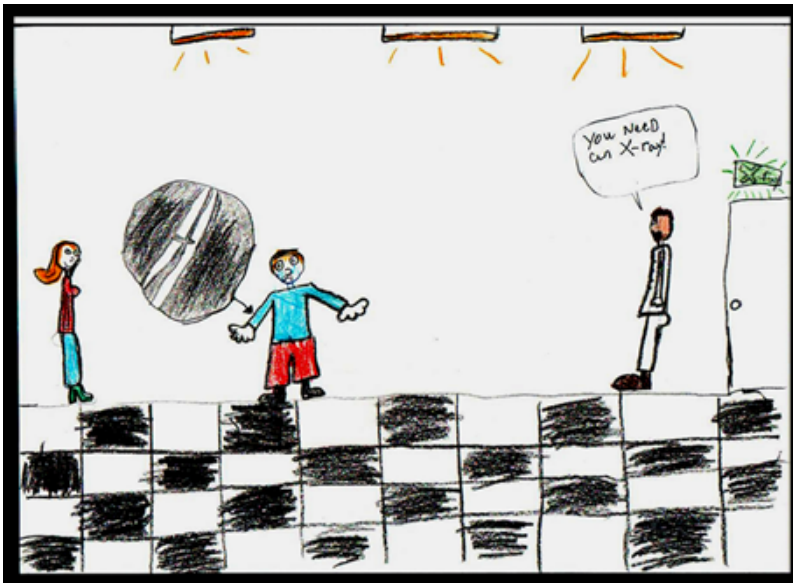


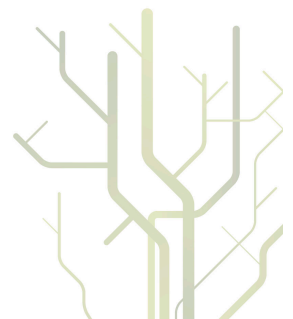
Establishment of Normative MRI Standards for the Paediatric Skeleton to better outline Pathology Focused on Juvenile Idiopathic Arthritis



Lil-Sofie Ording Müller

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Establishment of Normative MRI Standards for the Paediatric Skeleton to better outline Pathology

Focused on Juvenile Idiopathic Arthritis

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To Nicoline, Alvin, Andreas and Stig

*‘Nothing is wonderful except in the abnormal,
and nothing is abnormal until we have grasped the norm.’*

C. S. Lewis, God in the Dock: Essays on Theology and Ethics, 1972

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1.0 Preface

1.1 List of papers

1.

The pediatric wrist revisited: redefining MR findings in healthy children

Müller LS, Avenarius D, Damasio B, Eldevik OP, Malattia C, Lambot-Juhan K, Tanturri L, Owens CM, Rosendahl K

Ann Rheum Dis. 2011 Apr;70(4):605-10

2.

The pediatric wrist revisited-findings of bony depressions in healthy children on radiographs compared to MRI

Avenarius DM, Ording Müller LS, Eldevik P, Owens CM, Rosendahl K

Pediatr Radiol. 2012 Mar 20. [Epub ahead of print]

3.

High signal in bone marrow at diffusion-weighted imaging with body background suppression (DWIBS) in healthy children

Ording Müller LS, Avenarius D, Olsen OE

Pediatr Radiol. 2011 Feb;41(2):221-6

4.

MRI of the wrist in juvenile idiopathic arthritis: erosions or normal variants –can we tell?

Ording Müller LS, Boavida P, Avenarius D, Damasio B, Eldevik OP, Malattia C, Lambot-Juhan K, Tanturri L, Owens CM, Rosendahl K

Submitted to Pediatric Radiology, June 2012

1.2 Acknowledgements

My children have asked me why I wanted to write a PhD. The answer is; because I'm curious, I have been taught to try to seek answers to my questions and because I was lucky to get the opportunity to accomplish this task. I therefore want to acknowledge the people who have piqued my curiosity, inspired me and made it possible to write this thesis.

This thesis is based on studies carried out between March 2009 and June 2012 at the Department of Radiology at the University hospital of Tromsø, and in collaboration with Institute of Child Health/Great Ormond Street Hospital, London. The work is in part funded by HelseNord, I thank the unit lead Gry Andersen for her support. The data from children with juvenile idiopathic arthritis were acquired as part of a study funded by a grant from the European Union, Health-e- Child Integrated Project (IST- 2004-027749).

I wish to thank my mentor Petter Eldevik for his positivism, wisdom and visionary attitude towards research and development in radiology. You have brought the world into the Department of radiology in Tromsø. I hope your ideas will be cherished, and live on after your retirement. This research project was only possible due to your experience and decisiveness.

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Most importantly I thank my children Andreas, Alvin and Nicoline for being honest, brave and happy, you are my pride and joy! And my husband Stig for your patience, support and love. Together we stay strong.

1.3 Common abbreviations

ADC	Apparent diffusion coefficient
ANOVA	Analyses of variance
BMO	Bone marrow oedema
CMC	Carpo-metacarpal
CT	Computer tomography
DW	Diffusion weighted
DWI	Diffusion weighted imaging
DWIBS	Diffusion weighted imaging with body background suppression
EPI	Echo planar imaging
ERA	Enthesitis related arthritis
FSE	Fast spin echo
GOS	Great Ormond street hospital
HeC	Health-e-Child study
HeCC	Health-e-child cohort
ILAR	International league of associations for rheumatology
JIA	Juvenile idiopathic arthritis
MRI	Magnetic resonance imaging
MR	Magnetic resonance
NEM	Hopital Necker enfants malades
NSA	Number of signal averages
OMERACT	Outcome measures in rheumatoid arthritis
OPG	Ospedale Bambino Gesu
PET	Positron emission tomography
RA	Rheumatoid arthritis
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Studies
RF	Rheumatoid factor
RM	Radio-metacarpal length

STIR	Short tau inversion recovery
T1w	T1- weighted
T2w	T2- weighted
TC	Tromsø cohort
TCd	Tromsø cohort- DWIBS
TCw	Tromsø cohort -wrist
US	Ultrasonography
W	Width of the metacarpal bases

1.4 Errata

Errata: Paper I, results, line 2-3 says: '79 (40 boys) were right-handed'. The correct number should be (38 boys).

