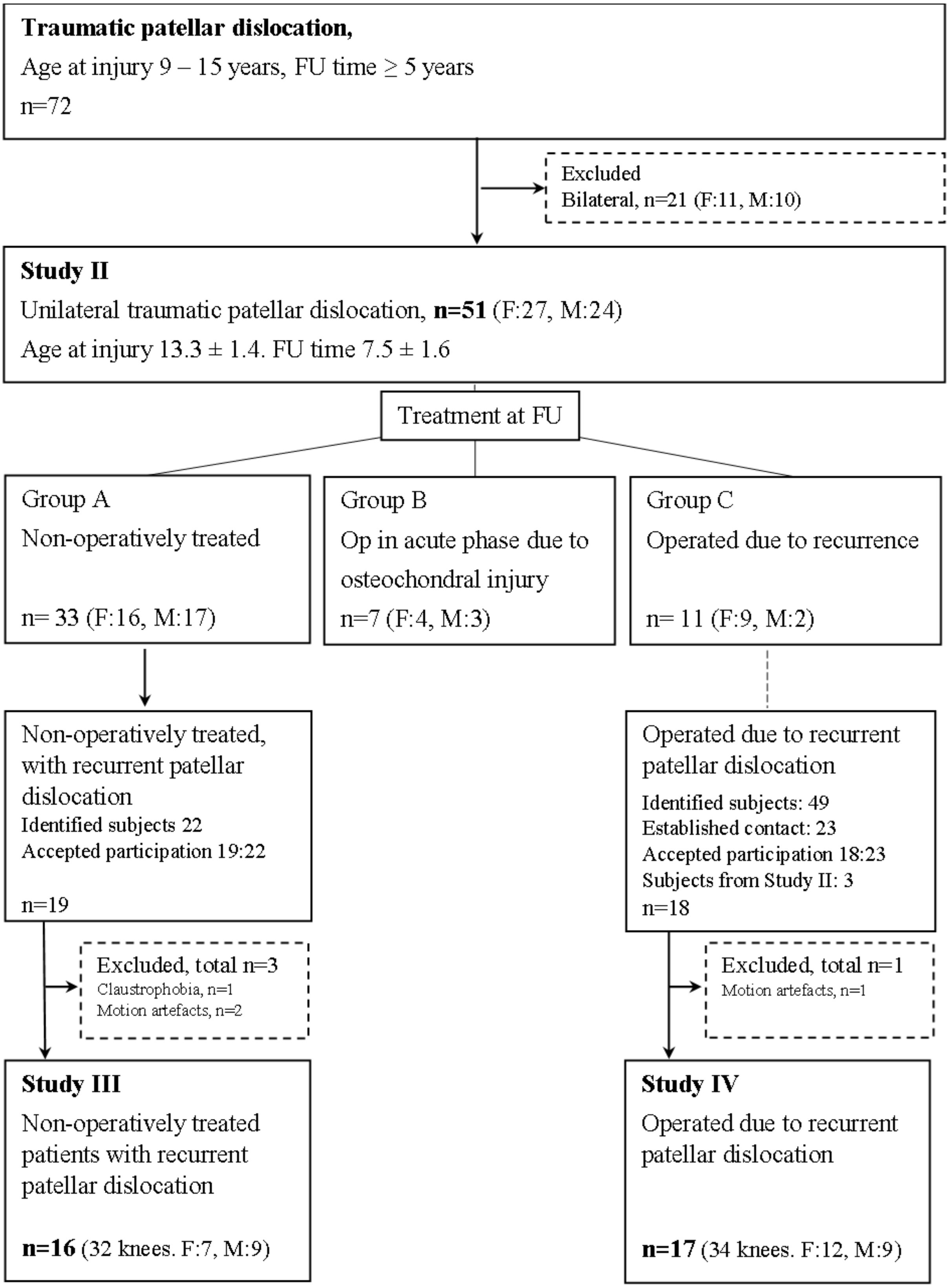

Figure 4. Participants in Study II, III and IV.

5.2 EVALUATION METHODS

5.2.1 Objective knee function

The Quadriceps–angle (Study I)
Measurement of the Quadriceps angle (Q-angle) was performed to evaluate the static medio-lateral knee position. With the child in supine position with hip and knee extended and the quadriceps muscle relaxed, the Q-angle was measured with a standardized goniometer with extended arms. The Q-angle (in degrees) was measured with one arm from the anterior superior iliac spine (ASIS) of the pelvic bone to the center of the patella and the other arm from the center of the patella to the tibial tubercle.

The Single-limb mini squat test (Study I, II and III)
The quality aspect of knee motion in this test entails observation of movement during test performance where the observer assess "knee medial to foot" position, whereas *the quantitative aspect* involves the maximum number of knee bendings on one leg in 30 seconds as a measure of knee function[192,193].
In study I, the Single-limb mini squat test was used as a functional and dynamic test of the medio-lateral knee position. In this study, the focus was on the quality aspect and assessment of the knee position in relation to the ankle, even though the number of knee bendings were registered simultaneously. A positive outcome was defined as the knee observed to be medial to the second toe of the foot any time during the 30 seconds of the test. The subject stood on one leg with fingertip support for balance and to direct the hip to decrease the risk of rotation from hip and trunk. The foot was placed on a T-shaped mark taped on the floor with the foot placed on the stem of the "T" with second toe on the stem. The subject was asked to bend the knee without bending the trunk forward until the subject could not see the foot and then return to extended position. This corresponds to approximately 50˚ of knee flexion. They were instructed to perform as many knee flexions as possible during 30 seconds. The subjects were not aware of the observation of the knee position during the test.
In study II and III the quantitative aspect of the Single-limb test was used and referred to as "the 30 s mini squat test" [192,193]. One 30 s mini squat test was performed on each side, and the maximum number of knee bends in 30 s was registered. The follow-up examination was conducted by authors who were not involved in the treatment of the patients. In study II and III the leg symmetry index (LSI) of the 30 s mini squat test was analyzed.

ROM (Study II)
The ROM in the lower extremities was evaluated and measured with a long arm goniometer.

Concentric thigh muscle torque (Study II and III)
A calibrated Biodex isokinetic dynamometer (Biodex Corporation, Shirley, New York, U.S.A.) was used to measure thigh muscle torque, defined as peak torque at a single maximal voluntary contraction. An angular velocity of 90°/s, and a ROM of 10-90° was chosen for all trials. Concentric knee extension and flexion were measured separately and five maximal trials were performed for each test; then the highest peak torque was selected for further analysis. Both knees were tested, and the healthy knee served as control. The muscle performance was expressed as peak torque/ body weight, and the hamstrings to quadriceps ratio (H/Q) was calculated. LSI of the muscle performance was analyzed.

Weight and Body mass index (BMI) (Study II, III and IV)
In study II and III, weight and height was registered to assess muscle function in relation to body size. BMI was calculated (weight (kg)/ (10 length (m)²) to enable BMI correction for the dGEMRIC results in study III and IV (see imaging section).

5.2.2 Subjective knee function

Study II, III and IV:
Kujala score[194]: A self-administered knee specific scale for anterior knee pain commonly used to assess patellofemoral problems. It contains 13 items that assess: limp, mobility, aid dependency, walking, stairs, squatting, running, jumping, prolonged sitting with knee flexed, pain, swelling, instability, thigh atrophy and flexion deficiency. The score range from 0 to 100, and low scores represent greater disability. A normal value is 99 in a healthy population. A change in 8-10 p is needed to detect a difference of clinical importance[195]. The Kujala score has been shown to be able to differentiate statistically between the first-time dislocation group and those with a history of subluxation/dislocation[52].

The knee injury and osteoarthritis outcome score (KOOS)[196]: A 42-item self- administered knee-specific questionnaire assessing *pain, symptoms, activities of daily living, sports and recreation,* and *quality of life* in five separate subscales. Lower scores representing greater disability. KOOS has been validated for short- and long-term follow-up studies of knee injury and OA. The minimal detectable change ranges from 6-12 for knee injuries[197]. A clinical significant difference is often considered to be 10 units. Normal reference values from a healthy population have been presented for different age groups[198].

Tegner activity level scale[199]: A self-administered activity level questionnaire. The subject chooses which level of activity best describes their function and sporting participation. Levels range from 0 to 10; a score between 0 and 4 covers activities in daily living and work, and a score between 5 and 10 indicates if the subject participates in recreational or competitive sports. Lower scores representing lower activity level in pivoting activities.

The redislocation rate
The redislocations were self-reported by the subjects.

5.2.3 Radiological evaluation

Study II
At follow-up, all available radiographs and MRI from the index injury were reassessed by two of the authors. The lateral view of the radiographs was evaluated for trochlear dysplasia according to Dejour and recorded as dysplastic or not[67,71]. In the absence of perfect lateral radiographs, the presence of dysplasia was based on both the lateral and the axial views (shallow trochlea >145°). Patella alta was defined as a CDI >1.2[76].

