MAGNETIC RESONANCE IMAGING OF MUSCULOSKELETAL INFLAMMATION IN CHILDREN

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<tr>
<td>C-HAQ</td>
<td>Child health assessment questionnaire</td>
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<tr>
<td>CMAS</td>
<td>Child myositis assessment scale</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>DWI</td>
<td>Diffusion weighted imaging</td>
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<tr>
<td>DAS</td>
<td>Disease activity score</td>
</tr>
<tr>
<td>DCE MRI</td>
<td>Dynamic contrast enhanced magnetic resonance imaging</td>
</tr>
<tr>
<td>dGEMRIC</td>
<td>Delayed gadolinium enhanced magnetic resonance imaging of cartilage</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>GRE</td>
<td>Gradient echo</td>
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<tr>
<td>HAQ</td>
<td>Health Assessment Questionnaire</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leucocyte antigen</td>
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<tr>
<td>IA</td>
<td>Infectious arthritis</td>
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<tr>
<td>ILAR</td>
<td>International League of Association for Rheumatology</td>
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<tr>
<td>IMACS</td>
<td>International Myositis and Clinical Studies Group</td>
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<tr>
<td>JAMRIS</td>
<td>Juvenile MRI scoring</td>
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<tr>
<td>JIA</td>
<td>Juvenile idiopathic arthritis</td>
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<tr>
<td>JDM</td>
<td>Juvenile dermatomyositis</td>
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<tr>
<td>MDI</td>
<td>Myositis damage index</td>
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<tr>
<td>MMT</td>
<td>Manual muscle testing</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NSF</td>
<td>Nephrogenic systemic fibrosis</td>
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<tr>
<td>OMERACT</td>
<td>Outcome measures in rheumatoid arthritis clinical trials</td>
</tr>
<tr>
<td>PA</td>
<td>Post-infectious arthritis</td>
</tr>
<tr>
<td>PACS</td>
<td>Picture archiving and communication system</td>
</tr>
<tr>
<td>PD</td>
<td>Proton density</td>
</tr>
<tr>
<td>PROPELLER</td>
<td>Periodically rotated overlapping parallel lines with enhanced reconstruction</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>RF</td>
<td>Radiofrequency</td>
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<tr>
<td>SAR</td>
<td>Specific absorption rate</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>SE</td>
<td>Spin echo</td>
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<tr>
<td>SF-36</td>
<td>Short Form 36</td>
</tr>
<tr>
<td>SI</td>
<td>Signal intensity</td>
</tr>
<tr>
<td>STIR</td>
<td>Short tau inversion recovery</td>
</tr>
<tr>
<td>TA</td>
<td>Transient arthritis</td>
</tr>
<tr>
<td>TE</td>
<td>Echo time</td>
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<tr>
<td>TMJ</td>
<td>Temporomandibular joint</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition time</td>
</tr>
<tr>
<td>TSE</td>
<td>Turbo spin echo</td>
</tr>
<tr>
<td>UTE</td>
<td>Ultra-short echo time</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cells</td>
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<td>WBMRI</td>
<td>Whole body MRI</td>
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1. LIST OF PAPERS


2. INTRODUCTION

This thesis explores the use of magnetic resonance imaging (MRI) as a diagnostic tool for juvenile idiopathic inflammatory musculoskeletal diseases, with focus on three different issues: the differentiation of subgroups in early childhood arthritis, disk damage in the temporomandibular joint (TMJ) of patients with juvenile idiopathic arthritis (JIA), and the correlation of MRI findings and clinical outcome in patients with juvenile dermatomyositis (JDM).

MRI and ultrasonography do not rely on the use of ionizing radiation and are therefore often the preferred examinations in children. X-ray imaging does not show early bone affection. MRI gives a more complete depiction of the musculoskeletal system than ultrasonography, but it is more resource demanding and may, especially in young children, require sedation.

Musculoskeletal inflammatory disorders may be infectious, due to bacteria, viruses or parasites, or autoimmune-mediated as in rheumatic disorders. An autoimmune disorder occurs when there is inflammation against the patient’s own tissue. The cause of autoimmunity is not fully understood, but an interaction between environmental factors and multiple genes has been proposed. Important issues in the immune response are the endocrine and the autonomic nerve system as mediators (1).

Paediatric rheumatic diseases comprise childhood arthritides and childhood connective tissue diseases, including JIA, reactive arthritis, systemic lupus erythematosus, JDM, scleroderma, the vasculitis syndromes, and other diseases (2). As childhood arthritis and JDM have predominantly musculoskeletal involvement, they are the focus of this thesis.

MRI provide high soft tissue contrast and high spatial resolution imaging of bone, joints and muscles, and it is presumably the most accurate method to depict soft tissue and bone marrow involvement in musculoskeletal inflammation (3-7). Early inflammation may be detected before visible skeletal destruction on conventional x-ray imaging (8, 9). An early and specific diagnosis will therefore be important for treatment stratification and treatment outcome. Today, effective medications, e.g. intra-articular steroid injections, methotrexate and biological
medication, have improved the outcome for several of the children with paediatric rheumatic diseases (10). Validated and reliable diagnostic and monitoring tools are therefore crucial.
3. BACKGROUND

3.1 The musculoskeletal system in children

3.1.1 The skeleton

The development of the musculoskeletal system is not complete until approximately the age of 20 years. In foetal life the bones are preformed in hyaline cartilage. At birth the skeleton is only partly ossified, whereas the mature adult bone consists of compact cortical bone and medullary cancellous bone (11). Diseases that involve the skeleton will alter the structures during a period of growth and will therefore appear differently in children than in adults (12).

Figure 1: The skeletal ossification of the femur and the red bone marrow (red) conversion to yellow marrow (yellow) in a): a new born with cartilaginous epiphysis (blue), b): a child with growth plates and partly ossified epiphysis and c): an adult with closed growth plates. Illustration: Øystein H. Horgmo, University of Oslo.

The gradual change of cartilage into bone (osteogenesis) starts in ossification centres. In a tubular bone the persistence of a cartilage layer (growth plate) between the metaphysis and the
epiphysis allows increase in bone length and bone shape modelling. From about one year of age until bony fusion, the vascular communication between the metaphysis and the epiphysis is minimal, but finally metaphyseal and epiphyseal vessels unit through channels of resorbed calcified cartilage in the growth plate, followed by the final bony fusion. The articular cartilaginous surfaces remain unossified (11).

The ossification process starts at a certain time and continues at a rate characteristic for each bone. There are individual differences, and females antedate males, but the sequences of events show minimal variation (11).

The bone marrow (progenitor cells for blood), vessels and nerves (autonomic and sensory nerves) are present in between the medullary cancellous bone. Simultaneous with the skeletal maturing, the red bone marrow converts to yellow bone marrow also with sequences of events that show minimal variation (Fig. 1). It occurs first in the long bones in the extremities, first in the epiphysis, then in the diaphysis, then takes place in the distal metaphysis and finally in the proximal metaphysis. In the adult, red marrow remains mainly in the axial skeleton (13).

3.1.2 The joints

A synovial joint is a freely movable joint with articulating cartilage (usually hyaline) surfaces and a synovial joint cavity between the articulating bones.

The joint capsule encloses the cavity (Fig. 2) and is composed of an outer fibrous layer and an inner synovial membrane, 1-3 cells thick. Due to the lack of a basement membrane, the synovial layer is an imperfect membrane. Through the perivascular supply, the synovial membrane therefore leaks fluid into the joint, lubricating and providing nutrients to the joint and the cartilage (14).
3.1.3 The temporomandibular joint

The TMJ is a bicondylar articulation involving the articular fossa and the mandibular condyle (Fig. 3). The growth plate is beneath the fibrocartilaginous articular surface of the condyle. At about 12-14 years of age, the cortical bone plate begins to form and is fully developed around the age of 20 (15, 16). The TMJ is divided (often completely) in an upper and a lower compartment by a biconcave non-vascularized fibrocartilaginous disk. The saddle-shaped disk with an anterior two millimetre thick band, a thin centre and a three millimetre thick posterior band, accommodates motion. The retrodiskal tissue is a bilaminar region with two layers of fibres separated by loose, highly vascularized and innervated connective tissue responsible for the production of synovial fluid. The superior temporal lamina (composed of elastic fibres) is attached to the postglenoid process, whereas the inferior lamina (composed of collagen fibres without elastic tissue) fuses with the capsule and the back of the condylar neck. The laminae prevents extreme movement of the disk. The junction of the posterior band and the laminae is normally within ten degrees of the vertical position (11). The anterior extension of the disk is attached to the fibrous capsule partly inserting on the lateral pterygoid muscle (17).
Figure 3: The TMJ in closed (a) and open mouth (b) position. The disk (D) is anteriorly anchored to the lateral pterygoid muscle (LP) and posteriorly to the retrodiskal tissue (RDT) with the superior lamina (S) and the inferior lamina (I). Illustrations: Øystein H. Horgmo, University of Oslo.