2.0 Introduction

Radiological investigations play an important role in the diagnosis and follow up of bone disorders. After Wilhelm Conrad Röntgen's discovery of the 'X-rays' in 1895, the skeleton, and in fact the wrist, was the first body part to be examined. Conventional radiography is still the most commonly used modality, but additional techniques such as computed tomography (CT), ultrasonography, nuclear medicine and magnetic resonance imaging (MRI) may add important information. MRI in particular, has become a frequently used modality in the routine diagnosis of many skeletal diseases, and the technique is still undergoing important improvements and developments [1, 2]. MRI has particular advantages in that it is non-invasive, using non-ionising radiation, and has excellent soft-tissue contrast resolution and discrimination in any chosen imaging plane. MRI can provide both morphological and functional information. The resultant MR image is based on multiple parameters, all having the ability to modify tissue contrast. The interpretation of the MR-images is based on our knowledge of the physical properties of the imaged tissue and the pathophysiological processes of disease.

2.1 Imaging of the paediatric skeleton

Children are not small adults and the knowledge of normal paediatric anatomy and physiology, but also the specific diseases related to childhood, is crucial when interpreting radiological investigations in children. Radiological evaluation of pathology in the skeletal system in children is further complicated by the process of skeletal growth and maturation, both due to the changes caused by maturation of cartilage into bone, and alteration of bone marrow composition with time. In the enchondral ossification process, the epiphyseal cartilage becomes gradually ossified, replacing this highly vascular cartilage with bony tissue[3, 4]. The paediatric bone marrow is different from adults in two ways; the cellular composition of the red bone marrow in children changes with age and the high cellular red marrow is gradually replaced by fatty white marrow in the normal bone-marrow conversion [5]. Therefore the imaging techniques and their interpretation must be specific to the developmental stage of the child [6-9].

MRI is an important diagnostic tool in children. It provides superb anatomical and functional information in most paediatric diseases without the use of ionising radiation. A multidisciplinary team of radiologists, technicians, clinicians and scientists have made, and are continuing to make, combined efforts in further extending the clinical usefulness and effectiveness of MRI in children, however, paediatric musculoskeletal imaging remains challenging [10]. Many MR-techniques used for adult imaging have not been validated for use in children and normal references for the age-specific anatomy on MRI are lacking. Despite this the use of MRI in children is expanding. One of the fields where MRI is increasingly used is in paediatric rheumatic diseases, in particular for Juvenile Idiopathic Arthritis (JIA) [11, 12].

2.2 Juvenile Idiopathic Arthritis

JIA has been defined as arthritis of unknown cause occurring in children under 16 years and is the most common rheumatic entity in childhood with a prevalence of 0.6-1.9 in 1000 children. JIA is not one single disease but includes a subset of childhood arthritis with disease course more than 6 weeks. The exact cause and pathogenesis of juvenile idiopathic arthritis are not fully understood but seem to include both genetic and environmental components [12, 13]. Historically, there have been different attempts to classify subsets of JIA. The International League of Associations for Rheumatology, (ILAR) provides the most recent classification based on new knowledge and with the intention to minimise and harmonise the differences in definitions and terminology previously used in Europe and America [14].

The diagnosis is made from clinical and laboratory presentation the first 6 months of the disease. Table 1 gives a brief overview over the different JIA-subtypes and their characteristics according to the ILAR-criteria. The outcome the disease varies with the clinical subtype of JIA, and persistent oligoarthritis has shown to have the best prognosis [15, 16]. A recent study including 440 patients from the Nordic countries show that 48.7% of the patients had persistent arthritis with minimum duration of 7 years after disease onset [16], however much of the existing data regarding long-term outcome of JIA are limited [17]. Despite the heterogeneity of juvenile idiopathic arthritis it is likely that there is some genetic overlap, because all subtypes share joint inflammation as the

most prominent disease feature [12, 18]. Joint pathogenesis involves inflammation of the synovial lining, with the potential to cause joint destruction [19-21]. There is infiltration of sub-lining layers of the synovium by mononuclear cells. The lining layers of the synovium then become hyperplastic with increased vascularity. The pannus is comprised primarily of invasive lining cells and the synovium becomes locally invasive at the synovial interface with cartilage and bone. Subsequent destruction of the bone and cartilage occurs as a result of antibody deposition and degradative enzymes [13]. It is thought that the osseous change in JIA is a consequence of overlying cartilage degradation. The peripheral joints are predominantly affected and wrist synovitis is associated with a severe course [22-24].