5.2.4 MR Imaging

Study III and IV
Serum creatinine was analysed before the MRI examination to ensure normal renal function (creatinine levels below 100 µmol/l). MRI examination of both the affected and the asymptomatic knee was conducted in a Philips Achieva®1.5T scanner with a dedicated

knee coil. The non-injured knee of each subject served as a healthy control. Pre-contrast T1 and T2 mapping of both knees was performed before contrast injection.
To achieve the same position in both the pre- and post-contrast series, the patella was marked at the apex, the proximal pole, and at the centre. The patients were scanned in supine position with the rectus femoris muscle relaxed and the patella stabilized with an inflatable cushion. Apex patella was placed according to the central line of the knee coil. The injured knee was scanned first, immediately followed by the non-injured knee. The slices used for T1 and T2 analysis were positioned centrally over the patella in the transverse plane. Anatomical landmarks were matched, and slice selection was made manually by the same researcher in order to obtain reproducible images between the pre-contrast and the post-contrast T1 series.

The following sequence was used for T1 mapping of the patellar cartilage, both pre-contrast and post-contrast: 2D inversion recovery fast spin echo (FOV=12 cm, matrix 256*256, TR=2000 ms, TE=15 ms, six TI's of 1600, 800, 400, 200, 100 and 50 ms, ETL=5, slice thickness=3 mm, number of averages=2).

Sequences for T2 mapping: Multi-slice multiecho spin echo (FOV=12 cm, matrix 256*256, TR=2000 ms, eight TE's between 9 and 72 ms, ETL=8, slice thickness=3 mm, number of averages=1). In addition to quantitative MRI, proton density weighted images were obtained in transversal, sagittal, and coronal orientations.

After the T2 mapping and pre-contrast T1 series, the patient was given a double dose, i.e. 0.2 mM/kg (0.4 ml/kg) injection of Gd-DTPA^{2-} (Magnevist®, Schering Ag, Berlin, Germany), intravenously. Five minutes after contrast injection, the subject walked up and down the stairs for ten minutes. The ten-minute exercise was performed to facilitate the diffusion of the contrast agent into the cartilage. Two hours after contrast injection, post-contrast imaging was performed. Each patient was carefully repositioned in the MR scanner, including slice selection, in order to achieve identical anatomical landmarks as with the pre-contrast scan.

Regions of interest (ROIs): Segmentation of ROIs for T1 and T2 calculations were done using an in-house MATLAB application (MATLAB R2010, MathWorks Inc, Natick, MA). The patellar cartilage was divided in a lateral and a medial area through the apex of the patella. The medial and the lateral cartilage were thereafter divided in two sections, thereby generating four sectors, sector I – IV from the lateral to the medial border. The patellar cartilage was further divided into a deep and a superficial half, resulting in eight ROIs, four deep and four superficial, see figure 5.

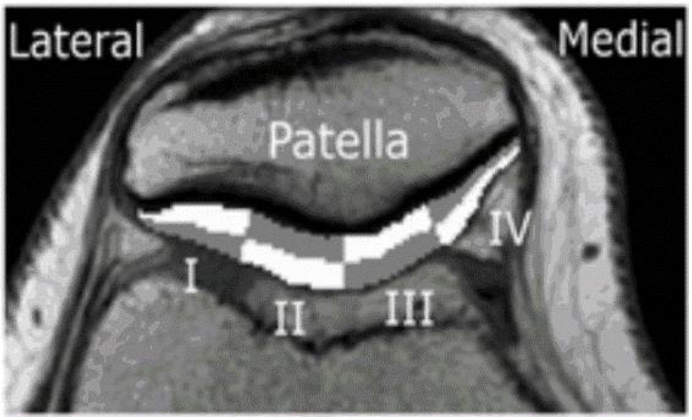

Figure 5. Regions of Interest (ROI) of the patellar cartilage. Sector I-IV, from lateral to medial.

To standardize the procedure, all ROI segmentations were done by one researcher and re-evaluated by another researcher. In cases of discrepancies between the two investigators, segments were re-evaluated, and a consensus was reached.

Post-contrast T1 and delta R1 values were corrected for BMI differences[200]. In study III, Delta R1 values were calculated according to the formula:

$$\text{Delta R1} = (1/\text{T1(Gd)}-(1/\text{T1precontrast}).$$

Conventional images (PD weighted, T1 and T2 series) obtained at the same level as the selected slice for the T1 and T2 analysis were evaluated for macroscopic cartilage lesions by a senior radiologist. Detected cartilage lesions were classified according to the modified Outerbridge classification system[201]. The relationship between cartilage status according to the Outerbridge classification and the functional imaging parameter, the T1 pre-contrast, the T1(Gd), and the T2 values were analyzed for all knees.

5.3 STATISTICAL METHODS AND DATA ANALYSIS

<u>Study I</u>

Analysis was performed using Statistica Software. The level of significance was set at $p < 0.05$. Reference values for the Q angle were presented as degrees and for the Single limb mini squat test the amount of subjects classified as positive.

Reliability

To analyze the data from the Single limb mini squat test, Cohen´s Kappa and percentage of perfect agreement were used to evaluate the reliability and the results interpreted according to Landis and Koch (0.80-1.00 almost perfect agreement, 0.61-0.80 substantial agreement, 0.41-0.60 moderate agreement, 0.21-0.40 fair agreement, and 0-0.20 poor agreement) [202]. An ANOVA was used to test if there was a systematic difference between examiners end test occasions. ICC was complemented with the Standard Error of Measurements (SEM) to measure the precision of the instrument [203]. The Smallest Detectable Change (SDC)/ repeatability coefficient was calculated to determine the clinical change apart from the measurement error.

Differences between legs, sex and age groups

To evaluate any differences in Q-angle between dominant and non-dominant leg, sex, and age groups, a three-way ANOVA was calculated. Possible leg asymmetry of the Q-angle was evaluated using the Leg Symmetry Index (highest Q-angle/ lowest Q-angle*100). For the Single limb mini squat test (categorical data), a Sign test was used when evaluating leg symmetry.

Association between tests was analyzed by using univariate linear regression analysis.

<u>Study II, III, and IV</u>

In study II, III, and IV, the software program IBM SPSS Statistics® was used (version 20 and version 22). In all studies, the level of significance was set at $p < 0.05$.

Using the Shapiro Wilks test of normality, the MR parameters in study III and IV were tested and found to be normally distributed, whereas the knee function was not (study II, III and IV).

In study II, an ANOVA was used in combination with non-parametric tests (i.e., the Mann Whitney U test, the Spearman rho correlation test, the Chi square test, and the Fisher exact test, respectively).

To evaluate any differences in quantitative MR parameters between affected knee and healthy control, region, and subject, a three-way ANOVA was used in study III. Paired T-tests were used thereafter to detect localization of regional differences. In study IV, we chose to analyse paired T-tests directly and present the separate regions. When analysing subjective and objective knee function and the correlations to MR findings in study III and IV, non-parametric tests were used (i.e. MannWhitney U test, Spearman rho correlation, and Wilcoxon signed rank test).

Power analysis and sample size calculation

To assess if the number of subjects identified in the different treatment groups in study II was sufficient to evaluate differences in recurrence rate between non-operatively treated patients and patients subjected to surgery due to recurrence a power analysis was conducted. The sample size calculation in study II was based on the results from two earlier publications of children: by Palmu et al. (recurrence rate of 71% in non-operatively treated patients) and Luhmann et al. (recurrence rate of 7% in operatively treated patients)[95,204]. To detect a reduction of the recurrence rate of 64% under the assumption of a one-sided type 1 error rate of 0.05 and a power of 80%, at least 8 patients were needed in each group.
To detect a significant difference of 10 units (SD ±15) in either the Kujala score or the KOOS under the assumption of a two-sided type 1 error rate of 0.05 and a power of 80%, at least 36 patients were needed in each group, and to detect a difference of 20 units, 9 patients were sufficient in each group.

Sample size calculations for study III and IV were based on the results from an earlier study of patellar cartilage[187] and the assumption that a difference in T1Gd between injured and healthy patellar cartilage of approximately 15 % would be of clinical importance in this young study population. We chose 17% in our calculations. The sample size requirement was calculated with a power of 80%, a type 1 error (α) 0.05, and an estimated effect size of 0.8. A minimum of 15 patients with unilateral, recurrent patellar dislocation needed to be enrolled in each study and the contralateral non-injured knees served as healthy controls.

5.4 ETHICAL CONSIDERATIONS

All studies were approved by the regional ethics board of Stockholm and conducted according to the Declaration of Helsinki. Participation was voluntarily. Oral and written information was given to all participants. Written consent to participate was obtained from the adults, and from parent or legal guardian when applicable.