3.1.4 The muscles

The skeletal striated muscles are via tendons attached to bones or cartilage. The muscle is sheathed by epimysium, anchoring the muscle tissue to the tendons. The muscle comprises bundles of fascicles each sheathed by perimysium, where the main nerves and blood vessels run (Fig. 4). Each fascicle comprises multiple muscle fibres (muscle cells) each sheathed by
endomysium (18). At birth the muscle fibres have a fixed size. During childhood the muscle fibres increase in diameter and length (19).

Figure 4: The skeletal striated muscle, sheathed with the epimysium (Ep), the fascicles (Fa) sheathed with the perimysium (P) and the main blood vessels (V), and the muscle fibers (Fi) sheathed with endomysium (En). Illustration: Øystein H. Horgmo, University of Oslo.

3.2. Childhood arthritis

3.2.1 Epidemiology and clinical manifestations

Arthritis is inflammation of one or several joints, defined as swelling of a joint or limited range of motion in combination with pain, heat and/or tenderness (20, 21). Childhood arthritis comprises the main subgroups JIA, infectious arthritis (IA), post-infectious arthritis (PA) and transient (also called serous) arthritis (TA), but may also be associated with other conditions.

The incidence of childhood arthritis (<16 years) is about 1/1,000 children per year (22-24). The incidence of IA is about 7/100,000 (22, 24), and TA (the most common subgroup) including PA, is about 80/100,000 (23). PA is a heterogeneous group, but the incidence of TA alone is 40-50/100,000 (22-24). The incidence of JIA is 13-23/100,000 children per year (22, 24-27) and the prevalence is 90-150/100,000 (26-28). IA has no gender predominance, TA and PA are most frequent in boys (22), whereas JIA is most frequent in girls (27). IA is most frequent before the age of 3 years (Fig. 5). Patients with PA are usually older at disease onset.
and are hardly found before the age of 5. TA is most frequent in the ages 3-8 years (24, 29). JIA has a bimodal age distribution with observed age of onset at 1-3 years and at about 9 years (24, 27).

The knee and the hip, followed by the ankle, are the most frequently affected joints in childhood arthritis (Fig. 6). In TA, the most frequently affected joint is the hip, while in JIA the knee and the ankle are the most frequent first manifestations (24, 30). In JIA the TMJ is frequently reported to be involved (31-33).

Diagnosis is based on laboratory tests, joint fluid aspiration and/or radiological imaging. The treatment and follow-up depend on the diagnosis.

3.2.2 Infectious arthritis

IA is usually defined as the presence of bacteria in the synovial fluid by Gram’s stain or culture, or as a white blood cell (WBC) count of at least 50 x 10^9/L (34). Staphylococcus aureus is the most common cause (35, 36). Kingella kingae is also an important pathogen in young children (35, 37). IA may be predicted by erythrocyte sedimentation rate (ESR) > 40 mm/h and WBC > 12 x 10^9 cells/L (38). Adjacent arthritis (septic or aseptic) has been found in up to 40% of children with acute osteomyelitis (39). Misdiagnoses of IA have been reported, and blood- and synovial fluid cultures are often negative (40, 41). It is important to exclude IA at an early stage as IA is potentially life-threatening and requires immediate surgical drainage and/or antibiotics (36, 42).
Figure 5: Age distribution of children with early onset arthritis by diagnostic groups. Adapted after Riise et. al 2006 (24).

Figure 6: Distribution of hip, knee and ankle involvement in children with early onset arthritis by diagnostic groups. Adapted after Riise et. al 2006 (24).
3.2.3 Post-infectious arthritis

PA comprises a heterogenic group including acute rheumatic fever, post-streptococcal arthritis, Lyme arthritis (arthritis following Borrelia burgdorferi infection), and arthritis after genitourinary tract or gastrointestinal tract infections (43-45). Disease duration and long-term course vary.

3.2.4 Transient arthritis

TA is defined as arthritis < six weeks duration (usually lasting 3-10 days) with unknown triggering agent. TA is a self-limiting disease, treated symptomatically (29, 46).

3.2.5 Juvenile idiopathic arthritis

JIA is defined by the International League of Association for Rheumatology (ILAR) as arthritis of unknown aetiology that has persisted for > six weeks with the onset before the age of 16 years, and when other known conditions are excluded (21). JIA is classified after clinical appearance into the following subtypes:

1. Systemic arthritis
2. Oligoarticular arthritis (persistent and extended)
3. Polyarticular arthritis rheumatoid factor negative
4. Polyarticular arthritis rheumatoid factor positive
5. Undifferentiated arthritis
6. Enthesitis related arthritis
7. Psoriasis related arthritis

JIA may lead to permanent disability, and early treatment is needed to prevent joint destruction and secondary growth disturbances (10, 47).

The inflammatory target in JIA is the articular synovial membrane (14). The inflammatory process is a complex biological cascade leading to vasodilation, increased blood flow, increased vascular permeability, exudate and invasion by leukocytes. The synovium may hypertrophy and extend over the articular surfaces (pannus). Pro-inflammatory mediators, such as cytokines, stimulate the inflammatory process including production of enzymes that lead to
damage of supportive tissue, cartilage and bone. More destructive processes may follow instability and dislocation, and the end result may be osseous fusion (14). The inflammation in the bone with hyperaemia and invasion of leucocytes changes the metabolic regulation, inducing the osteoclasts, leading to resorption and local osteoporosis, making the bone vulnerable to damage. Both osteonecrosis and erosions may occur. The growth zones may be affected leading to bone shape abnormalities, bone length discrepancy and axis deviation (48).

3.3 Juvenile dermatomyositis

3.3.1 Epidemiology and clinical manifestations

JDM is a rare disease, but the most frequent juvenile idiopathic inflammatory myopathy (49). Other subtypes are very rare. In contrast to adult dermatomyositis, there is no increased likelihood for developing cancer. The incidence is 0.19-0.32/100,000 children < 16 years per year (49, 50). In the Western world there is a female predominance (50) in contrast to a male predominance in Japan and Saudi Arabia (51, 52). The average age at disease onset is 7 years (50).

3.3.2 Diagnostic criteria

Bohan and Peter’s revised diagnostic criteria for dermatomyositis and polymyositis (53, 54) are not validated for the juvenile population, but are also used in children (55). The criteria are symmetrical reduced muscle strength, elevation of serum muscle enzymes (e.g. creatinine kinase), a characteristic electromyography (EMG), a typical histological pattern in the biopsy and a characteristic rash. For definitive JDM diagnosis, the skin criterion and at least three other criteria must be present, for probable diagnosis, the skin criterion and at least two other criteria must be present.

3.3.3 Clinical manifestations

The onset symptoms are symmetric proximal reduced muscle strength and a characteristic rash; purple discoloration over the eyelids (heliotrope rash) and erythematous patchy skin on extensor surfaces (Gottron papules). Sustained weakness can be caused by chronic inflammation, inactivity or be the consequence of muscle damage (atrophy, fatty infiltration and/or calcinosis). Calcinosis (dystrophic calcifications) occurs in about 30% of the patients
and may occur in muscle, fascia, subcutaneous and/or cutaneous tissue and give persistent soft tissue irritation and oedema. Lipodystrophy, slow loss of subcutaneous and visceral fat and lipoedema may also be a late sequela. Manifestations can be generalized, subtle localized or unilateral (56).

Clinical arthritis has been found to be a common manifestation in patients with JDM, and has been reported to occur in 23–64% of the patients (57). The varying results may indicate that clinical signs of arthritis may be difficult to separate from inflammation in tissues surrounding the joint. The arthritis is often non-erosive.

With treatment the outcome, including the physical function, has improved, and the mortality has been reduced from 30% (before 1960) to less than 2%. Still about 60% of the children have a polycyclic or chronic continuous course (56, 58).

3.3.4 Pathogenesis

JDM is a systemic autoimmune vasculopathy. The inflammatory target is the perivascular tissue, which involves endomysial and perimysial capillaries and arterioles. Endothelial swelling is followed by endothelial necrosis and capillary loss leading to perifascicular atrophy (56).