Table 1. Subgroups of JIA [13, 17]

Subset of JIA	Frequency	Age at onset	Clinical characteristics	Male/Fem
Oligo	27-56%	Early childhood, peak 2-4y	Four or fewer joints involved the first 6 months. Lower extremity more often affected, generally good prognosis, worse prognosis if more than 4 joints affected after 6 months (extended oligo JIA). Risk of developing iridocyclitis.	F>>>M
Poly, RF negative	11-28%	Early peak 2-4y, late peak 6-12y	Four or more joints involved within the first 6 months, absence of IgM RF. Heterogeneous disease with three subsets. Prognosis varies with the disease-subset.	F>>M
Poly, RF positive	2-7%	Late childhood-adolescence	Four or more joints involved within the first 6 months, IgM RF positive. Resembles adult RA. Involvement of small joints. Progressive and diffuse joint involvement.	F>>M
Enthesitis related arthritis (ERA)	3-11%	Late childhood-adolescence	Characterised by enthesitis and arthritis. Often HLA-B27 positive. Commonly hip-involvement at presentation. Often a mild and remitting course but may progress with sacroiliac and spinal joints-involvement, resembling ankylosing spondylitis.	M>>F
Psoriatic	2-11%	Early peak 2-4y, late peak 9-11y	Arthritis and psoriatic rash or psoriasis in close family. Controversial definition, resembles oligoarthritis but more often with dactylitis and involvement of both small and large joints.	F>M
Systemic	4-17%	Throughout childhood	Arthritis and quotidian fever plus one or more of the following symptoms: characteristic rash, hepatomegaly, splenomegaly, lymphadenopathy, serositis. Variable course. 5-8% develop macrophage activation syndrome.	F=M

2.3 The role of imaging of joint pathology in Juvenile Idiopathic Arthritis

There have been major advances in the treatment of JIA in the last decade. The development of new therapeutic agents and new, individually tailored, treatment strategies has led to significant improvement in functional outcome in children with JIA [13, 25-28]. The paramount goal of current treatment in JIA is to achieve inactive disease and remission, with or without medication [29-31]. In order to evaluate therapeutic response, sensitive tools for assessment of early inflammation and bony destruction have become crucial. Of the diagnostic tools currently available, imaging studies are best suited for these purposes [11]. The radiological investigations in JIA should ideally be able to determine the presence and degree of 1) active inflammation 2) precursors of bony destructions 3) established erosions. Synovial contrast-enhancement, bone marrow oedema (BMO) and increased joint fluid are thought to be signs of active inflammation. The presence of bone erosions is a sign of established bony destruction and the presence of BMO may be predictive of later bone erosions [32-35].

2.3.1 Radiography

Joint misalignment and joint damage evaluation in JIA has traditionally been performed by X-ray scoring methods. Radiographs are quick and easy to obtain, cost effective and give low radiation exposure to the child. Radiographs can show bone erosions and it may depict cartilage loss indirectly through joint space narrowing [36]. Joint space narrowing, misalignment and focal concavities or lytic lesions of the bones are perceived as signs of joint destruction [37].



Fig. 1 Joint-space narrowing on a plain radiograph (arrows)

Radiographic scoring systems specific for juvenile idiopathic arthritis have been devised [38-40]. However, plain radiographs cannot visualize synovium, joint effusion, articular cartilage, bone marrow, or ligaments and tendons directly, and are not sensitive for bony destruction [41]. The sensitivity is particularly low for disease in the early stages of evolution [40, 42, 43].

2.3.2 Ultrasonography (US)

US is a non-invasive, non-ionizing radiation and child-friendly technique that allows for dynamic evaluation of several joints. The periarticular soft tissue, joint fluid, cartilage and the articular surface of a joint may be assessed by US. Ultrasonography with power Doppler examination has shown higher sensitivity than clinical examination for detecting synovitis [44-46]. Erosions and cartilage destruction may also be depicted by US, but the whole articular surface can be assessed only in small joints hence the sensitivity may be low [47]. The major problem, however, is the lack of standardised imaging techniques and scoring systems for inflammation and the lack of normal standards of anatomy on US in children [48].

2.3.3 Computer Tomography (CT)

CT may show the skeletal structures in greater detail and spiral CT imaging with isotropic resolution with 3D reformatted images, may be useful when investigating complex joint misalignment, and as a roadmap for surgeons in preoperative planning [49]. However few data are available which address the modality's ability to define erosions and this modality has a relatively high radiation burden and should not be used in the routine imaging of JIA [50, 51].

2.3.4 Positron Emission Tomography (PET)

There are a few studies on the use of 18-F FDG- PET in the assessment of synovitis in adults where the degree of 18-fluorodeoxyglucose (FDG) uptake is reported to correlate

with physical examination and laboratory tests for evaluating disease activity in patients with rheumatoid arthritis [52, 53]. Similar findings have been reported in a study by Tateish et al in children with JIA [54]. FDG PET may be used to quantify the degree of synovitis and could be useful in the therapeutic management of JIA. Further evaluation of this technique is needed before it may be applied in clinical practice [54]. Radiation doses are however relatively high at the current time.

2.3.5 MRI

MRI is the only diagnostic tool that can assess all relevant anatomical structures in joint inflammation [55]. A broad range of MR-techniques, with different pulse-sequences, are used to improve the visualisation of the relevant tissue. Erosions are difficult to assess clinically and MRI has shown promising results in the assessment of bone erosions, and is thought to have greater sensitivity than radiography in early detection of destructive disease [47]. Magnetic resonance imaging (MRI) is able to image synovitis and bone oedema/inflammation, as well as damage to cartilage and bone. MRI is therefore a potentially powerful imaging tool to assess joint inflammation and the progression of joint-damage. The Outcome Measures in Rheumatoid Arthritis (OMERACT)-group has, over the last decade, done an extensive amount of work on creating validated and reproducible scoring system for these features, using standard MR-sequences, in adult patients with Rheumatoid Arthritis (RA) [35, 56-64]. This scoring system is based on standard MRI-sequences, with and without contrast-administration.