6 RESULTS

6.1 EVALUATION OF TWO CLINICAL TESTS MEASURING MEDIO-LATERAL KNEE POSITION (STUDY I)

The Single Limb Mini Squat test
During assessment of medio-lateral knee position in healthy children, 36% of the patients were classified as “knee medial to foot”. No side-to-side difference could be seen (p=0.27). A moderate reliability was noted: Intra-rater: kappa 0.48 CI 0.16-0.79, 76% perfect agreement; Inter-rater: kappa 0.57 CI0.30-0.85, 79% perfect agreement.

The Q-angle
A fair to moderate reliability was found for the Q-angle measurements: Intra-rater: ICC 0.42, 95% CI 0.11-0.66, SEM 1.4˚, repeatability coefficient 3.9˚ n.s.; Inter-rater: ICC 0.35, 95% CI 0.14-0.52, SEM 1.9˚, repeatability coefficient 5.3˚ n.s. Hence, the ICC values were below the suggested criterion values for good reliability in terms of both intra- and inter-rater reliability[202].

The pediatric reference values (mean ± SD) of the static medio-lateral knee position measured by the Q-angle ranged between 13.5 (1.9) – 15.3 (2.8) (Table 2). No side-to-side difference and no gender difference was detected. There was a difference between the age groups (p=0.034).

No association was found between the single limb mini squat test (dynamic knee position) and the Q-angle (static knee position).

Age	Boys dominant	Boys Non-dominant	Girls dominant	Girls Non-dominant
9-11	13.5 (1.9)	13.4 (2.0)	14.3 (2.1)	14.4 (2.0)
12-14	14.3 (1.8)	14.2 (2.0)	15.3 (2.8)	15.3 (2.8)
15-16	14.7 (2.5)	14.5 (2.9)	14.2 (2.0)	14.3 (2.1)

Table 2. Q-angle, reference values, mean and standard deviation (SD).

6.2 LONG-TERM RESULTS REGARDING RECURRENCE RATE AND OBJECTIVE- AND SUBJECTIVE KNEE FUNCTION AFTER FIRST-TIME TRAUMATIC PATELLAR DISLOCATION (STUDY II)

The study group consists of 51 patients, 29 girls and 22 boys, mean age of 13.3±1.4 at the time of injury, mean follow- up time 7.5 ± 1.6 years.

Group A (n=33): non-operatively treated patients at follow-up. 22 (67%) of these patients reported recurrent dislocations, but had not sought medical care. The mean recurrence rate was 3.9 (range, 2–11).
Group B (n=7): operated in the acute phase due to a torn osteochondral fragment ≥1 cm^2, from weight-bearing joint surface. Three of the patients (43%) reported redislocations
Group C (n=11): operatively treated patients due to recurrence. Mean time from operation to follow up 4.3±3.1 years. Preoperatively, these patients had a mean recurrence rate of 4.5 (range, 1–15). Two patients (18%) had a single redislocation postoperatively.

At the time of the index injury, 20 (39%) patients had normal radiographs, and 26 (51%) patients had torn fragments from the medial border of the patella. In addition, in five (10%) patients, the radiographs disclosed loose bodies. 41 patients (80%) underwent MRI or arthroscopy in the acute phase.

Articular cartilage lesions (i.e., osteochondral fracture fragments, chondral fragments, or fissures) were reported in 32 cases (78%) of the patients who underwent MRI or arthroscopy. A lesion on the non-weight-bearing surface of the lateral femur condyle/epicondyle was observed in 22 knees. In 10 knees, a lesion on the patellar joint surface and/or the weight-bearing surface of the lateral femur condyle was observed. In seven patients, an osteochondral fragment ≥ 1 cm^2 in diameter was torn from weight-bearing joint surface, and they were operated on in the acute phase (group B). Six of the patients were treated with re-fixation of the fragment, but in one case, the osteochondral injury was fragmented and consequently removed. In all seven cases, proximal realignment was conducted.

At follow-up, all patients had a normal ROM. According to KOOS the patients were mainly affected in *sports and recreation* and *quality of life*, if the mean values are compared to normal for the age. No significant differences in PRO could be detected between the groups. The recurrence rate did not correlate with objective knee-function or PRO. There was no difference in the rates of trochlear dysplasia or patella alta between patients with or without recurrence. The presence of cartilage lesions did not influence either objective knee function or PRO. The redislocation rate in the non-operated patients in study group A was significantly higher than in the operated group C, although, no significant differences in terms of objective knee function or PRO were observed between the groups. Details are presented in Table 3 a, and b.

Unilateral Patellar dislocation n= 51	**Group A Non-operatively treated** n= 33	**Group B Treated operatively during acute phase** n=7	**Group C Treated operatively due to recurrence** n= 11
Girls : Boys	16 : 17	4 : 3	9 : 2
Age at injury (years)[a]	13.5 ± 1.3	12.6 ± 2.3	13.3 ± 1.5
Follow-up time (years)[a]	7.7 ± 1.5	7.0 ± 1.4	7.3 ± 1.5
Trochlear dysplasia	67% (22 of 33)	83% (5 of 6)	64% (7 of 11)
Patella Alta	33% (11 of 33)	33% (2 of 6)	38% (3 of 8)
Redislocation after latest treatment [b]	67% (22 of 33)	43% (3 of 7)	18% (2 of 11)

Table 3a. Study II**,** patient demographics and recurrence rate at follow-up.
[a] The results are presented as the mean ± 1 SD
[b] ≥1 redislocation

Unilateral Patellar dislocation **n= 51**	**Group A** **Non-operatively treated** **n= 33**	**Group B** **Treated operatively during acute phase** **n=7**	**Group C** **Treated operatively due to recurrence** **n= 11**
Subjective knee function[a] KOOS subscales at follow-up[b]			
- Pain (M=92, F=92)	90 ± 14	92 ± 8	86 ± 9
- Symptoms (M=87, F=89)	82 ± 14	82 ± 11	78 ± 12
- Activities in daily living (M=94, F=95)	94 ± 12	97 ± 4	93 ± 6
- Sports and recreation (M=85, F=86)	77 ± 24	79 ± 15	66 ± 17
- Quality of life (M=85, F=84)	69 ± 20	76 ± 19	60 ± 14
Kujala at follow-up[c]	84 ± 10	84 ± 7	75 ± 15
Objective knee function[a] Peak torque/body weight			
- Extension (90 degr/s)	187.2 ± 59.5 M: 220 ± 43 F: 152 ± 56	195.6 ± 57.4 M: 242 ± 50 F: 161 ± 34	157.9 ± 63.2 M: 231 ± 30 F: 142 ± 57
- Flexion (90 degr/s)	106.3 ± 34.4 M: 128 ± 26 F: 83 ± 27	103.6 ± 31.7 M: 124 ± 36 F: 88 ± 20	113.8 ± 57.6 M: 208 ± 77 F: 93 ± 26
- H/Q ratio[e]	0.58 ± 0.16	0.54 ± 0.12	1.03 ± 1.30
LSI, peak torque in extension[f]	86 ± 17%	89 ± 15%	81 ± 32%
30 s mini squat test injured[f]	35 ± 15	36 ± 18	34 ± 13
LSI, 30 s mini squat test[g]	93 ± 21%	97 ± 8%	99 ± 32%

Table 3b. Study II, knee function at follow up.

[a] The results are presented as the mean ± 1 SD
[b] KOOS values in parentheses are the reference mean values reported for males ,M, and females, F, 18-34 years of age in a population-based study by Paradowski et al.[198].
[c] Healthy individuals score 99.9 [194]
[d] Mean values of 42 knees
[e] HQ ratio: Hamstrings to Quadriceps ratio, normal value <0.6 [59]
[f] Healthy adults mean 30 knee bends in 30s [193]
[g] LSI: leg symmetry index, < 85% of the unaffected side is considered pathological [56]

6.3 THE QUALITY, AND RISK OF DEGENERATIVE CHANGES, IN THE PATELLAR CARTILAGE AFTER NON-OPERATIVELY TREATED RECURRENT PATELLAR DISLOCATIONS IN CHILDHOOD (STUDY III)

The mean age at injury was 13.7 years (11.9-15), and age at follow-up 22.2 years (17.9-26.2). The follow-up time 8.5 years (5.8-11.5) after the first patellar dislocation, and the mean number of redislocations was 5.3 (2-10).

T1 pre-contrast

T1 pre-contrast was longer in the superficial compared to the deep half of the cartilage in both the injured and the non-injured knee. No difference was detected between injured and the control knee in either the superficial half or in the deep half of the cartilage.

T1 post-contrast, T1(Gd)

T1(Gd) was longer in the deep compared to the superficial half of the cartilage in both injured and control knees. Comparing T1(Gd) of the injured and the non-injured knee, a significant decrease in T1(Gd) in the superficial half of the cartilage in the injured knee was detected ($p= 0.046$). In the central sector of the medial patellar cartilage (sector III), T1(Gd) was 317 ± 45 ms in the injured knee compared to 340 ± 49 ms in the control knee ($p= 0.031$). No significant difference was found in the deep cartilage regions.