3.4 MRI

3.4.1 Basic principles of MRI

MRI exploits the magnetic properties of hydrogen atoms. When these positively charged nuclei are placed within the static magnetic field, the hydrogen atoms will align either parallel or antiparallel to the direction of the magnetic field and precess with the Larmor frequency ($\omega$) around the axis of the static magnetic field. The Larmor frequency is given by the gyromagnetic ratio ($\gamma$) of the hydrogen atom (42.576 MHz/tesla) and the strength of the magnetic field ($B_0$) as expressed in the equation:

$$\omega = \gamma \cdot B_0$$
Applying an electromagnetic radiofrequency (RF) pulse with Larmor frequency, the hydrogen atoms will absorb the energy and become excited. The magnetic direction is then destabilized, and the net magnetization vector is tilted away from the z-axis. Once the RF transmitter is turned off, the hydrogen atoms return to equilibrium by energy absorption in the tissue (T1 relaxation) and loss of phase coherence (T2 relaxation). The radiation emitted by the relaxation nuclei is the nuclear magnetic resonance (NMR) signal being the basis for all MR applications. By advanced computing the distribution of hydrogen atoms and their relaxation properties are identified (59).

### 3.4.2 Pulse sequences in musculoskeletal imaging

A large variety of pulse sequences are used to obtain different types of diagnostic information in musculoskeletal imaging. Different information is obtained by altering the MR acquisition parameters. The most important acquisition parameters are the echo time (TE) and the repetition time (TR). Slice thickness, slice gap, matrix (number of phase and frequency encodings), field of view, flip angle, and echo trains will also affect signal to noise ratio and contrast to noise ratio of the MR images. The most frequently used sequences in musculoskeletal imaging and their application at the time of our studies are summarized in Table 1.
**Table 1. Commonly used pulse sequences in musculoskeletal MRI.**

<table>
<thead>
<tr>
<th>Pulse sequences</th>
<th>Image characteristics</th>
<th>Application</th>
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<tbody>
<tr>
<td>T1-weighed TSE</td>
<td>Fat appears bright</td>
<td>Anatomical imaging</td>
</tr>
<tr>
<td></td>
<td>Water and fibrous tissue appear dark</td>
<td>Volume loss of muscle</td>
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<tr>
<td></td>
<td></td>
<td>Fatty infiltration of muscle</td>
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<tr>
<td></td>
<td></td>
<td>Bone marrow</td>
</tr>
<tr>
<td>T2-weighed TSE</td>
<td>Fat and water appear bright</td>
<td>Fluid collections, oedema and highly vascularized tissue</td>
</tr>
<tr>
<td></td>
<td>Fibrous tissue appears dark</td>
<td>Ligaments</td>
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<tr>
<td>STIR</td>
<td>Water appears bright</td>
<td>Fluid collections, oedema and highly vascularized tissue</td>
</tr>
<tr>
<td></td>
<td>Fat and fibrous tissue appear dark</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>PD-weighted TSE</td>
<td>Water appears medium bright</td>
<td>Fluid collections, oedema and highly vascularized tissue</td>
</tr>
<tr>
<td></td>
<td>Fat appears medium bright</td>
<td>Cartilage and menisci</td>
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<tr>
<td></td>
<td>Fibrous tissue appears dark</td>
<td></td>
</tr>
<tr>
<td>PD-weighted TSE with fat</td>
<td>Water appears bright against dark fat</td>
<td>Fluid collections, oedema and highly vascularized tissue</td>
</tr>
<tr>
<td>saturation**</td>
<td>Fat and fibrous tissue appear dark</td>
<td></td>
</tr>
<tr>
<td>Contrast-enhanced T1-weighed TSE</td>
<td>Water and fat appear dark</td>
<td>Inflammation and other vascularized tissue</td>
</tr>
<tr>
<td>with fat saturation***</td>
<td>Enhanced tissue appears bright against non-enhanced tissue and dark fat</td>
<td>Ischemia</td>
</tr>
<tr>
<td>T2*-weighted GRE</td>
<td>Cartilage, fat and water appear bright</td>
<td>Cartilage and menisci</td>
</tr>
<tr>
<td></td>
<td>Fibrous tissue and degraded blood products appear dark</td>
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</table>

TSE: turbo spin echo; STIR: **Short tau inversion recovery**; PD: Proton density; GRE: gradient echo; **frequency selective

Recent advances in MRI technology may also be included in the protocols of musculoskeletal imaging:

1. High-resolution isotropic 3D sequences give multi-planar reformatted images of high image quality (60).
2. Periodically rotated overlapping parallel lines with enhanced reconstruction, (PROPELLER), is a specialized technique for reducing motion artefacts (61).
3. Dynamic contrast enhanced (DCE) MRI provides high temporal resolution, depicts the exchange of contrast agent between the vascular space and the extravascular extracellular space as a function of time and yields information about microvasculature and thereby the grade of inflammation (62).
4. Modern Dixon techniques (fat suppression techniques named after WT Dixon) combine images acquired at different TEs to produce four image sets: water only, fat only, in-phase, and out-of-phase (63). The images achieve both high spatial and high contrast resolution, and the techniques reduce fat inhomogeneity artefacts (64).

5. Diffusion weighted imaging (DWI) measures the random Brownian motion of water molecules (65).

6. T1ρ mapping, delayed gadolinium enhanced MRI of cartilage (dGEMRIC), and T2 mapping are techniques used to visualize the cartilage biochemical composition (proteoglycans and collagen) (66).

7. UTE (ultra-short echo time) T2*-sequences detect signals from tissue with very short T2, such as cortical bone, osteochondral junction, meniscus, tendon, ligaments, synovium and deep layers of articular cartilage (67).

### 3.4.3 Specific absorption rate

The RF pulses used in MRI interact with the tissue and produce heating due to energy absorption. The absorption of RF fields in tissues is measured as a Specific Absorption Rate (SAR) and measured in watts per kilogram (59). Children are more vulnerable than adults with increased risk for heating because of a greater body surface to weight ratio. It is therefore lower SAR limits for children than for adults. 3-tesla machines have improved the image quality, but have also increased the RF deposition.

### 3.5 Assessment of muscle strength and health status

The International Myositis and Clinical Studies (IMACS) Group has developed a consensus on core set domains and measures for the assessment of disease activity in idiopathic inflammatory myopathy (68, 69). Commonly used measures of muscle strength and endurance are:

- **Childhood Myositis Assessment Scale (CMAS):** Comprises observation of performance of 14 functional tasks. Muscles are weighted differently; proximal > axial muscles and lower extremities > than upper. Scores range from 0-52. Performance time is about 15 minutes (70).
• Manual muscle testing (MMT): Unilateral MMT 8 (shown to be comparable with bilateral MMT 24) comprises tests of 8 muscles using a 0-10 scale (0 = no contraction, 10 = full muscle strength). Score ranges from 0-80. Performance time is < 10 minutes (71).

Commonly used measures of assessment of health and disease status are:
• The Norwegian version of Short Form 36 health survey (SF-36), version 1.0 measuring a physical and a mental component summary scale (72).
• The Disease Activity Score (DAS), consisting of a skin score and a muscle score (73).
• The Myositis Damage index (MDI) measures cumulative organ damage; damage defined in 11 organ systems (muscular, skeletal, cutaneous, gastrointestinal, pulmonary, cardiovascular, peripheral, vascular, endocrine, and ocular organ systems, and infection and malignancy). MDI muscle damage is muscle atrophy, reduced muscle strength due to damage or muscle dysfunction (74).
• The Health Assessment Questionnaire (HAQ) and the Childhood Health Assessment Questionnaire (C-HAQ) measures physical function in patients ages ≥ 18 and ages < 18 years, respectively (75).

3.6 MRI in childhood arthritis

MRI detects joint effusion, synovitis, bone marrow and soft tissue oedema, articular and epiphyseal cartilage changes, changes in the menisci or discs and tendinopathy, all of which can be manifestations of childhood arthritis. Knowing the normal age-dependent appearance, growth disturbance may be acknowledged.

When our study of childhood arthritis (paper 1) was initiated, it was known that MRI was sensitive for joint inflammation (Fig. 7), but its ability to separate subgroups of arthritis in children was questioned (4-6, 76). Studies of MRI findings that could differentiate the subgroups of acute arthritis were few with the focus so far being the differentiation between TA and IA in the hips (77-79). Studies in hips and knees in JIA patients had been performed (80-84), but the MRI characteristics during the early phase of the disease had not been investigated.
Figure 7. Sagittal fat-saturated contrast-enhanced T1-weighted MR image of the knee in a child with JIA shows joint effusion and thickened pathologically enhanced synovium.