The core set of MRI-sequences and the definition of important RA-joint pathologies are presented in table 2 and examples of the MRI-features are shown in figure 2.

The OMERACT-definitions for disease activity and bony destruction on MRI, have in part been adapted for use in children with JIA [65]. However, these definitions have never been validated for use in children, hence feasible systems for assessment of the MRI in JIA are lacking and there is no consensus on how to interpret the imaging findings in these patients. Another disadvantage with the use of MRI in children is the need for deep sedation or general anaesthesia in uncooperative patients, due to relatively long

scanning time. However, using an optimised scanning protocol, children as young as five years of age may undergo an MRI without sedation[66].

Table 2. Standard MR-sequences and definitions of pathology as defined by OMERACT [56]

MR-sequences
-Imaging in two planes* with T1 weighted images before and after intravenous gadolinium contrast
-A T2 weighted fat saturated sequence or, if the latter is not available, a STIR (short tau inversion recovery) sequence
*Can be acquired by obtaining a two dimensional sequence in two planes, or a three dimensional sequence with isometric voxels in one plane allowing reconstruction in other planes. Intravenous gadolinium injection is probably not essential if only destructive changes (bone erosions) are considered important
Definitions of pathology
-Synovitis: an area in the synovial compartment that shows above normal post-gadolinium enhancement** of a thickness greater than the width of the normal synovium
-MRI bone erosion: a sharply marginated bone lesion, with correct juxta-articular localisation and typical signal characteristics, which is visible in two planes with a cortical break seen in at least one plane
-MRI bone oedema: A lesion within the trabecular bone, with ill defined margins and signal characteristics consistent with increased water content

*imaging in 2 planes can be acquired by obtaining 2D sequence in 2 planes or a 3D sequence with isometrical voxels in 1 plane allowing reconstruction in other planes

** Enhancement (signal intensity increase) judged by comparison of T1-weighted images, obtained before and after i.v. Gadolinium contrast

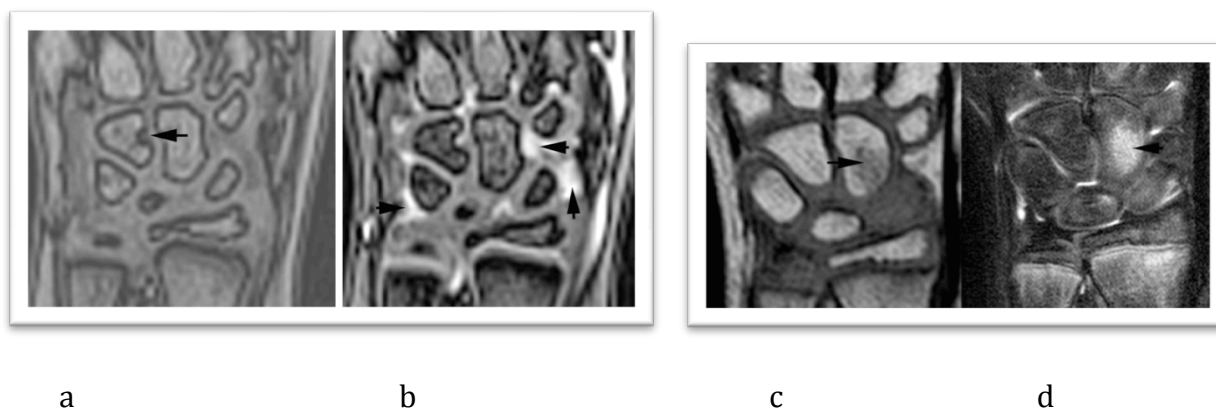


Fig. 2 Example of a) cortical breach (T1) b)contrast enhancement(T1) and c&d) bone-marrow signal suggestive of BMO (T1 and STIR).

In addition to the standard MR-sequences, new MR-techniques tailored to visualize certain anatomical or pathological details have emerged. Some techniques are developed

to assess cartilage and have shown promising results in showing early signs of cartilage degeneration in adult patients, like the Gadolinium- enhanced MRI of cartilage (dGEMRIC), ²³Na MRI and T1p-imaging [67]. Diffusion weighted imaging (DWI) has been used to assess cartilage, but also in assessment of inflammation [68, 69]. Some of these methods may play an important role to answer specific questions regarding joint inflammation and destruction in JIA. However, further research is needed to assess the usefulness of these sequences, particularly in children.

3.0 Imaging techniques used in this thesis

3.1 MR

3.1.1 T1

The T1-weighted Spin Echo (T1wSE) images provide good depiction of skeletal anatomy and bone marrow and is also used for post contrast imaging. The cortex returns very low signal on T1w sequences and contrasts the high signal from the fatty marrow. T1-w images are used for the depiction of bone erosions, while post contrast T1 images are used for the assessment of inflammation and synovial enhancement. T1w images are acquired using short repetition- and echo time and can be obtained using spin echo- or gradient echo technique. The spin echo sequences have better ability to depict fat and have the highest specificity for marrow disorders.

3.1.2 T2

T2-weighted Spin Echo (T2wSE) sequences are also called 'water-sensitive' sequences. Fat-suppressed T2w images are sensitive for inflammatory changes like bone marrow oedema and presence of joint fluid, with water being of high signal and fat of low signal. T2wSE imaging is obtained using long repetition- and echo time, showing differential contrast in tissues with different T2 relaxation time. There are principally two methods of fat- suppression. The short tau inversion recovery (STIR) is an inversion recovery pulse sequence with specific timing, so as to maximally suppress the signal returned from fat. It produces a robust fat suppression, despite in-homogeneity in the magnetic field. The other fat-suppression technique is a spectral pre-saturation sequence that selectively saturates protons within fat prior to acquiring data. This fat suppression is less robust but the sequence has a higher signal-to-noise-ratio [10].