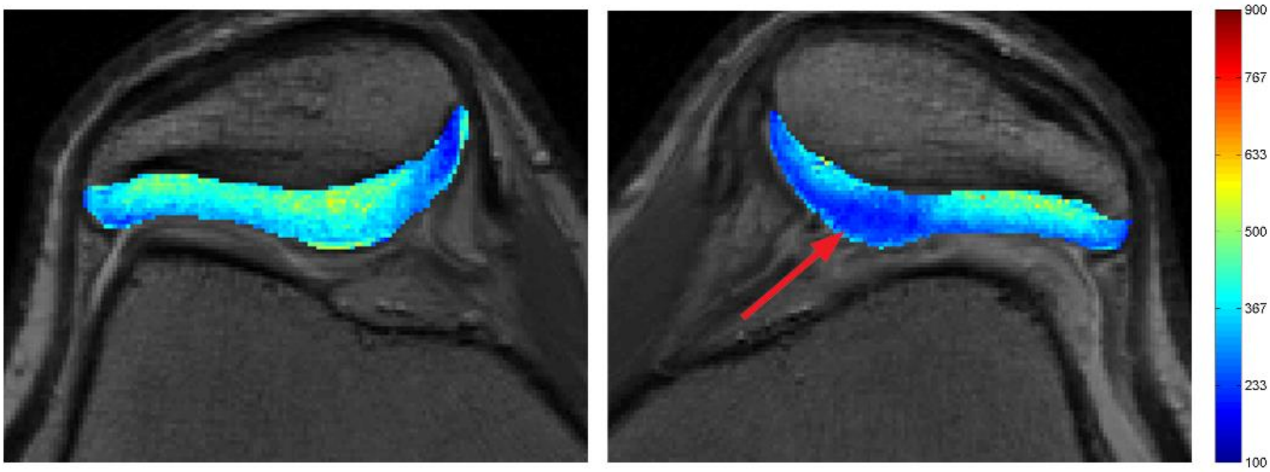

Figure 6. T1(Gd) images of the patellar cartilage of a patient with non-operatively treated unilateral recurrent patellar dislocations. The right, non- injured patella and the left, injured patella. Note the low dGEMRIC index in the central region of the injured knee (arrow).

Delta R1

When analysing delta R1, which reflects the contrast medium concentration in the cartilage, the results corresponded well with T1(Gd); a significant increase in sector III in injured knees (delta R1= $3.12 \pm 0.5\ s^{-1}$) compared to non-injured knees (delta R1= $2.92 \pm 0.5\ s^{-1}$), ($p=0.048$).

T2

Longer T2 values were found in the superficial half of the cartilage compared to the deeper layer in both injured and control knees. When comparing the injured to the control knee, a significant difference was seen in the superficial half of the cartilage in the peripheral regions, i.e., in other cartilage areas than what was seen with T1(Gd). In the most lateral sector (I) and the most medial sector (IV), the injured knee demonstrated significantly *shorter* T2 values compared to the non-injured side. For example, T2 of the superficial half of the cartilage of sector I was 42.0 ± 5.1 ms in the injured knee compared to 44.8 ± 5.1 ms in the contralateral side ($p = 0.003$). There were no significant T2 differences between injured and reference knees in the deep layer.

Outerbridge classification and correlation with quantitative MRI

According to the modified Outerbridge classification of cartilage lesions, 3 patients had a grade 1 lesion (abnormal signal in the cartilage, without contour defects), and 4 patients had a grade 2 lesion (contour defects of less than or equal to 50% of the cartilage thickness) of the patella. All lesions were located centrally, corresponding to sector III. No patients were diagnosed with grade 3 (contour defects >50% and < 100% of cartilage thickness) or grade 4 lesions (full-thickness contour defects). No significant correlations were found between the T1 pre-contrast, T1(Gd) or T2 values and the grade of the cartilage lesions.

Knee function

In general, subjective knee function was fairly good according to KOOS and Kujala. However, the patients had a lower KOOS than a corresponding age group regarding quality of life and participation in sports and recreations[198]. The Kujala score revealed problems related to patellar dislocations. Activity level according to Tegner showed a mean value of 5.1.

The single limb mini squat test did not reveal any significant differences between the injured and non-injured side, and functional results were normal. The extensor muscle function (peak torque of the injured knee as a percentage of the non-injured knee) was impaired with a mean value of 82%, which is slightly under what is considered normal (i.e., ≥85%). The difference could not be explained by the influence of the dominant leg.

Neither the subjective nor the objective knee functions were correlated to any of the MR parameters used in this study. Gender, age at injury, recurrence rate, and activity level did not correlate to degenerative cartilage changes measured by dGEMRIC or T2.

6.4 THE QUALITY, AND RISK OF DEGENERATIVE CHANGES, IN THE PATELLAR CARTILAGE AFTER OPERATIVELY TREATED RECURRENT PATELLAR DISLOCATIONS IN CHILDHOOD (STUDY IV)

The mean age at index injury was 11.8 years (8.0-15.0). The mean time from index injury to operation was 1.8 years (0.4-5.7), the mean follow-up time from index injury was 13.4 years (10.7-19.3), and from surgery to follow-up 11.6 years (8.8-15.0).

The mean number of redislocations prior to the operation was 8 (2-22). Six patients experienced 1-2 subluxations within the first 12 months after surgery. 3 patients had proximal realignment surgery only, and in 14 the distal alignment was also in need of correction. The recurrence rate or the type of surgery was not correlated to PRO, T2, or T1(Gd) findings at follow up.

T2

The T2 values were longer in the superficial half of the cartilage in both operated and control knees. The analysis of the T2 bulk values of operated compared to healthy control knee detected significantly longer T2 in the most medial sector (IV) of the operated knee ($p=0.023$). When the cartilage was divided into a deep and a superficial half, the difference between the operated and control was located in the deep half of sector IV. T2 in the deep half of sector IV was 34 ± 7 ms in the operated knee compared to 28 ± 6 ms in the healthy knee ($p= 0.016$). No significant difference could be seen in the superficial half of the cartilage.

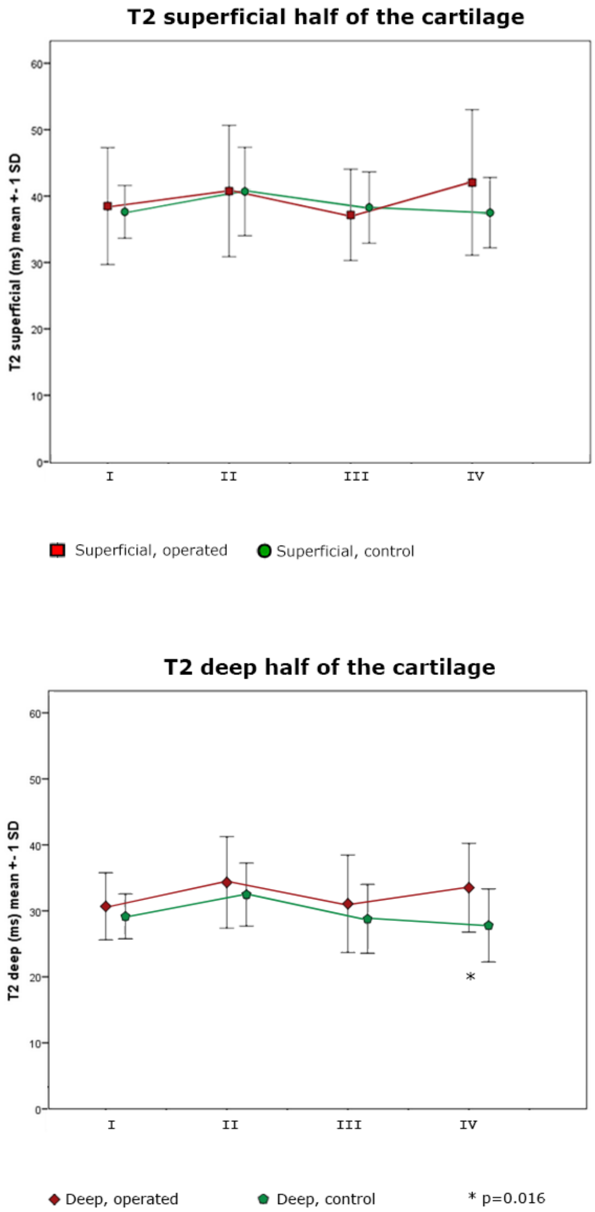

Figure 7. T2 mapping. A significant difference was detected most medially in the deep half of the patellar cartilage with longer T2 on the operated side ($p= 0.016$), but not in the superficial half. Operated (red) and control (green) side. Sectors from lateral (I) to medial (IV).