The TMJs are frequently involved in JIA (31). Inconsistent definitions and reporting of TMJ involvement may be one reason for the variation in the frequency of TMJ involvement in the literature (32, 33, 85-87). Normal variations of MRI findings in children are not well known, and there are only few studies of healthy TMJs (88-90).

A number of studies have demonstrated MRI abnormalities that may occur in the TMJs of patients with JIA. Little attention has been given to the disk abnormalities, and in the majority of studies disk abnormalities were not reported (33, 85, 87, 91-95). To our knowledge only three studies have reported disk abnormalities, two in children (32, 96) and one in adults with JIA (31). In both studies on children, disk abnormalities predominantly occurred in joints with long-standing changes; the frequencies of abnormal bone shape were 87% and 96% (32, 96). In
adults with JIA with long-standing TMJ involvement, disk abnormalities were frequently observed (31).

MRI-based scoring systems have been developed for arthritis in adults (97), but at the start of our study there was no established scoring system for arthritis in children.

3.7 MRI in juvenile dermatomyositis

MRI may distinguish active inflammation (symmetric, widespread muscle oedema) from signs of muscle damage such as fatty infiltration and/or volume loss, typical findings in JDM patients, and may thus have a role both in detecting early disease and long-term complications of JDM. Long-term complications as calcifications, lipodystrophy and lipoedema may also be depicted at MRI (98-100).

The STIR sequence is very sensitive in detecting muscle oedema, and therefore in showing the most inflamed areas. This may guide the surgeon to choose the optimal site for biopsy and thus increase the accuracy of the biopsies (101). In children, however, invasive methods as EMG and biopsy are often not indicated when MRI has proven bilateral and symmetrical muscle oedema (Fig. 8) accompanied by a characteristic rash (55).

At the start of the study there was no consensus about MRI scoring methods, but several attempts of MRI-based scoring systems for evaluation of oedema and fatty infiltration of muscle (99, 102, 103) besides a widely used CT-based scoring system for fatty infiltration of muscles (104).
Figure 8: Axial T1-weighted (a) and STIR (b) MR images of the thighs in a child in the early phase of JDM show no fatty infiltration of the muscles, but symmetrical, extensive muscle oedema.

Figure 9: Axial T1-weighted MR image of the thighs of a long-term adult JDM patient show extensive muscular, fascial and subcutaneous calcifications (* and other dark soft tissue regions).
4. AIMS

The main aim of this thesis was to explore MRI as a diagnostic tool for the assessment of paediatric musculoskeletal inflammatory disease.

The specific aims were to:

1. Describe and assess the extent of MRI findings in recent onset childhood arthritis.

2. Investigate whether MRI can distinguish between subgroups of childhood arthritis.

3. Describe, define and assess MRI findings in symptomatic TMJs in children with JIA.

4. Assess the frequency of effusion, bone marrow oedema, erosions and disk abnormalities in four categories of TMJs in children with JIA. The categories were based on the presence of synovitis and/or abnormal bone shape.

5. Assess the extent of thigh muscle involvement at MRI in patients with long-term JDM.

6. Establish the correlation of MRI assessed muscle damage and muscle strength.

7. Correlate the MRI assessed muscle damage with early disease characteristics to identify early predictors for organ damage.
5. MATERIAL AND METHODS

5.1 Study design and patients

5.1.1 Paper 1

The study population was from a cross-sectional prospective epidemiological multicentre study of recent-onset arthritis and osteomyelitis in three counties in south-eastern Norway (255,303 children < 16 years) performed between May 2004 and June 2005 (24).

Patients with suspected inflammatory disease in bone or joint with duration < 6 weeks, were referred from primary care, paediatricians, orthopaedic surgeons and rheumatologists. All patients were examined within three days at one of the paediatric or paediatric rheumatologic departments in the counties.

The inclusion criteria were: 1) joint swelling, 2) limited range of motion in ≥ 1 joint, walking with a limp or other functional limitations affecting arms and legs, 3) pain in ≥ 1 joint or extremity together with C-reactive protein (CRP) level > 20 mg/L and/or ESR > 20 mm/h and/or WBC > 12 x 10⁹/L.

Four hundred and twenty-seven children fulfilled the recruitment criteria for possible arthritis; of these 216 had recent onset arthritis. The diagnosis was based on clinical findings, laboratory tests, joint fluid aspiration, and ultrasonography of the affected joint, and the children were followed up with clinical examination after six weeks and six months. Final diagnosis was made after six months of follow-up and re-evaluated by chart review after two years.

The arthritis was classified as IA, PA/TA or JIA. A diagnosis of IA was made when there were verified bacteria in the joint fluid, arthritis combined with positive blood culture and/or adjacent osteomyelitis, or at least 50 x 10⁹ WBC/L in the joint fluid in combination with clinical signs consistent with IA. PA was diagnosed when evidence of recent infection was verified by antibodies against bacterial agents such as Streptococcus pyogenes, Borrelia or Enterobacter, or a positive throat culture for Streptococcus pyogenes. TA was defined as arthritis < six weeks duration with no verified triggering agent. JIA was diagnosed according to the preliminary criteria for the classification of JIA.
The indications for MRI were clinical suspicion of inflammatory joint or bone disease combined with fever > 38.5°, ESR > 30 mm/h, CRP > 30 mg/L, WBC > 12 × 10^9/L and/or an excessively painful joint. MRI was also obtained if clinical signs of arthritis continued for > 2 weeks. Based on these criteria, MRI was performed in 59 children (mean age 3 years (1.5-10 years). Written informed consent was obtained from the parents of the children included in the study. The Regional Committee for Medical Research Ethics approved the study (REC S-04097).

5.1.2 Paper 2

The study was a cross-sectional study of MRI of symptomatic TMJs in children with JIA. It was part of a retrospective study of ultrasonography compared to MRI as the gold standard, with a time interval less than seven days between the two examinations.

The patients were younger than 18 years and identified through search in the institutional picture, archiving and communication system (PACS). The patients were referred to the Department of Radiology and Nuclear Medicine, Oslo University Hospital during the period 2005-2012 due to symptoms or clinical findings like TMJ pain, joint sounds, restricted mouth opening or facial growth disturbances suspicious of TMJ arthritis.

Forty-six patients (mean age 12 years, range 5-17) diagnosed with JIA according to the criteria of the ILAR (21) were included in the MRI part of the study. The patients were mostly under medical treatment.

Chart reviews were performed. Laboratory tests (CRP, ESR), the number of active joints and medications were registered. Active joints were defined as swollen joints or mobility restricted plus tender or painful joints (21).

The study was approved as a quality assurance study by the Data Protection Officer Authority at Oslo University Hospital (2010/537).
5.1.3 Paper 3

The study was a cross-sectional case-control study performed in the period 2005-2009. Inclusion criteria were disease onset ≤ 18 years of age, age ≥ 6 years at follow-up, minimum 24 months of disease duration, and a probable or definitive diagnosis of DM according to the criteria by Bohan and Peter (53, 54).

Norwegian JDM cases diagnosed from 1970-2006 were identified through search in the chart archives at the Department of Rheumatology, Oslo University Hospital, and through contact with the other Departments of Paediatrics and Rheumatology in Norway (105). Sixty-six patients fulfilled the inclusion criteria and four were diseased. Of the remaining 62 patients, 59 participated in the study (mean age 21.5 years, range 6.7-55.4). MRI was performed in 58 patients. The median time between disease onset and examination was 16.8 years (range 2.0-38.1). There were age- and gender-matched controls for the clinical tests, but not for the MRI.

Human leucocyte antigen (HLA) DRB1 genotyping was performed, and laboratory measures were obtained. Outcome domains and core sets (SF-36, DAS, MDI, HAQ, C-HAQ, MMT 8 and CMAS) for idiopathic inflammatory myopathy were assessed. A retrospective chart review was done, where the DAS and MDI total score (including MDI muscle score) were calculated 1 year post-diagnosis.

Informed consent was obtained from all of the patients and the controls (and their parents if age < 16 years). The study was approved by the Regional Committee for Medical Research Ethics (REC S-05144).