3.1.3 Diffusion weighted sequences

Diffusion weighted imaging (DWI) is not yet part of the standard imaging protocol in paediatric musculoskeletal (MSK) imaging. It is thought to have a high sensitivity for bone marrow pathology, and is particularly used in adult oncology imaging. However it has also been shown to have a role in detection of active inflammatory changes [70] and

a possible future role in the detection of cartilage degradation [71]. Diffusion weighted imaging is a functional MR-sequence that uses Brownian motion to create tissue-contrast. Tissues with high cellularity, like tumours or inflammatory infiltrates, will often have restricted water diffusion. This gives a high signal on DWI. Diffusion weighted imaging with body-background suppression (DWIBS) is a novel diffusion weighted sequence, particularly suitable for whole-body imaging [72].

3.2 Radiography

Radiographs provide an overview of the anatomy of the wrist. The bone trabeculae, cortex and the alignment of the joints are well visualized on radiographs. Modern radiographs obtained using digital techniques with direct radiography and electronic display and interpretation, have largely replaced x-ray-films. In studies with patients with RA, digital radiography has shown equally good image quality compared to screen-films [73]. Using digital flat-panel detector the diagnostic performance may even be superior to screen films [74].

4.0 Work leading up to this thesis

In order to validate a scoring system for disease activity and destructive bone change, 350 children with JIA involving the wrist and/or hips were enrolled in a large multicentre-study during 2006-2010, the 'Health-e-Child-study' (HeC). The study was designed to a) identify more homogeneous groups of patients b) early predictors of poor outcome c) markers of either permanent or reversible organ damage and d) measures that could allow for early detection of progressive organ damage, to be used in clinical trials. During the project, we noted wide variations in bone shape, signal intensity returned from the bone marrow and amount of joint fluid as shown by the core set of MRI-sequences suggested by the OMERACT-group. The findings appeared in part to be unrelated to disease activity [75, 76]. This made us question whether the definitions of pathology based on an adult population could be extrapolated for use in children.

Although not established as a standard MR-sequence for skeletal imaging, the DWIBS sequence is a novel technique with potential future applications within paediatric skeletal investigations. In clinical practice we found that DWIBS-sequences were difficult to interpret when applied to the paediatric population, because children were seen to commonly have foci of restricted diffusion in their skeleton, which were unrelated to pathology, sometimes occurring in a bilateral and an asymmetrical pattern.

We therefore found it expedient to examine these features in a population of healthy children.

5.0 Aims of the thesis

Firstly, in the cohort of healthy children, we aimed at describing:

- Bony depressions resembling erosions, marrow signal resembling bone marrow oedema and the presence and amount of joint fluid on MRI of the wrist

(Paper 1)

- The findings of bony depressions at the wrist on plain radiography compared to MRI

(Paper 2)

- The distribution of restricted diffusion in the lumbar spine and pelvic skeleton

(Paper 3)

Secondly we wanted to compare the findings of bony depressions at the wrist as assessed by MRI in healthy children and in children with JIA in order to find true markers for disease

(Paper 4)

6.0 Material and methods

This thesis is based on data from 2 different paediatric cohorts; the Tromsø Cohort (TC) (papers 1-4) and the Health-E-Child Cohort (HeCC) (paper 4).

6.1 The Tromsø Cohort – wrist (TCw)

Following Ethical approval healthy children were invited to participate in this study via announcements on clip-boards and via e-mail at the University Hospital of North Norway, Tromsø. Exclusion criteria were contraindications for MRI, history of cancer, current infection, musculo-skeletal disorders, metabolic disorders, and recent trauma to the left wrist. Information about handedness and sports-club membership was collected. Between March and October 2009 88 children age 5-15 years, residing in Tromsø, Norway accepted and underwent MRI imaging and a plain radiograph of the left wrist.

Table 3. Characteristics of the TCw

	Female	Male	Total
Number	44	44	88
Age, years (mean)	9.74	9.71	9.73
Left-handed	3	6	9
Sportsclub-membership	30	36	66
-ballsports	15	25	40
-dance/gymnastics	9	2	11
-alpine/swimming/athletics	6	5	11
-martial arts	0	4	4

The MR examinations were performed on a 1.5 T MR scanner (Philips Medical Systems, Best, The Netherlands), Intera model release 2.3 with master gradients and a four-element wrist coil. The children were not sedated. A coronal T1 Fast Spin Echo (FSE) was performed as part of a research protocol. We found that a 2D-sequence with high resolution images in the coronal plane gave less motion artefacts and took less time to obtain than a 3D sequence, which was an important consideration when using healthy, non-sedated children. The reformatted images were of sufficient quality to confirm the findings done in the coronal plane. The parameters used were: TR 561, TE 6.8, with three echoes and number of signal averages (NSA) was performed with 40 slices in three stacks. The slice thickness was 0.9 mm and acquired voxel size was 0.69×0.72×0.9 mm, with a reconstructed voxel size of 0.25×0.25×0.9 mm. The coronal T2 FSE scan, TR 3165, TE 70, 10 echoes, was fat suppressed using Spectral Selection Attenuated Inversion Recovery. The NSA was four, with 14 2.5 mm slices, giving an acquired voxel size of 0.31×0.40×2.5 mm and a reconstructed voxel size of 0.15×0.15×2.5 mm. Scan time was 3 min 56 s. Parallel imaging was used with a reduction factor of 1.6, giving a scan time of 4 min 11 s.