T1 Post contrast, T1(Gd)

T1(Gd) revealed longer values in the deep compared to the superficial half of the cartilage in both injured and asymptomatic knees. Comparing T1(Gd) of the operated with the control knee, a significant decrease in bulk T1(Gd) in the central sector of the medial patellar cartilage III (p=0.048) was detected. When the superficial half- and the deep half of the cartilage were analysed separately, a significant difference was seen in the deep half of sector III. In the deep cartilage of sector III the T1(Gd) was 497 ± 94 ms in the operated knee compared to 562 ± 96 ms in the healthy knee (p= 0.016).Whereas no differences could be detected in the superficial half of the cartilage.

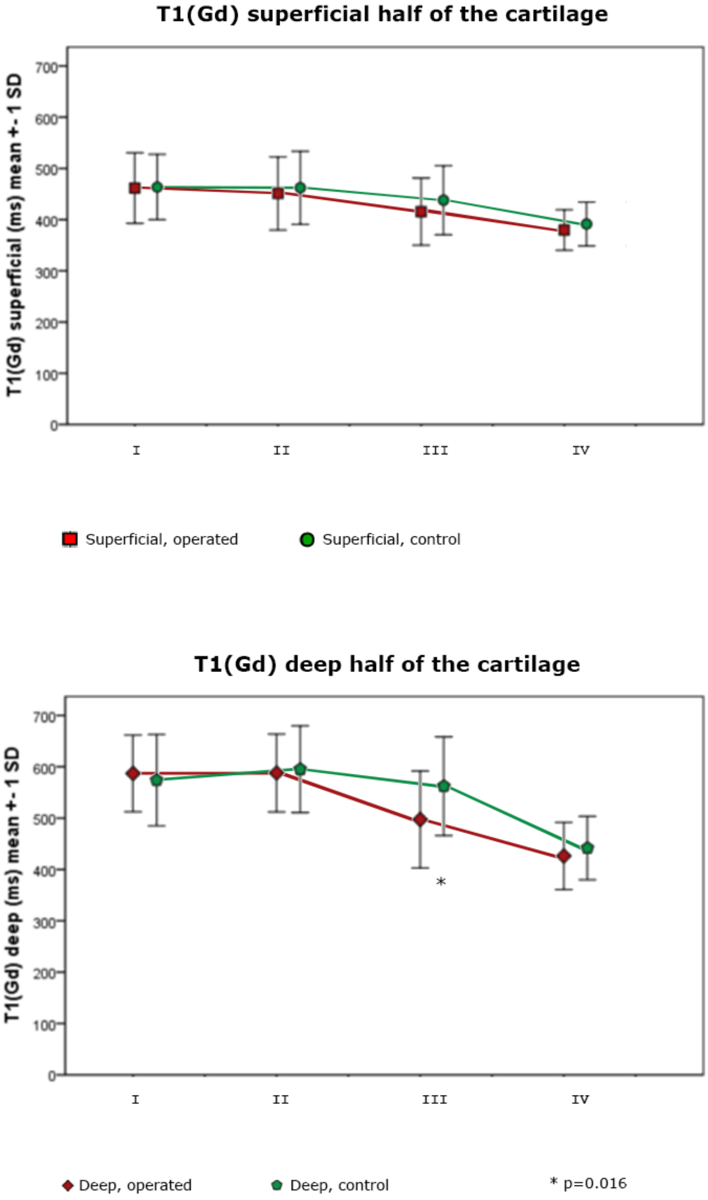

Figure 8. T1(Gd) in the superficial half of the patellar cartilage did not reveal any significant differences between operated (red) and control (green) side. In the deep half of the cartilage T1(Gd) was significantly shorter in the central part of the medial facet (sector III) on the operated side compared to control(p=0.016). Sectors from lateral (I) to medial (IV).

Outerbridge classification and correlation with quantitative MRI
The modified Outerbridge classification of cartilage lesions revealed 2 patients with grade 1 lesions (abnormal signal in the cartilage, without contour defects) and 4 patients with grade 2 lesions (contour defects of less than or equal to 50% of the cartilage thickness) of the patella. All lesions were located centrally, corresponding to sector III. No significant correlations were found between the T1(Gd) or the T2 values and the grade of the cartilage lesions.

Subjective Knee function
In all five subscales of the KOOS, the patients scored lower than a corresponding age group of asymptomatic individuals [198]. They had significantly lower values in KOOS *ADL, Sports and Recreation* and *Quality of life* when compared to non-operatively treated patients with recurrent patellar dislocations (Study III).The Kujala score revealed problems related to anterior knee pain. The patients participated in recreational sports activities 1-5 times a week. The mean activity level according to Tegner was 4.

There was no correlation between sex, age at injury, number of redislocations, PRO, activity level, and the T2 values. The T1(Gd) of the deep half of the cartilage in sector III in the operated knee, was correlated to *both* the KOOS *symptom* ($p = 0.041$) *and* KOOS *sports and recreation* ($p=0.041$) but not to sex, age at injury, recurrence rate, activity level, or follow-up time.

7 DISCUSSION

7.1 EVALUATION OF TWO MEASUREMENTS OF MEDIO-LATERAL KNEE POSITION (STUDY I)

The Single-Limb Mini Squat test
The Single-limb mini squat test is a reliable method to evaluate the dynamic medio-lateral knee position in adults with osteoarthritis[192,193]. Visual assessment of the medio-lateral knee position has been found to have a good validity in adults evaluated using movement analysis[192]. As previously mentioned, the Single-limb mini squat test has a quantitative and a qualitative aspect. In this study the Single-limb mini squat test was evaluated for reliability regarding the qualitative aspect in children, assessing the position of the knee in relation to the foot while performing the knee bends (“knee-neutral-to foot” or “medial-to-foot”). The findings in this study support the use of the Single limb mini squat test to evaluate the dynamic medio-lateral knee position in a pediatric population because the intra-and interrater reliability results agreed in more than 75% of the cases.

When evaluating the validity of the Single limb mini squat test in adults Aageberg et al. found that the knee was in more valgus in patients with “knee-medial-to-foot” compared to “neutral” in the 2D motion analysis (frontal plane) and regarded the test as valid, although, the 3D analysis demonstrated that the appearance of a “knee- medial-to-foot” was mainly exhibited as an increased internal rotation of the hip[192]. Even so, the qualitative aspect of the test can be of value as greater internal hip rotation has been seen in knee disorders, for example in patients with patellofemoral pain syndrome[205]. However, in children, the range of motion in the lower extremities is age dependent, and changes over time. For example, the anteversion of the femoral neck, is approximately 25˚ at 8 years of age and gradually decrease to the adult mean of 16˚ around 14-16 years of age[16]. Since the internal rotation is related to the anteversion of the femoral neck this might affect the quality aspect of the

Single-limb mini squat test in the younger children. The validity of the test has not yet been evaluated in children and needs to be considered in future research.

The Q-angle
In the literature there has been a debate of the clinical relevance of the Q-angle[52]. The result that the Q-angle has low reliability (ICC 0.35-0.42) in children is an important finding that points to the importance of more thorough evaluation tools to assess the knee in a child. The high Smallest Detectable Change (SDC) for the Q-angle ranged from 4˚ to 5˚, which means that a difference of more than 5˚ is needed to detect a "true" difference beyond the measurement error. This is a rather high value, considering the mean value in the population was found to range between 13˚ and 23˚. A statistical difference was found between age groups in this study, but the clinical importance of that is questionable as the mean difference was only 1.2˚ between the groups with a correspondingly large measurement error. There was a lack of difference between girls and boys in the present study is inconsistent with some previous studies that report higher q-angles among female than male subjects[206,207]. This may be explained by different measuring points applied, or by differences in how the age groups were divided.

Correlations between the Q-angle and its radiological equivalent, the TTTG distance, has been reported to be good in adults[208]. On the contrary, it has also been reported a negative correlation between the Q-angle and the TTTG distance[209]. With respect to the low reliability of the Q-angle shown in this study it is not advisable to solely rely on the clinical measurement. Instead of measuring the Q-angle, other attempts to evaluate the patellofemoral joint geometry by external measuring points have been done. Shakespeare et al. aimed to evaluate the TTTG distance clinically, and compared the measurements with MRI but with poor results, constantly underestimating the distance in the patients with patellar instability[210].On the contrary, measuring the TTTG distance on CT or MRI scans is a reliable method to estimate the direction of the quadriceps acting on the patella in adults[78,79] and is regarded as a more adequate assessment tool. When this study was conducted no studies of the TTTG distance in a pediatric population were available. In later years, the TTTG distance has been found to increase with age and height in children and adolescents[80]. Consequently, what can be regarded as a pathological TTTG distance may wary with maturity and further studies of children are needed.

Not only is the reliability of measuring the Q-angle in children low, but it may also be an inadequate estimate of the patellar alignment as the center of the patella may not lie directly over the center of the femoral groove when the knee is in full extension; furthermore, the patellar ridge is usually asymmetrically placed. Because of the low reliability, we do not recommend the Q-angle as a measurement of the static medio-lateral knee position.