5.2 MRI and scoring systems

All MRIs were performed on 1.0 or 1.5 tesla scanners. The MRI sequences included in the examinations were predefined and centrally devised. Pre-contrast sequences were T1-weighted TSE, and STIR or PD/T2-weighted TSE with fat suppression. In order to avoid metal artefacts from braces, some of the TMJ examinations were performed with PD/T2-weighted TSE without fat suppression. The sequences were used to detect bone marrow oedema, effusion and
soft tissue oedema (including muscle oedema), and to evaluate anatomical details. Post-contrast T1-weighted TSE with or without fat suppression was acquired for the patients included in papers 1 and 2. Synovial enhancement and bone marrow vascularity were evaluated. T2*-weighted GRE at open mouth (paper 2) was used to evaluate disk displacement. Choice of contrast agents varied because the institution changed product. The post-contrast imaging started immediately after contrast medium injection.

In paper 1, two radiologists in consensus registered the presence of excessive amounts of joint fluid and synovitis. One of the radiologists assessed the additional findings. In papers 2 and 3, the MRI findings were scored in consensus by two radiologists. An intra-observer evaluation was performed in paper 2.

Self-designed scoring schemes were used in all three papers. These were deduced from available literature at the time of scoring.

Arthritis-related changes at MRI in bone, joint and soft tissue were scored in papers 1 and 2. Myositis-related changes at MRI in muscles, fascia, subcutaneous and cutaneous tissue were scored in paper 3.

In paper 1, synovitis and/or effusion at MRI were considered consistent with arthritis when no other obvious causes were present. In paper 2, a joint was considered to be affected by JIA when synovitis and/or abnormal bone shape was present.

MRI-detected muscle damage was defined as at least one of the following: calcinosis in the muscle or fascia, muscle atrophy, or muscle fatty infiltration. Oedema in muscle or fascia was interpreted as possible inflammatory disease activity.

MRI findings defined in the papers:

- Synovitis was defined as evident post-gadolinium enhancement on T1-weighted images in thickened synovium. Thickened synovium was ≥ 2 mm (paper 1) and more than dots or thin lines (paper 2). “Low signal intensity synovial tissue” was defined as the presence of non-enhancing focal synovial areas with low signal intensity at all contrast weightings (paper 1).
• Effusion was defined as joint fluid more than dots or lines (traces) with high signal on T2-weighted images, and showing no contrast enhancement on T1-weighted images (paper 1 and 2).

• Bone marrow oedema was defined as diffusely circumscribed areas in trabecular bone with low signal intensity on T1-weighted images and corresponding high signal intensity on T2-weighted images, typically higher signal intensity than that of red bone marrow, indicating increased water content (paper 2).

• Bone erosion was defined as a sharply marginated bone lesion visible in more than one slice. The definition did not include cortical breaks due to undeveloped cortical bone plate (which is not fully developed before the approximate age of 20 years). Irregular but intact articular surfaces were not considered erosions but abnormal bone shape. Erosion alone was not considered abnormal bone shape (paper 2).

• In the TMJ, a flat disk was either evenly thin or thin at the anterior band. An adherent disk did not move normally together with the condyle at the mouth opening. A displaced disk could have an anterior, posterior, lateral or medial position relative to the condyle at closed mouth. At mouth opening, anteriorly displaced disks could reduce to normal position or remain anteriorly displaced (paper 2).

• Calcinosis was tumour-like, linear or speckled areas with low signal on both T1-weighted spin-echo sequences and STIR sequences. Despite the lack of radiographic confirmation of density, we chose to name these findings as calcinosis, but fibrosis may have the same appearance (paper 3).

The assessments of MRI findings in the three papers are summarized in Tables 2-4.
**Table 2: Assessment of MRI findings in paper 1.**

<table>
<thead>
<tr>
<th>MRI findings</th>
<th>Score values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of joint fluid</td>
<td>0 - no&lt;br&gt;1 - trace of effusion&lt;br&gt;2 - continual effusion&lt;br&gt;3 - effusion with distension of the capsule</td>
</tr>
<tr>
<td>Synovial thickness</td>
<td>Maximum thickness of the synovium in any part of the joint (pathological thickness ≥2 millimetres)</td>
</tr>
<tr>
<td>Synovial surface appearance</td>
<td>0 - smooth, 1 - irregular, 2 - villous extensions</td>
</tr>
<tr>
<td>Synovial enhancement</td>
<td>0 - no&lt;br&gt;1 - yes</td>
</tr>
<tr>
<td>Synovial non-enhancing and low SI** focal areas</td>
<td>0 - no&lt;br&gt;1 - yes</td>
</tr>
<tr>
<td>Amount of bone marrow oedema</td>
<td>0 - none, 1 - ≤1/3 involvement of the epi-, meta- or diaphysis&lt;br&gt;2 - &gt;1/3 involvement of the epi-, meta- or diaphysis</td>
</tr>
<tr>
<td>Amount of soft-tissue oedema</td>
<td>0 - none, 1 - trace of oedema&lt;br&gt;2 - marked oedema</td>
</tr>
<tr>
<td>Reduced perfusion of bone or cartilage</td>
<td>0 - no&lt;br&gt;1 - yes</td>
</tr>
<tr>
<td>Focal contrast-enhancing lesions in the epiphyseal cartilage or in the knee menisci</td>
<td>0 - no&lt;br&gt;1 - yes</td>
</tr>
<tr>
<td>Regional lymph nodes (knee)</td>
<td>Short axis diameter of the largest lymph node (millimetres)&lt;br&gt;Number</td>
</tr>
<tr>
<td>Tenosynovitis (hands / ankles)</td>
<td>0 - no&lt;br&gt;1 - yes</td>
</tr>
</tbody>
</table>

*adapted after Mitchell at al. (106); **SI: signal intensity
**Table 3: Assessment of MRI findings in paper 2.**

<table>
<thead>
<tr>
<th>MRI findings</th>
<th>Score values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of synovitis*</td>
<td>0 - no</td>
</tr>
<tr>
<td></td>
<td>1 - slight synovial thickening more than dots or lines</td>
</tr>
<tr>
<td></td>
<td>2 - moderate band-like thickening including slight distension of the joint space</td>
</tr>
<tr>
<td></td>
<td>3 - extensive thickening with extensive distension of the joint space</td>
</tr>
<tr>
<td>Abnormal bone shape of fossa/eminence or</td>
<td>0 - no</td>
</tr>
<tr>
<td>the condyle</td>
<td>1 - yes</td>
</tr>
<tr>
<td>Effusion</td>
<td>0 - no</td>
</tr>
<tr>
<td></td>
<td>1 - yes</td>
</tr>
<tr>
<td>Bone marrow oedema</td>
<td>0 - no</td>
</tr>
<tr>
<td></td>
<td>1 - yes</td>
</tr>
<tr>
<td>Bone erosion</td>
<td>0 - no</td>
</tr>
<tr>
<td></td>
<td>1 - yes</td>
</tr>
<tr>
<td>Disks</td>
<td>1 - absent,</td>
</tr>
<tr>
<td></td>
<td>2 - atrophic</td>
</tr>
<tr>
<td></td>
<td>3 - ruptured/fragmented</td>
</tr>
<tr>
<td></td>
<td>4 - displaced</td>
</tr>
<tr>
<td></td>
<td>5 - adherent</td>
</tr>
</tbody>
</table>

*adapted after Mitchell et al. (106)
Table 4: Assessment of MRI findings in paper 3.

<table>
<thead>
<tr>
<th>MRI findings</th>
<th>Score values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle oedema*</td>
<td>0 - no (inactive) 1 - yes: scale 1 (mild) - 4 (extremely active)</td>
</tr>
<tr>
<td>Muscle calcification</td>
<td>0 - no 1 - yes</td>
</tr>
<tr>
<td>Muscle volume loss</td>
<td>0 - no 1 - yes</td>
</tr>
<tr>
<td>Fatty infiltration of muscle **</td>
<td>0 - no fatty depositions 1 - some fatty streaks 2 - more muscle than fat area 3 - as much muscle as fat area 4 - less muscle than fat area</td>
</tr>
<tr>
<td>Fascial oedema</td>
<td>0 - no 1 - yes</td>
</tr>
<tr>
<td>Fascial calcification</td>
<td>0 - no 1 - yes</td>
</tr>
<tr>
<td>Subcutaneous oedema</td>
<td>0 - no 1 - yes</td>
</tr>
<tr>
<td>Subcutaneous calcification</td>
<td>0 - no 1 - yes</td>
</tr>
<tr>
<td>Subcutaneous volume loss</td>
<td>0 - no 1 - yes</td>
</tr>
<tr>
<td>Cutaneous oedema</td>
<td>0 - no 1 - yes</td>
</tr>
<tr>
<td>Cutaneous calcification</td>
<td>0 - no 1 - yes</td>
</tr>
</tbody>
</table>

* adapted after Kimball et al. (107); ** adapted after Goutallier et al. (104)
5.3 Statistical approach

Statistical analyses were performed using SPSS version 15 and 16 (SPSS inc., Chicago, IL, USA) and SPSS version 20 (Armonk, NY: IBM Corp.). Continuous data was described by means and standard deviation when normally distributed and by median and range when skewed. Categorical data were described as frequency and percentage.