The radiographs of the left hand were performed on a Triathlon direct digital system, Decothron AS, Skedsmo, Norway, using the 50kVp and 2.0 mAs standardized setting for this age group. The Varian x-ray tube has a permanent filtration of 0.7Al at 75kV and gives a typical radiation dose of and 11.3 mGycm².

6.2 The Tromsø cohort - DWIBS (TCd)

Thirty-four of the patients from the Tromsø cohort were also invited to participate in the DWIBS-study and underwent a DW-sequence of the abdomen in addition to the wrist-examination. Eight children aged 0–5 years were recruited from patients referred for an MR scan under sedation, mostly brain examination, using the same exclusion criteria as for the wrist-cohort. Forty-two children with caretakers accepted and were thus included. All examinations were undertaken at the Radiology Department at University Hospital North Norway, Tromsø, from March to June 2009.

An 8-element flexible SENSE body coil was used for all examinations. An axial short-tau inversion-recovery (STIR) echo-planar imaging (EPI) TR/TE/TI, 3200/65/ 180 ms pulse sequence was used. Pixel size in plane, 3×3 reconstructed to 1.56×1.56; 5-mm slice thickness. Parallel imaging reduction factor, 2; EPI factor, 41; receiver band width, 2,668 Hz; number of excitations, 3; b value, 1,000 s/mm² applied in 3 orthogonal directions. Scan time was 3 min 20 s per scan station. The DWIBS sequence is meant for whole-body DW screening. One potential problem with DW-images is the T2 shine through effect, where the high signal is due to a T2-effect and not restricted diffusion. The Apparent Diffusion coefficient (ADC) is then calculated to depict the true restricted diffusion. However, the standard DWIBS-parameters have shown to provide good background suppression so that only restricted diffusion will show high signal, hence ADC-values are not calculated [77]. Two scan stations were used to obtain images from the diaphragm to the pelvic floor.

6.3 The Health-E-Child Cohort (HeCC)

The Health-A Child Cohort comprises all consecutive patients with JIA according to ILAR revised criteria [14], with active arthritis in the wrist and/or hip referred to Great Ormond Street Hospital, London, United Kingdom (GOS), Hopital Necker Enfants Malades, Paris, France (NEM), Ospedale Gaslini, Genoa, Italy (OPG) and Ospedale Bambino Gesù, Rome, Italy between October 2006 to March 2010. Patients with severe wrist or hip deformity or damage, such as subluxation or extensive joint destruction were excluded. 200 children with wrist involvement were thus enrolled. 78 age-equivalent subjects from GOS, NEM and OPG, with clinical signs of active inflammation of the wrist, were selected for comparison with the healthy children, 68 of which had synovial enhancement on MRI hence included in the study. MRI was performed only in cooperating patients without contraindications (i.e. previous allergic contrast reaction, metallic clips etc.) None of the children required general anaesthesia. A fat saturated 2D spin echo T2-weighted sequence; 3D T1-sequences and pre-and post contrast sequences were performed according to standardized research- protocols in each centre with a field of view extending from the distal radio-ulnar joint to the metacarpal diaphyses.

Table 4: Characteristics of the HeCC

	Female	Male	Total
Number	52	16	68
Age, years (mean)	10.13	11.44	10.44
Age at diagnosis	6.82	7.44	6.97
JIA subgroup:			
Oligo	8	1	9
Extended oligo	10	1	11
poly, RF neg	27	9	36
poly, RF pos	2	0	2
systemic	3	5	8
psoriatic	2	0	2

The MRI examinations at GOSH were performed using a 1.5T Advanto (Siemens) scanner, with up to 40mT/m gradient strength. A flex coil was used and the following sequences were obtained: T1w Coronal fast spin echo (TR 556, TE22, slice thickness 3mm, gap 0mm, NEX 2, matrix 512 x 250), T1w 3D spin echo (TR 600, TE 2, slice thickness 3mm, gap 0mm, NEX 2, matrix 512 x 288), T2w coronal turbo spin echo (TR 3600, TE 95, slice thickness 3mm, gap 0.3mm, NEX 3, matrix 512 x 192), VIBE fat sat, pre and immediate post-contrast (TR 4.3, TE 2.02, slice thickness 2mm, gap 0.4mm, NEX 1, matrix 256 x 192) as well as a 10min post-contrast (TR 550, TE 22, slice thickness 3mm, gap 0mm, NEX 2, matrix 512 x 154).

At NEM a 1.5T GE Signa HDx and HDxt scanner (General Electric Healthcare, Waukesha, Wisconsin, USA) was used and phase array coils were applied and the following sequences were obtained: 3D fast gradient Echo T1 (TR 7.4msec, TE 4.2msec, flip angle 25 degrees, acquisition voxel size 0.5 x 0.8 x 0.66 mm), fast spin echo T2 weighted

sequence with fat saturation (TR 2720-3120 msec, TE 70.5 msec, slices thickness 3mm, interslice gap 0.3mm) and contrast enhanced 3D fast gradient echo T1w with iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) sequences (TR 8.6-13.2msec, TE 4.2-6msec, flip angle 10 degrees, acquisition voxel size 0.5 x 0.43 x 0.48 mm) immediate post-contrast and 7 minutes post-contrast.