7.2 LONG-TERM RESULTS REGARDING RECURRENCE RATE, OBJECTIVE- AND SUBJECTIVE KNEE FUNCTION AFTER FIRST-TIME TRAUMATIC PATELLAR DISLOCATION (STUDY II)

At index injury, the rate of trochlear dysplasia and patella alta were similar to the frequency observed in other studies of skeletally immature patients with patellar dislocation. Lewallen et al. reported trochlear dysplasia in 69% of cases and patella alta in 42% of cases with open physes and patellar dislocation. They presented a significant hazard ratio of 3.3 for redislocation in patients with trochlear dysplasia and open growth plates, but patella alta was *not* correlated to recurrence[89]. Several other studies have reported opposite results regarding patella alta in adults[211]. In the present study, neither trochlear dysplasia nor patella alta were correlated to the recurrence rate. The lack correlation between the above mentioned anatomical risk factors and recurrence rate might be due to the relatively small number of patients.

Articular cartilage lesions were reported in 78% of the cases, which is an incidence consistent with previous reports of skeletally immature patients[48,212].The presence or the site of the osteochondral injury did not affect the outcome.

Patients who were surgically treated due to persistent instability (group C) had a significantly lower recurrence rate than the non-operatively treated group (group A): 18% compared to 67%. Even though surgery prevented recurrence in group C, the subjective outcome was worse than expected. Similar findings have also been reported by Luhmann et al.[204]. In the group of patients subjected to surgery during the acute phase, due to a large osteochondral fragment (group B,) the recurrence rate was as high as 43%. The groups are too small, and the retrospective design of the study, limits the ability to draw any firm conclusions from this difference.

Despite that all patients were participating in physical activities on a weekly basis patients operated due to recurrence had a persistent reduction in the knee extensor muscle function with pathological mean H/Q ratio value (>0.6). This relative weakness of the knee extensor muscles was the only pathology related to objective knee function that was observed in our study might indicate a permanent change in the musculature after injury and surgery[115,213]. Similar to our results in the surgically treated patients (group C), Oliva et al. also disclosed residual lower extensor muscle performance in the operated limbs after patellar stabilizing surgery[214]. An increased co-activation of the hamstrings in daily life due to instability or early osteoarthritis may contribute to the pathological H/Q ratio[215].Even though we found a relative weakness in the extensor muscles in group C, the great variability in within the group (H/Q-ratio 1.03 ± 1.30) calls for caution in the interpretation of the result.

Traumatic patellar dislocation in skeletally immature patients influences subjective knee function in the long-term. According to the PRO a negative impact on the KOOS variables *sports/recreation* and *quality of life* were detected, and the Kujala score was also lower than in healthy individuals. This is in accordance with a previous study of the outcome after acute surgical repair of the medial structures compared to conservative treatment of children with acute patellar dislocation[95]. Impaired subjective knee function was seen in all three treatment groups with a tendency towards lower PRO in group C, but the present study is underpowered for statistical analysis regarding a clinical significant difference in PRO of 10 units[216]. The similarity between the treatment groups might be related to development of degenerative changes in both operated and conservatively treated patients[111,187,217,218]. Both the instability and the altered biomechanics after surgery can contribute to a negative processes in the cartilage[144,145]. Perhaps the cartilage degeneration is of greater significance in the long run than a reduced recurrence rate.

In this study, the surgery of choice was not individualized enough and failed to properly address the predisposing factors and the injury pattern to the MPFL. MPFL reconstruction might be a more anatomic approach in several cases with recurrence[106,219,220]. MPFL reconstruction in children and adolescents with recurrent patellar dislocation has been shown to be an effective method with respect to recurrence and return to sports in a 2.8 (2.0-3.6) year follow up, but a high-grade trochlear dysplasia might be a risk factor for inferior results[100]. However, there is a need to evaluate the results of MPFL reconstruction in skeletally immature patients in an even longer perspective to detect eventual differences compared to traditional surgical methods regarding knee function and risk of cartilage degeneration. The results after the traditional surgical treatment in the present study can serve as a baseline when newer and more customized surgical techniques for skeletally immature patients are evaluated in the future.

7.3 THE QUALITY, AND THE RISK OF DEGENERATIVE CHANGES, IN THE PATELLAR CARTILAGE AFTER NON-OPERATIVELY AND OPERATIVELY TREATED RECURRENT PATELLAR DISLOCATIONS (STUDY III AND IV)

Despite fairly young and active subjects, there were differences between injured/ operated and control knees in both the T1(Gd) and the T2 series. The conventional MR sequences did not reveal high grade cartilage lesions that could be explanatory to the findings. What we detected with quantitative MRI can be considered as early cartilage changes involving different processes in the cartilage. Detecting these early cartilage changes is a very important first step. Based on the knowledge that physical activity has a positive effect on the GAG content, and that the GAG can be improved by physical exercise[221,222]; specific physical exercise programs could be the next step as a preventive strategy for these patients.

Analysis of the quantitative MR parameters revealed a depth-wise difference between the superficial and the deep half of the cartilage. This was detected for both the T1 and the T2 series in both the patients with recurrent patellar dislocation and those who were operated due to recurrence. The depth-wise differences resemble what can be expected in healthy cartilage, indicating that a very early stage of impaired cartilage function was observed in the studies. The generally longer T1(Gd) in the deep compared to the superficial cartilage was in accordance with previous findings by Hawezi et al.[190]. Longer T1(Gd) in the deep cartilage not solely depends on the molecular integrity, such as a higher GAG concentration, but also on slower diffusion of the contrast medium from the synovial fluid into the deep cartilage regions[121,190]. Consequently, the difference we observe in T1(Gd) between the deep and the superficial half of the cartilage after 2 hours was expected. The T2 series presented longer T2 values in the superficial compared to the deep half of the cartilage in both affected and control knees in both patient groups. This T2 pattern has previously been described in normal cartilage[165]. In the growing child, the histological pattern, and thereby also the T2 relaxation time, will gradually mature to adult T2 pattern with a gradual lengthening of the T2 towards the surface[10,165]. Our findings indicate that despite recurrent dislocations or patellar stabilizing surgery, during growth, organisation of the collagen network has occurred. Though, the two studies revealed different findings when the ROIs were further analysed.

Shorter T1(Gd) indicates less GAG in the affected knee compared to the healthy contralateral knee[223,224]. The localization of the early cartilage changes reflected by shorter T1(Gd) are similar to where degenerative changes were described in previous studies of patellar dislocations in adults with recurrent patellar dislocations[151,187]. Notably, in the patients with non-operatively treated recurrent patellar dislocations (Study III), a low dGEMRIC index was observed only in the *superficial half* of the cartilage. In patients operated on due to recurrences (Study IV) the decreased dGEMRIC index was found only in the *deep half* of the cartilage and not in the superficial part.

Most likely, the different dGEMRIC pattern in the two studies reflects different aspects of altered biomechanics in the patellofemoral joint in recurrent instability compared to the conditions after surgery. First, in recurrent patellar dislocation, it is most likely that in the central part of the patella, which is highly exposed to the shear force, there is loss of tissue integrity and an insufficient attempt of reparation. This leads to loss of proteoglycans, reflected by the decrease in T1(Gd) superficially. Incongruence and instability in the femuropatellar joint might influence the load of the cartilage altering the metabolic activity of the chondrocytes[132]. Secondly, the surgical stabilization, which was successful with respect to recurrence, might have altered the biomechanics. The axial load, i.e., the pressure between the patella and the femur may have increased. Several studies have demonstrated a potential risk of shift in load from lateral to medial (corresponding to our sector III) after patellar stabilizing surgery[25,109,225–227]. It could be hypothesised that increased focal strain in sector III after surgery has impeded the synthesis of proteoglycans in the deep cartilage layer[133,226,228,229]. Perhaps also the diffusion could be affected.

Similar to what we saw in the T1(Gd) series, the T2 series differed between the non-operatively treated and the surgically stabilized subjects; with changes in the superficial half of the cartilage in study III and in the deep half of the cartilage in study IV. Unexpectedly, analysis of the T2 series in the non-operatively treated patients (Study III) showed slightly *shorter* T2 values in the superficial half of the cartilage in the peripheral sectors (Sector I and IV) of the injured knee compared to healthy control knee. According to most published data, degenerative cartilage changes are associated with longer T2 values as a result of cartilage swelling secondary to disruption of the collagen network[230,231]. There are, however, other *in vivo* studies that have also reported shortening of T2 in cartilage pathology. Most of these studies did not analyze native hyaline cartilage, but fibrous cartilage after micro-fracturing or repair tissue after autologous chondrocyte transplantation[176,232]. A shortening of T2 has also been reported after running; as an effect of cyclic compressive loading of the cartilage[233]. The decrease in T2 noted in the periphery might be the result of an up-regulation and an increased synthesis of extracellular matrix proteins at this very early stage of cartilage degeneration. This contention was also suggested in a publication by Casula et al. where middle-age patients with early cartilage pathology at arthroscopy demonstrated shorter T2 values than patients with arthroscopically normal cartilage[234]. We consider that the observed T2 decrease in study III indicates a reparative attempt in the cartilage and reflects a very early stage of joint pathology. In later stages of the degenerative disease, T2 increases as a result of fibrillation and disruption of the collagen network.