In paper 1, the Kruskal-Wallis test and in cases of statistical significance, pair-wise analyses by the Mann–Whitney U test were used to determine differences between groups. For categorical variable Pearson chi-square or Fisher exact test, and for continual variables one-way ANOVA test were used. Logistic regression analyses were performed for each diagnostic subgroup to assess the most important correlates among the MRI joint characteristic variables, with the diagnosis of JIA or IA versus other types of arthritis as the dependent variables.

In paper 2, Cohen kappa statistics were performed to determine intra-observer consistency. Odds ratio was calculated in order to explore the associations between the patient characteristics and MRI findings suggestive of TMJ involvement.

In paper 3, differences between patients and matched controls were tested by the paired-sample t-test, Wilcoxon’s rank sum test, or McNemar’s test. Differences between patient groups were tested by the independent-sample t-test, the Mann-Whitney U test, or the Pearson chi-square test. Correlations were determined by the Spearman’s correlation coefficient. In order to identify possible early risk factors for an unfavourable muscular outcome (low MMT score, low CMAS score, and MRI-assessed muscle damage), logistic regression analyses were performed on the relationship between the outcome variables and the patient characteristics (disease variables) assessed at diagnosis and one year post-diagnosis.
6. SUMMARY OF RESULTS

6.1 Paper 1: Differences in MRI findings between subgroups of recent-onset childhood arthritis

Of the 59 included children, 16 were clinically classified as having IA, 16 as PA/TA and 27 as JIA. All IA patients had soft-tissue oedema. Reduced contrast enhancement in the epiphyses was only found in four of the IA patients and in none of the JIA and PA/TA patients. Bone marrow oedema (OR 7.46, P=0.011) and absence of T1-weighted and T2-weighted low signal intensity synovial tissue (OR 0.06, P=0.015) was suggestive of IA. Low signal intensity synovial tissue (OR 13.30, P<0.001) and soft-tissue oedema (OR 0.20, P=0.018) were suggestive of JIA. No significant positive determinants were found for PA/TA, but bone marrow oedema, soft-tissue oedema, irregular thickened synovium and low signal intensity synovial tissue were less frequent than in IA/JIA.

This study showed that in children with clinical suspicion of recent onset arthritis, there was a significant difference in the distribution of specific MRI findings among the diagnostic groups.

6.2 Paper 2: Disk abnormality coexists with any degree of synovial and osseous abnormality in the TMJs of children with JIA

Of the 46 patients, 78% had synovitis and 72% had abnormal bone shape, most frequently in combination (65%). Disk abnormalities; flat disk, fragmented disk, adherent disk and displaced disk, were found in 63% of the 46 patients. The 92 TMJs (46 patients) were categorized as A: No synovitis and normal bone shape (30/92; 33%), B: Synovitis and normal bone shape (14/92: 15%), C: Synovitis and abnormal bone shape (38/92; 41%) and D: No synovitis, but abnormal bone shape (10/92; 11%). Disk abnormalities were found in all categories of JIA involved TMJs (A: 3%; B: 57%; C: 66% and D: 70%). We found displaced disks to be most frequent in category B; flat disk most frequent in category C, and adherent disk most frequent in category D. Only two TMJs had fragmented disk, both in category C. Disk displacement was found in half of the joints in category B, and synovitis was most pronounced in this category.
Our results show that disk abnormalities together with synovitis and abnormal bone shape were frequent in symptomatic TMJs in children with JIA. Disk displacement in particular, occurred in joints with early TMJ arthritis, i.e., with normal bone shape. Other disk abnormalities were found in joints with bone abnormalities. Thus, attention should be paid to disk abnormalities both in early and long-standing TMJ arthritis in children with JIA.

6.3 Paper 3: Long-term muscular outcome and predisposing and prognostic factors in JDM: a case control study

After median disease duration of 16.8 years, reduced muscle strength and endurance were found in 42% with MMT (score <78) and in 31% with the CMAS (score <48), whereas MRI assessed muscular damage (calcinosis of muscle or fascia, muscle atrophy, or muscle fatty infiltration) was found in 52% of the patients. Of the 58 patients, 9% had signs of active disease (muscle oedema), 29% had muscle atrophy (volume reduction), 43% muscle fatty infiltration, 16% muscle calcinosis, and 19% fascia calcinosis. Subcutaneous atrophy and subcutaneous calcinosis were found in 19% and 7% of the patients, respectively.

The results showed that many years after diagnosis, JDM patients have reduced muscle strength and poorer physical health compared to the general population. Early predictors of unfavourable outcome, including MRI assessed muscle damage, were high MDI muscle score and high DAS score one year post-diagnosis.
7. DISCUSSION

7.1 Methodological considerations

7.1.1 Study design and study population

All the three studies were cross-sectional studies, but the study designs varied depending on the research question.

**Paper I**

The study was part of a large prospective and population-based study. The population of children < 16 years in the three explored counties in South-Eastern Norway was 255,303, and the annual incidence was found to be 71 per 100,000 children (24). TA, JIA, PA and IA were found in 43, 14, 9 and 5 of 100,000 children, respectively. The patient population was similar to previous epidemiological studies regarding age at onset, gender and subgroup/subtype distribution (22-24, 27), supporting that the background patient population comprise a representative cohort of children with recent onset childhood arthritis including JIA. The selection criteria for MRI were however stricter and the population therefore more like a hospital-based one.

As in hospital-based populations (79, 80, 84), the inclusion criteria in the MRI study may have resulted in a selection of the most severely ill children, e.g. IA and polyarticular JIA. This is supported by the high percentage of JIA/IA (73%) subjected to MRI compared to PA/TA (27%). This also suggests that our selection criteria for MRI were sufficient to detect cases of JIA and IA in need of early treatment, avoiding unnecessary MRIs. MRI was performed in all patients with IA. A limitation of our study is that we did not know the patient characteristics of those not having MRI.

Due to the limited number of milder cases of arthritis, TA and PA were considered as one entity. This is a limitation as these two diagnoses may have different characteristics at MRI.

The strength of our study design was the epidemiological design providing the opportunity to look at early arthritis (first doctor visit), important in our research question to differentiate between subgroups of recent onset childhood arthritis.
**Paper 2**

The study was a hospital-based study of children with JIA referred to the Department of Rheumatology at Oslo University Hospital. The frequency of JIA subtypes was similar to other hospital-based studies (92, 108) and included more severely involved joints than population-based patient groups (25).

The high frequency of severe JIA subtypes with long disease duration may be the reason for the high frequency of TMJs in category C (synovitis and abnormal bone shape), reflecting advanced TMJ involvement. A population-based study or a study performed at the time of the first doctor visit would probably have included a higher frequency of newly discovered JIA and may have resulted in more TMJs in category B (synovitis without abnormal bone shape), a prognostic interesting category.

The main limitation of the study was the small sample size recruited from a single institution. The patients were obtained from a study where the aim was to compare ultrasound and MRI findings in patients with inflammatory musculoskeletal disease with TMJ symptoms. The requirement of ultrasound and MRI obtained within the same week lead to the exclusion of patients where the interval was longer. A new study should include a larger study population.

**Paper 3**

The study was a long-term follow-up of a retrospective inception cohort of Norwegian patients with JDM diagnosed between 1970 and 2006. JDM is a rare disease and in order to obtain a study cohort of sufficient size, patients have to be recruited from large populations. In the present study patients were identified through search in the chart archives at the Department of Rheumatology, Oslo University Hospital, and through contact with the other Departments of Paediatrics and Rheumatology in Norway. A limitation was that there were no complete search at the other departments, but Oslo University Hospital is responsible for the care of children with rheumatic diseases in the largest region in Norway, and is referral centre for the others (105). Thus our study cohort was referral-based and not population-based and consequently may have comprised a predominance of severe cases. In 2000-2006 the annual incidence was 2.9 /million children per year corresponding with other studies (49, 50). The annual incidence before 2000 was however only 1.8/million children per year, and the study
cohort diagnosed these years may therefore also have comprised a predominance of severe cases.

A limitation of our study is that MRI of the control group was not performed. MRI of the control group may have reduced the effect of confounders like age and gender in findings like muscle volume loss and fat infiltration (109).