MRI-examinations at OPG were performed on a 1.5 Tesla MR system (Achieva Intera, Philips Medical Systems, Best, The Netherlands), using a flex wrist coil. The following sequences were obtained: three dimensional (3D) FSE T1-weighted (TR600, TE10, isotropic voxel size 0,8 mm, matrix scan 176 rec 352, acquisition time about 5 min, NSA 2), coronal T2-weighted turbo spin echo (TSE T2) with fat saturation (TE70, TR2715, matrix scan 218, rec512, slice thickness/gap3/0,3.mm, NSA4, acquisition time 2min 40 sec), 3D fast field echo (FFE) with fat saturation (TR 40, TE 7, matrix scan 304 rec 448, acquisition time about 4 min, isotropic voxel size 0,7 mm, flip angle 25) after gadolinium injection.

The radiographs of the hand were performed with postero-anterior views and a standardised positioning on the same day as the MRI's for both cohorts.

6.4 Image reading

The wrist MRIs and the radiographs were analysed in consensus, using a high-resolution viewing screen. The wrists from the TCw, were initially assessed by two paediatric radiologists with a special interest in musculoskeletal radiology (LS.Ording Müller, K.Rosendahl). The presence and distribution of bone marrow change and bony depressions were noted for each of the following bones: distal radius and ulna, all carpal bones except for the pisiform and the basis (distal 1cm) of the 1st to 5th metacarpals. Bone marrow change suggestive of bone marrow oedema (BMO) was defined as a lesion within the trabecular bone with ill-defined margins and signal characteristics consistent with increased water content, returning high signal on T2-wSE and low signal on T1-wSE images. A bony depression was defined as a bony indentation other than the normal vascular channels on T1-weighted images, seen in the coronal plane and confirmed in at least one of the reformatted sagittal or axial planes. The presence and volume of joint

fluid within the carpal- and carpometacarpal joints was assessed based on the T2 weighted images, and scored as 0 (none), mild (max thickness < 2mm) or moderate (≥ 2 mm). All scoring criteria were based on the definitions of inflammatory changes in Rheumatic Arthritis, presented by the OMERACT-group. [35, 56, 78].

When comparing the healthy children with the JIA-group we found that small differences in protocols and coils used in the different centres could potentially make determination of an “obvious vascular channel” inaccurate. We therefore refined the scoring system and assessed the number of bony depressions in both groups strictly as defined by the OMERACT_RAMRIS- criteria for erosive change: ‘A sharply marginated bone lesion, with correct juxta-articular localization and typical signal characteristics, which is visible in two planes with a cortical break seen in at least one plane’ [57]. In a second session, the wrist MRI’s from the TWC and the HeCC were assessed by two observers (LS.Ording Müller and P.Boavida), using the refined scoring system for bony depressions. In addition, the pre- and post contrast T1 weighted images were assessed for synovitis.

The same bones as studied with MRI were assessed for bony depressions on radiographs, defined as a focal bony concavity or a well-defined lytic lesion within the bone by two observers (LS.Ording Muller and D.Avenarius). It was also noted whether the lesion had a sclerotic rim. The radiographs were anonymised and the readers were blinded for the results of the MRI.

Depressions identified on MRI and radiographs were marked on separate templates and the scoring templates were compared side by side.

The Poznanski score was calculated from the radiographs. Poznanski-scores may be calculated using either the length of the wrist from the distal radial epiphyses to the 3rd metacarpal (RM) divided by the width of the bases of the 2nd to 5th metacarpals (W) or the length of the wrist divided by the length of the second metacarpal. The normal range of RM/W is independent of age and was therefore used to describe the findings in our cohorts of children at different ages [42].

Bone age was calculated from the radiographs using the computer program BoneXpert® (Visiana Aps, Holte, Denmark).

The children were grouped into four age groups (Group 1= 5-7y, Group 2= 8-9y, Group 3= 10-11y, Group 4= 12-15y).

The DWIBS-images were firstly read by two radiologists in consensus (LS.Ording Muller and D.Avenarius) and, in a second session, by a third radiologist (T.Köhler) separately. A visual evaluation of restricted diffusion, defined as high signal compared to the background, was performed [72]. The presence and distribution of high signal was noted. To assess the extension of high signal, each bone was given a score of 0 to 4, with quarterly intervals of volume involvement. Presence (yes/no) and localisation of asymmetry was noted. High signal within the vertebral bodies were characterised as central or peripheral. This was done based on the impression from preliminary observations that there could be an age specific pattern of high signal within the spine.

6.5 Statistical analyses

Papers 1 and 2:

One-way between-group analyses of variance (ANOVA) were conducted to explore the impact of age on the number of bony depressions. Post hoc tests were used to determine where the differences among the age groups occurred. χ^2 Tests were used to examine possible associations between age and the proportion of children with bone marrow changes (dichotomised) and visible joint fluid with linear by linear associations with exact tests as appropriate and to examine possible associations between MRI-findings and sex, sports club membership, time of the year for the examination. The analyses were performed using SPSS Statistics 17.0 (IBM SPSS, Chicago, IL, USA).

Paper 3: Cohen's Kappa inter-observer agreement coefficients of signal distribution and asymmetry were calculated using SPSS Statistics 18.0 (IBM SPSS, Chicago, IL, USA). The relation between total scores and age was explored in a scatter plot. The distribution of scores at the different ages was shown in a bar chart.

Paper 4: Independent t-tests were used to explore differences in Poznanski scores and number of bony depressions between TCw and HeCC. Paired t-test was used to examine differences in the number of carpal depressions as assessed by the initial and by the

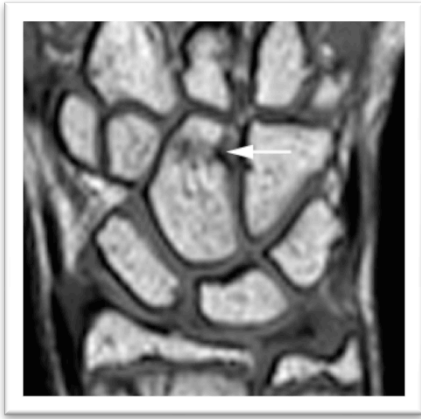
refined scoring systems. Statistical analyses were performed using the program SPSS Statistics 18.0 (IBM SPSS, Chicago, IL, USA). All significance tests were two-sided $P < 0.05$ was considered significant.