In study IV, *longer* T2 was registered most medially (sector IV) in the deep half of the cartilage of the operated compared to the healthy side. The longer T2 is consistent with most published data, and longer T2 is associated with degenerative cartilage changes and a risk of future development of OA[175,231]. It could also be speculated that the potential shift of load due to the surgical procedures tightening the medial structures also affect the collagen network orientation and integrity in the most medial aspect of the patellar cartilage.

In Study III, we could not detect any correlation between the dGEMRIC index and the peak torque muscle strength, which is inconsistent with the results from adult meniscectomized patients[186]. This might be due to the relatively small size of our study or to the fact that our young patients have very early cartilage changes without major functional deficits. Based on these findings, we decided to abstain from using muscle function tests in study IV.

Surgical treatment almost eliminated the number of patellar dislocations, but the PROs were not restored to normal for their age. Furthermore, the operated patients reported lower KOOS scores compared to the non-operatively treated patients, which is of concern, especially the remarkable low scores in KOOS *Quality of Life*. This difference between non-operatively treated patients and patients operated due to recurrence was not detected in study II.

A shorter T1(Gd) value of the deep half of the cartilage in sector III in the operated knee in study IV was correlated to lower values on KOOS *Symptom* and *Sports and recreation*, but if it is a clinically significant finding is difficult to evaluate. Despite these findings, we consider that the PROs alone might not catch the young patient with very early cartilage degeneration. The number of participants in the studies are too few to draw any firm conclusions of the evaluation tools for subjective knee function in relation to the MR findings.

The pathophysiology of cartilage degeneration is a complex matter, and as described above, several factors may contribute to the findings in this thesis. The effect of repeated trauma to the joint surface of a growing child and the knowledge about potential healing capacity is limited. To the best of our knowledge, these are the first reports using both T2 and dGEMRIC to describe how the cartilage quality is affected by patellar instability and subsequent patellar stabilizing surgery in childhood. The quantitative MR data characterizing these patients are unique; the methods have never been used in this kind of frame of reference before. This project is on the border zone between method development, application and implementation, and provides a survey of cartilage quality in very early degenerative processes

7.4 METHODOLOGICAL CONSIDERATIONS

In study I, both children and adolescents were evaluated. The required number of subjects for reference values was estimated to be 250, and for the reliability calculations at least 32[235]. During data collection children 9-11 years of age were observed discussing their performance scores of the Single-limb mini squat test. Even though the quantitative aspect was not what was evaluated, and despite that the children were tested individually, the children begun performing the test with less accuracy owing to a growing competition. Therefore, we did not include the data from the youngest participants in the analysis of the Single-limb mini squat test. Nevertheless, the final number of participants was considered sufficient. Adolescence is a difficult period to define because of different maturity levels and maturity level according to pubertal grade was not conducted in this study; we therefore chose the term children for all subjects. In study I, the children were divided into age groups 9-11, 12-14 and 15-16; this might have influenced the interpretation of the results and needs to be considered when comparing the results with other studies.

There are limitations in the recruitment process of study II, III and IV. We could not establish contact with all cases with the diagnostic code for traumatic patellar dislocation; and there was also a number of patients who declined participation (13% - 22%). Due to ethical considerations, those who declined participation were not asked why they did not want to participate. Also, the recruitment process differed between study III and IV. In study III all patients were recruited from study II, whereas the majority of patients in study IV were recruited through mail after identification in the hospital charts, and without any prior contact with the examiner. Perhaps an established contact might influence the responses in the PRO measurements and it might also increase the propensity to accept participation in a time consuming examination (3.5 – 4 hours) on a weekend. It could be speculated that persons without limitations, and with good knee function, are less willing to participate in a study and this might have influenced the results.

Dividing subjects into subgroups according to obtained treatment in study II may also influence the results. Due to the relatively small subgroups the study is underpowered to draw valid conclusions regarding the differences in KOOS values in relation to type of obtained treatment. Comparison between the groups may be regarded as descriptive. Despite that acute patellar dislocation is as common among girls as boys, and no differences were found in sex in the non-operatively treated group with recurrence, we saw a tendency to female dominance in the group of patients operated due to recurrence. This female dominance was seen also when searching the medical charts to identify participants for study IV. Whether there are more males than females adapting and adjusting their activities to the condition, or if females experience more instability, cannot be further analyzed in these studies.

We did not find any correlation between sex and MRI findings in either study III or study IV. The sample size in study III and IV is most likely to small to detect differences according to sex. Perhaps the female to male ratio 12:5 in study IV could have influenced the results.

Regarding the patients with motion artefacts in Study III (n=2) and IV (n=1), we chose not to schedule a second examination to avoid contrast agent exposure as we already had reached the required participant number based on the power analysis.

Study III was the first study with detailed segmentation (8 ROIs) of patellar cartilage in patients with recurrent patellar dislocation using T2, T1 pre-contrast, and T1 post-contrast series to evaluate the cartilage quality in vivo. Therefore, we chose to present the T1precontrast, T2 mapping, T1(Gd) series, and the results from Delta R1 calculations in Study III. Based on the results from Study III, where the T1(Gd) and Delta R1 provided us with approximately the same results, we concluded that the dGEMRIC series alone would be sufficient for estimation of the GAG content.

In the time period between study III and IV, the MR scanner was under service and an upgrading of coils and gradient system was done as part of a regular routine. Due to this, the T1 and the T2 relaxation times have most likely been affected, and the actual values from the two studies cannot be statistically compared. Despite this limitation, it is still of interest to see the difference in pattern in the affected knees, where changes in the superficial half was revealed in the non-operatively treated patients, and the changes were seen in the deep half of the cartilage in the operated patients.

7.5 LIMITATIONS

In Study I the children were stratified for age and sex in the statistical analysis. We did not evaluate the pubertal stage or the height or weight. This might have facilitated the interpretation of our results.

The retrospective design of Study II and the heterogenic study population is a limitation. There was a lack of strict indications for surgery; and the compliance to the rehabilitation might influence the outcome but cannot be controlled in this setting. Furthermore, despite the clinical guidelines neither MRI nor arthroscopy was performed at the time of injury in one fifth of the knees.

In study III and IV, the pre- and post-contrast positioning of the patient is done according to marks on the skin, and the selected slice of the post contrast series (T1(Gd)) is fitted to be in level with the pre-contrast series, but even if it is thoroughly done, it might give a small difference between the slices.

Imaging patellar cartilage in vivo at 1.5 T (Study III and IV) provide good resolution but the three histological layers of the cartilage cannot be visualized, segmented, and analyzed separately. This is a limitation of in vivo studies of cartilage. Even if we would have used a 3T scanner available in the clinical practice at our hospital, it would also have been insufficient in that perspective. At 3T one might see the histological zones if high in-plane resolution and large slice thickness is used, though that would mean averaging values across the whole slice depth. Furthermore, the three layers could only be seen where the cartilage is not curved in all directions. Hence, due to the shape of the patella, it is most likely that it could not be visualized in the whole of the patellar cartilage even at 3T. Probably not even clinical 7T can provide that reliable resolution needed, but experimental scanners from 7T upwards equipped with a small bore and a high power gradient amplifier are able to do that. For further knowledge of the histological layers of the cartilage we are still dependent on studies of in vitro samples.

8 CONCLUSIONS AND CLINICAL IMPORTANCE

According to the reliability results the Single-limb mini squat test can be used in a pediatric population, but the Q-angle does not meet suggested criterion values for good reliability. The smallest detectable change in the Q-angle when used in children was 4-5˚, indicating that the difference of <5 ˚ found between age and sex may not be clinically relevant.

Primary patellar dislocation in childhood influence the subjective knee function in a long-term perspective. Traditional surgical methods were successful to reduce the recurrences but did not restore the knee-function.

Recurrent patellar dislocation and patellar stabilizing surgery seem to have a negative effect on cartilage quality; most likely through different biological mechanisms and at different depths of the cartilage. The results from quantitative MRI of the patellar cartilage indicate changes in both GAG content and collagen structure. These new findings show that dGEMRIC, in combination with T2 mapping, are feasible methods to detect early degenerative changes in vivo in this condition.

9 FUTURE PERSPECTIVES

In pediatric orthopedics, there is a need of further development of evaluation methods and treatment guidelines adopted for children. In clinical practice, we need to improve and individualize the treatment and surgical technique according to risk factors, age and maturity of the child. Also, treatments and outcomes after structured rehabilitation in children with patellar dislocation should be evaluated.