Strengths of our study are that all patients alive were identified, and that 95% of them accepted to participate, and that the matched control group reduced the influence of age and gender as possible confounders for the clinical tests.

7.1.2 MRI technique and sequences

Challenges in performing MRI in children are communication, immobilization, energy absorption from the RF pulses, and the exposure for gadolinium-containing contrast media. Communication must be appropriate to the age of the child to motivate the child and if possible make the child understand why the examination is needed. It should be sufficient time to prepare and customize the child and its parents for the situation. In our studies this was taken care of by radiographers experienced in MRI examination of children.

Young children (< 5 years) usually need sedation to undergo MRI. Children have small anatomical parts, and the spatial resolution needed may increase the acquisition time and consequently also the need for sedation. In order to minimize the examination time the selected sequences were few and robust (T1-weighted TSE, STIR and PD/T2-weighted TSE), sufficient to evaluate synovitis, effusion, bone marrow, cartilage and muscle. These are still the most commonly used sequences, (71, 81, 82, 99, 100, 110-115). The protocols that we used are similar to those in other recent reports and proposed protocols concerning MRI of joints in children; the juvenile MRI scoring (JAMRIS) system (116-118), the outcome measures in rheumatoid arthritis clinical trials (OMERACT) MRI in JIA working group and health e-child (119), and a scoring system for the JIA wrist (114). To minimize scan time we did not include pre-contrast fat-saturated T1-weighted sequences or newer MRI techniques that possibly could have provided additional information, especially about tissue vascularity (e.g. DCE MRI).
Recent technological developments such as increased field strength, more sophisticated coils and new MR techniques (isotropic 3D sequences, DIXON, PROPELLER, DCE MRI, DWI) may lead to a change in the protocols for musculoskeletal MRI and improved image quality and diagnostic performance (60-62, 64, 120-123). DIXON reduces fat inhomogeneity artefacts compared to conventional T2-weighted MRIs making T2-weighted DIXON images an alternative to STIR, but with higher spatial resolution (64). Furthermore pre-contrast T1-weighted DIXON has potential for quantification of fatty infiltration of muscles in JDM patients (124), and DIXON reduces scan time doing T1 TSE with and without fat saturation at the same time. PROPELLER techniques improve image quality and perhaps also the need for sedation (122). The time-activity curve obtained from DCE MRI is anticipated to provide superior information on vascularity and grade of inflammation (differentiate active from inactive synovial disease) (62, 120, 123, 125) compared to a single series of post-contrast images. DWI depicts early ischemia (126), osseous oedema and soft tissue oedema, and DWI has been proposed as a contrast-free approach to imaging of synovitis (121, 127, 128). T1ρ mapping, delayed gadolinium enhanced MRI of cartilage (dGEMRIC) and T2 mapping of the biochemical composition of cartilage (proteoglycans and collagen) may have potential in children since the ossification of the skeleton in children is incomplete (66). T2 mapping has also potential to quantify muscle oedema (129). UTE T2*-sequences depict cortical bone, osteochondral junction, meniscus, tendon, ligaments, synovium and deep layers of articular cartilage due to their very short T2-times (67).

Although synovial thickening is depicted on high-resolution conventional pre-contrast sequences, the use of gadolinium increases the sensitivity for detecting synovial disease in JIA (81, 82, 84, 130). The contrast agent also leaks through the synovial membrane, enhancing the synovial fluid. This may complicate the interpretation of synovitis (contrast enhancement in thickened synovium) (131, 132). In our studies, the post-contrast sequence was therefore performed shortly after the contrast-injection. In addition T2-weighed images were helpful in differentiating synovial thickening from fluid, the fluid having higher signal intensity than the synovium.

Since 2006, nephrogenic systemic fibrosis (NSF) has been associated with intravenous administration of gadolinium-containing contrast media in patients with severely reduced renal function (GFR < 30 ml/min/m²) (133-135). NSF in children is rare, but serious,
characterized by fibrosis of the skin and other tissues. With respect to risk of NSF, the current gadolinium-based contrast media are divided into high-, medium-, and low-risk agents. High-risk agents are contraindicated in newborns, and are not recommended in children less than one year of age. Gadolinium is a heavy metal and recent studies have indicated an accumulation of gadolinium in the brain of patients given repeated doses of gadolinium-based contrast media, seen at T1-weighted MRI as increased signals in the dentate nucleus and the globus pallidus (136-138). Thus, these contrast media should be minimized in small children with immature kidneys and especially in patients requiring repeated examinations. The goal must be to replace contrast-enhanced sequences with other sequences providing similar information.

7.1.3 MRI-based scoring systems

Validated and reliable image based scoring systems are important for clinical diagnosis, outcome and research of JIA-involved joints and JDM-involved muscles. An MRI based scoring system should include the required diagnostic information, e.g. synovitis and bone marrow oedema (predictors for erosions) (139-141). Small differences in definitions of the MRI variables may result in significant frequency variations in the outcome variables. At the time of the study start there was no consensus on the definitions of MRI findings of inflammatory changes in JIA-involved joints or JDM-involved muscles or consensus on MRI scoring systems. Consequently, the definitions of normal and inflammatory MRI findings were based on previous studies (97), but are still similar to definitions in the most recent reports (116).

The scoring systems for childhood arthritis, TMJ arthritis and inflammatory myopathy used in the three studies included in this thesis were self-designed, but based on various reports in the literature (99, 104, 106, 107). The subjective assessment of MRI findings including the number of grades and the relative weights of the different findings may influence the outcome of the test. Too many scoring grades do not necessarily improve diagnostic accuracy as shown in an MRI study of carpal erosions (114) where the 0-10 score had lower reliability than the 0-5 score. For most of the MRI findings we used binary scoring. With this approach equivocal cases might have been wrongly assigned to one of the groups.
A research collaboration was recently established to develop MRI scoring systems for JIA (117, 119, 142). Based on previous studies the research collaboration suggests different MRI scoring systems in large joints (knee) (117), in small joints (the wrist) (114, 118), in the tendon sheaths (143) and in the TMJ (142). The research collaboration also focuses on technical requirements (MRI protocols, sequences, performance) and the definitions of MRI findings. Despite being performed prior to these proposed guidelines the assessment of MRI findings in our three papers are similar to these suggestions.

Oedema, atrophy (volume loss and fatty infiltration of muscle) and calcification in the subcutaneous tissue, muscle fascia and muscles in the thighs were assessed in paper 3. With the exception of the use of a 5-point score of fatty infiltration of muscle, binary scoring was used. Multi-level scoring of muscle oedema was attempted, but due to a small number of patients in our study cohort of long-term JDM patients, the scores were converted into a binary score. It is likely that the extent of signal changes and the signal intensity on STIR in muscles are related to disease activity.

Our method for scoring fatty infiltration of muscles was adapted from Goutallier et al. (104, 144) where the percentage of fatty infiltration of a muscle is visually graded from 0 (no fatty deposits) to 4 (less muscle than fat). To account for the age-dependent amount of fat streaks we chose to define grades 0 and 1 as normal (145). Another frequently used method, first used in muscle dystrophy, by Mercuri et al. (103) uses a similar scale evaluating the volume of fat in individual muscles: 0: normal; 1: scattered small areas of fat infiltration; 2: <30% of the volume; 3: 30%-60% of the volume; and 4: >60% of the volume. The values are comparable with the values of Goutallier et al, but it would be an advantage in disease monitoring and research to have one standardized method. Other reports have tried to establish more objective quantifying measure of fatty infiltration of muscles using DIXON-sequences (124, 146).

7.2 Radiological and clinical implications of study findings

7.2.1 MRI as a tool to differentiate subgroups of childhood arthritis (paper 1)

We found differences in MRI joint characteristics between subgroups of early childhood arthritis (JIA, IA and PA/TA), and identified findings suggestive of JIA and IA. Despite the
heterogeneity of the subgroup PA/TA, caused by the classification as one group, our findings of MRI’s ability to differentiate between IA and PA/TA were similar to several other groups studying IA and TA (77-79, 125).

Except for reduced contrast-enhancement in the epiphyses seen only in the IA group, no pathognomonic findings were identified for any of the arthritis subgroups. Furthermore, reduced contrast enhancement as a sign of epiphyseal avascularity has also been reported in TA and JIA, but less frequently (79). All patients in the IA group had soft tissue oedema, but so had also half of the patients in the other subgroups. The strong association between IA and soft tissue oedema, bone marrow oedema and avascularity is probably due to IA being a more abrupt and aggressive form of inflammation than the two other groups. Another reason for frequent bone marrow oedema is that osteomyelitis and infectious arthritis often co-exist due to direct spread (42, 147).

In our study we found more frequent involvement of non-ossified cartilaginous epiphysis in patients with IA. This is in accordance with two recent MRI studies of patients with methicillin-resistant Staphylococcus aureus (MRSA) (148, 149). In the MRSA study, contrast-enhanced MRI was especially important in detecting the growth cartilage involvement (148). In a study of osteoarticular infections caused by Kingella Kingae and gram positive cocci, epiphyseal cartilage abscesses were present only in the Kingella Kingae group, and bone reaction and soft tissue abscesses were less severe than in gram positive cocci (149). No MRSA infections were included in this study. Thus, different infections may not have the same appearance at MRI.

Due to the unspecific nature of MRI findings and the frequent negative blood- and synovial fluid cultures, a combination of radiological, laboratory and clinical findings seems mandatory in the diagnosis of IA. Of importance are recent advancements in development of more sensitive laboratory methods for detecting bacterial infection (e.g. molecular detection of bacterial nucleic acid, and detection of markers for bacteraemia e.g. procalcitonin) (150).

Lack of soft tissue oedema and findings of areas with decreased T2 signal in thickened synovium had high association with early JIA. The presence of synovial thickening may be a sign of more longstanding arthritis. The reason for such a finding in the early phase of JIA,
may be the clinically silent insidious onset of JIA, and consequently a longer disease duration than assumed (81).

Our study shows that articular MRI may provide valuable information for the diagnosis of JIA and IA, and that MRI is important for early diagnosis and treatment to prevent long-term joint damage.

7.2.2 Disk abnormalities in the TMJs of children with JIA (paper 2)

Several studies have demonstrated various MRI findings in JIA-involved TMJs (32, 33, 85-87, 90), but little attention has been paid to the involvement of the disks. Disk-abnormalities are often not reported (33, 85, 87, 91-95), or reported in long-standing arthritis with manifest bone abnormalities (31, 32, 96).

We found displaced disks to be frequent in JIA-involved TMJs with synovitis before bone abnormality (category B) had taken place, indicating that this might be part of an early process in a diseased joint. Both early TMJ arthritis and displaced disk with reduction at mouth opening may be clinically silent (151, 152). A recent study shows that TMJ with condylar deformity (disks not reported) has higher association with clinical symptoms than joints with only synovitis (153). Five out of the seven TMJs included in category B in our study had displaced disk without reduction, and displaced disk without reduction is reported to be symptomatic (154, 155). These patients with presumably early arthritis also had the most extensive synovial thickening and high frequency of bone marrow oedema and effusion, indicating a more pronounced inflammation. Rupture of the thin TMJ retro-diskal ligaments may be caused by inflammation and result in displaced disk (156, 157).

Flat disk was most frequently found in TMJs belonging to category C (synovitis and abnormal bone shape). Mechanical stress may play a role in the development of the flattening (158). Due to biomechanics, displaced disks in healthy people may lead to shape deformity of the condyle and early degenerative changes (159, 160). Synovitis is present also in degenerative disease, but is often described as more modest with less intense contrast enhancement than the autoimmune form (161). In our study many of the joints in category C had only modest synovitis. This may be due to the high frequency of patients on medication, but it is also reasonable to ask if these findings may be secondary to degeneration rather than the idiopathic
inflammation, and that the joint deformity and mechanical conditions itself maintain the synovial reaction.

Our study indicated that disk displacement may provide prognostic information and should therefore be included in a scoring system.

7.2.3 Muscle damage shown at MRI corresponds with clinical findings in patients with long-term JDM (paper 3)

We showed that MRI findings of chronicity (calcification, fibrosis, and fatty-infiltration and volume loss of muscles) were associated with reduced muscle strength (low MMT and CMAS score). In accordance with other studies, we found that long term JDM patients had reduced muscle strength. Muscle strength was persistently reduced in 42% based on MMT 8 and in 31% based on CMAS, whereas MRI-detected muscle damage was found in 52%. Low MMT score and CMAS score have been found in 41% and 53% of JDM patients in another study with 7 years follow-up time (162), but no controls were included in that study. The frequency variation in muscle strength may be due to the use of different cut-off values. In our study the cut-off values were based on the score from our control group. Normal variation and ageing may be misinterpreted as muscle damage at MRI (109), and MMT 8 and CMAS may underscore muscle strength, due to short performance time, patient motivation and cooperation, and in CMAS, due to difficulties in performing complex movements allowing compensatory strategies (74).

The MRI protocol included only the thighs, and the thigh muscles accounted only for a small number of the muscles tested in MMT 8 and CMAS. Despite this limitation, the association between MRI findings and muscle strength suggests that in a systemic disease such as JDM, whole body MRI (WBMRI) may be omitted. The MRI findings in the thigh muscles may be representative of the disease. However, WBMRI depicts the muscle-involvement more completely and correlates with MMT and CMAS (112, 163). Besides, WBMRI has been suggested to map subcutaneous changes (112). Subcutaneous and myofascial findings are predictors for worse outcome and more aggressive calcification (107, 111). Other limitations of our study were the lack of MRI of the control group, and the lack of MRI at the time of the
diagnosis and at one-year follow-up. This made it impossible to assess longitudinal image changes.

Our study showed that high disease activity present one year post-diagnosis correlated with persistently reduced muscle strength and later muscle damage at MRI. The knowledge of early predictors for muscle damage may guide treatment and follow-up.
8. MAIN CONCLUSIONS

1. In children with recent onset arthritis, there were significant differences in the distribution of certain MRI findings in the subgroups of childhood arthritis JIA, IA and PA/TA. Nearly all MRI findings were found in all groups, but there were predominant findings in each group.

2. IA was suggested by bone marrow oedema and absence of synovial tissue with low signal intensity on T1-weighted and T2-weighted MR images. Furthermore, soft-tissue oedema and reduced contrast enhancement in the epiphyses were more frequent in children with IA than in those with other arthritides. Soft tissue oedema was always found in the IA group. JIA was positively correlated to low signal intensity synovial tissue and negatively correlated to soft-tissue oedema. JIA had more irregular synovia, also in the early phase. No significant determinants were found for PA/TA, but bone marrow oedema, soft-tissue oedema, irregular thickened synovium and low signal intensity synovial tissue were less frequent in PT/TA than in IA/JIA.

3. A classification of the TMJs in patients with JIA was based on MRI findings of synovitis and abnormal bone shape: A: No synovitis and normal bone shape; B: Synovitis and normal bone shape; C: Synovitis and abnormal bone shape; D: No synovitis, but abnormal bone shape. TMJ category C was most frequent in this hospital-based population of JIA. TMJ category B had the most frequent findings of active inflammation as effusion and bone marrow oedema. The synovial thickness was also highest in this category.

4. Disk abnormality was frequent in all TMJ categories: disk dislocations were most frequent in category B; flat disks were most frequent in category C, and adherent disks were most frequent in category D.

5. Fifty-two percent of the JDM patients at median 16.8 years follow up had muscle involvement at MRI (fatty infiltration of muscle, 43%; muscle oedema, 9%; calcifications in any tissue layer, 24%).
6. Muscle damage shown at MRI correlated with muscle strength and endurance shown in MMT 8 and CMAS.

7. MDI muscle damage and sustained disease activity one year after JDM diagnosis, were identified as early predictors of reduced muscle strength and MRI-detected muscle damage at follow up.

8.1 Concluding remarks

Development of efficient medications in the treatment of inflammatory juvenile musculoskeletal diseases in the past decade has increased the need for validated and reliable diagnostic tools. In this respect, the present thesis is a contribution to the understanding and the use of MRI as a tool in primary diagnosis, follow-up and research. We have focused on several MRI findings in general joints, TMJs and muscles, and identified variables that probably should be parts of MRI scoring systems.

8.2 Implications for further research

Future studies of childhood arthritis should focus on:

1. Improvement of MRI scoring systems in inflammatory joint disease and inflammatory muscle disease.

2. Improvement of MRI techniques and protocols in juvenile inflammatory joint and muscle disease with focus on reducing the exposure to gadolinium and the need for sedation.

3. Further exploration of the prognostic importance of early MRI findings of inflammatory musculoskeletal disease in patients with JIA and JDM.

4. Comparison of MRI and other radiological methods in the diagnosis of juvenile inflammatory joint and muscle disease.

5. Further follow-up of muscle MRI findings in the cohort of JDM patients.
9. REFERENCES


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