Traumatic patellar dislocation affect both the articular cartilage and the subchondral bone; also, bleeding incite an inflammatory response that might disrupt the biology of chondrocytes. These mechanisms should be studied. To evaluate if there are reparative attempts in the cartilage after trauma, experimental in vitro studies in combination with in vivo studies, are necessary. Since patellar dislocations affect a large group of healthy children annually, quantitative MRI studies of this group of patients could increase the knowledge of eventual healing capacity after injury to the joint surface. Also, the role of physical activity and training on the health of cartilage in both children and adults would be valuable to investigate further in order to develop prevention programs for OA.

Longitudinal studies of cartilage quality is necessary to detect up to which stage the degenerative process might be reversible and hopefully respond to treatment in the future. T2 mapping and dGEMRIC can be valuable tools in both research and clinical assessment of other conditions with increased risk of early cartilage degeneration and impaired joint function.

10 SWEDISH SUMMARY

Sammanfattning
Knäskålen (Patella) är en del av sträckapparaten på knäledens framsida, den bidrar till en god funktion genom att centrera lårmuskeln och förbättrar den mekaniska kraftutvecklingen när man sträcker i knäleden. Vid stukning av knäleden kan knäskålens infästning i ledkapseln skadas och den glider ur led (luxerar). Årligen drabbas ca 1: 1 000 barn i åldern 9-15 år. Den första luxationen inträffar vanligen i samband med idrott. Luxationen är smärtsamt, ger upphov till ledutgjutning och hos en hög andel av barnen uppstår skador på ledytan när knäskålen glider ur led. Omkring 50 % riskerar att få upprepade luxationer, vilket kan medföra rädsla och oförmåga att delta i lek och aktiviteter. För upprepade luxationer finns ett flertal kirurgiska behandlingsmetoder föreslagna i den vetenskapliga litteraturen, alla med målet att åstadkomma ökad stabilitet. Trots att knäskålsluxationer är vanliga är det få studier som beskriver hur det går för barnen på längre sikt och behandlingsresultat från vuxna kan inte direkt översättas till barn och ungdomar. Avhandlingen syftar därför till att beskriva hur knäskålsluxation i barndomen påverkar individen i ett långtidsperspektiv.

Utöver problem med upprepade luxationer rapporteras om ogynnsamma långtidsresultat med bl.a. risk för ledförslitning, artros, bland vuxna med knäskålsluxationer. Artros har setts både hos patienter som behandlats icke-kirurgiskt och hos dem som genomgått stabiliserande operation. Ledytebrosket skiljer sig dock mellan barn och vuxna. Under uppväxten mognar och anpassar sig barnets brosk efter ledens belastning; om knäskålsluxationer, eller stabiliserande operation, påverkar ledytebroskets kvalitet är ännu inte beskrivet i detalj.

En välfungerande ledyta är beroende av en balans mellan uppbyggnad och nedbrytning av de beståndsdelar som utgör själva stödjevävnaden. Skador mot ledytan kan starta en ogynnsam nedbrytning, vilket kan leda till artros på sikt. Artros tar decennier att utveckla, men långt innan förlust av brosk kan ses på röntgen sker en nedbrytning av molekyler; proteiner, kollagen och negativt laddade socker kedjor (GAG). Förlust av GAG och kollagen minskar broskets stötdämpande kapacitet.

För att bedöma ledytebroskets molekylära kvalitet i ett tidigt skede har olika avbildningstekniker med magnetkamera (MR) utvecklats. I denna avhandling används kontrastförstärkt MR (dGEMRIC) för att i ett mycket tidigt skede bedöma halten GAG, samt en MR sekvens inriktad på att värdera kollagen och vattenhalt i ledytebrosket. När man ska undersöka halten av negativt laddade GAG får patienten en injektion av likaledes negativt laddat kontrastmedel ($Gd\text{-}DTPA^{2-}$) 2 timmar före MR undersökningen. Kontrastmedlet tas upp i ledytebrosket i omvänd proportion mot koncentrationen av GAG, vilket gör att områden med tidiga tecken på brosknedbrytning mättas med mer kontrastmedel. Den ökade mängden kontrastmedel i brosk som har förlorat GAG påverkar MR-signalen (T1(Gd) blir kortare), vilket ger oss en möjlighet att uppskatta halten GAG. Tekniken gör det möjligt att hitta förändringar i ledytebroskets kvalitet innan det kan ses med konventionella avbildningstekniker.

Avhandlingen består av fyra delarbeten, i det första delarbetet undersöktes friska barn i efterföljande tre undersöktes långtidseffekter av knäskålsluxation i barndomen.

I delarbete I undersöktes 243 barn i åldern 9-16 år utan knäskador för att utvärdera två olika kliniska tester som avspeglar knäledens position. Studien genomfördes för att det finns få kliniska tester som har utvärderats vetenskapligt för bedömning av barns knän och

normalvärden från friska barn har saknats. Delarbete II är en långtidsuppföljning av 52 unga vuxna som i åldern 9-15 år haft en akut knäskålsluxation. I studien undersöktes rörelseomfång, muskelstyrka, samt hur patienterna själva upplevde sin knäfunktion och detta ställdes i relation till vilken typ av behandling de hade fått. Resultaten påvisade att knäskålsluxationer i barndomen har en negativ inverkan på livskvalitet och förmåga att delta i idrottsaktiviteter. En hög andel hade haft upprepade luxationer, för vilket vissa hade sökt vård och genomgått operation. Den kirurgiska behandlingen för upprepade luxationer hade stabiliserat knäskålen väl, men trots att luxationerna upphörde fann vi att förmågan att delta i fysiska aktiviteter och livskvaliteten inte var lika god som bland jämnåriga i befolkningen. I delarbete III och IV undersöktes ledytebroskets kvalitet hos patienter som på en sida haft upprepade knäskålsluxationer. Med ovan beskrivna MR metoder utvärderades knäskålens brosk på skadad sida och jämfördes mot icke-skadad sida. I delarbete III undersöktes patienter som inte hade opererats trots att de haft flera luxationer, medan de som genomgått stabiliserande operation deltog i Studie IV. Syftet var att kartlägga om ledytebroskets kvalitet påverkas om skadorna inträffar i barndomen och om det kan relateras till patientens knäfunktion.

Resultaten visade att i båda patientgrupperna fanns tecken på förändringar i ledytebrosket; både förlust av GAG och påverkan på kollagen påvisades på skadad sida. Förlusten av GAG var belägen centralt, medan kollagenförändringar sågs i utkanten av ledytebrosket i båda studierna. Vad som dock skiljde sig åt var att de icke-opererade hade förändringar i de ytliga delarna av brosket, medan de opererade patienterna endast hade förändringar i den djupare halvan. Fynden påvisar mycket tidiga tecken på nedsatt broskkvalitet som innefattar både förlust av GAG och påverkan på kollagen hos unga vuxna med upprepade knäskålsluxationer.

Sammanfattningsvis stödjer resultaten i delarbete I att undersökning av knäts position vid upprepade mindre knäböj (”The Single-limb mini squat test”) kan användas vid undersökning av barn.

Delarbete II, III och IV visar på att upprepade knäskålsluxationer med debut i barndomen har en negativ inverkan på knäts funktion och individens livskvalitet i ett långt perspektiv. Tidigare kirurgiska behandlingsmetoder för barn med upprepade luxationer gav stabilitet men lyckades inte återupprätta funktionen tillräckligt väl.

Studierna av ledytebrosket påvisade försämrad kvalitet redan i ung vuxen ålder. Våra fynd talar för att både GAG och kollagen strukturen är påverkade. Sannolikt sker dessa förändringar i brosket via olika mekanismer. Hos patienter med upprepade luxationer är det troligt att ytskiktet skadas när knäskålen glider ur led. Hos opererade patienter är det troligt att den förändrade biomekaniken i knäleden också påverkar trycket på ledytan och försämrar broskcellernas kapacitet och funktion på sikt.

Kunskapen om ledytebroskets kapacitet att läka skador är begränsad; risken för framtida artros anses ökad om man drabbas av en ledyteskada. Dessvärre finns ännu inget botemedel för artros. Fysisk aktivitet och riktad träning har dock visat sig medföra gynnsamma effekter på halten GAG i ledytebrosk, vilket talar för att viss kapacitet till reparation och läkning kan finnas i ett tidigt skede. För att möjliggöra framtida prevention och behandling måste man kartlägga och finna stadier där den nedbrytande processen kan vara reversibel, innan artrosen är manifest. Det finns också ett stort behov av att utveckla undersökningsmetoder, kliniska riktlinjer och kirurgiska behandlingar som är anpassade för barn, så att man i framtiden kan erbjuda en mer individualiserad och åldersanpassad behandling av knäskålsluxationer.

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