7.0 Main results

7.1 Paper 1

“The paediatric wrist revisited: redefining MR findings in healthy children”

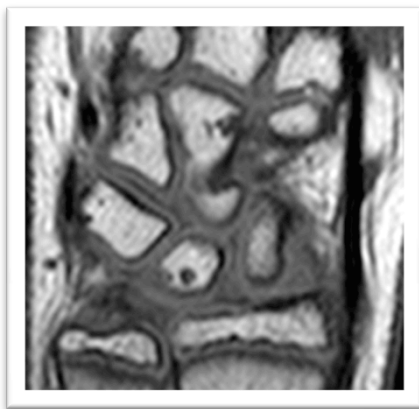
This study was undertaken to examine shape, signal intensity and volume of joint fluid at the wrist as shown by MRI in a cohort of healthy children. Eighty-eight healthy children (44 males) aged 5-15 years residing in Tromsø, underwent a T1w and a fat-suppressed T2-sequence of the wrist. The examinations were performed from March –October 2009. Four examinations were limited by artefacts, leaving 84 (43 males) for analyses. Nine children (6 males) were left-handed, 76% of the children were sports-club members. No differences in the results were seen according to gender and these results were pooled for analyses. Bony depressions in the carpal bones were seen in all age groups, with a significant increase in number with advancing age ($p < 0.001$). All children had joint fluid in at least one of the carpal- or carpometacarpal joints and approximately half of the children had more than 2mm fluid in at least one joint. In the second carpometacarpal joint moderate volume of joint fluid was seen in seven boys versus two girls ($p = 0.040$). No other associations were seen between the amount of joint fluid and gender. No associations were seen with joint fluid or marrow signal and handedness or sports-club membership. Bone marrow signal suggestive of BMO was seen in 53.6% of the subjects. No associations were seen between BMO and sports-club membership nor sex. Marrow change suggestive of BMO was seen more frequently in the examinations performed in the snowy period (from March to May and October month) compared to the summer months (June to September).



a)



b)



c)



d)

Fig 3. Examples of features seen in the cohort of healthy children: a) and b) BMO with low signal on T1 and high signal on STIR (arrows). c) Bony depressions seen as cortical break on T1. d) Joint fluid is shown as high signal within the carpal joints on STIR.

7.2 Paper II

“The Paediatric wrist revisited- findings of bony depressions in healthy children on radiographs compared to MR.”

This study was performed to assess findings of bony depressions on radiographs at the wrist in healthy children and compare those with findings of bony depressions on MRI. Eighty-eight children (the same cohort as in paper I) were included in the study. One child did not have a radiograph taken, and 4 of the MR-examinations were limited by artefacts, leaving 87 radiographs for analyses, and 84 for comparison with the MRIs. A total of 75 bony depressions in the carpal bones of 50 children were seen on the radiographs compared to 715 on the MR. No differences in number of depressions were seen for any of the carpals across the age groups and there were no differences according to sex, handedness nor sports-club membership. 64 of the 75 radiographically detected depressions were also seen on MRI and 11 depressions were seen on radiographs alone. In the proximal metacarpals, 65 depressions in 55 children were seen on the radiographs, with no difference across the age groups and no association with sex, handedness or sportsclub membership. On MRI, 81 depressions in 53 children were seen. Sports club members had significantly more depressions than non-members ($p=0.013$, Pearson chi square test) but no associations were seen according handedness or sex and there were no differences across age groups. 53 of the depressions in the proximal metacarpals were seen on both modalities, 22 were seen on MR alone and 6 were seen only on radiographs. No depressions were seen at the articular surface of the metacarpals, except for the very dorsal aspect of the second metacarpal where an indentation was seen in 52.3% of the children.

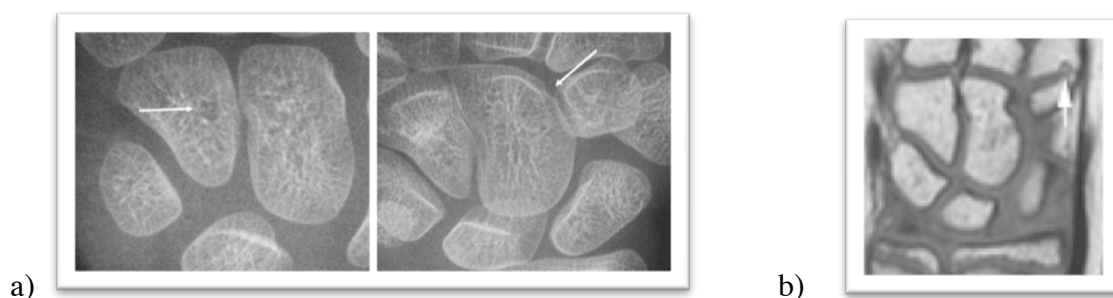


Fig. 4 Bony depressions seen on radiographs (a). Example of the bony indentation seen at the dorsal aspect of the 2nd metacarpal in 50% of the children on MRI but never on radiographs (b).

7.3 Paper III

'High signal in bone marrow at diffusion-weighted imaging with body background suppression (DWIBS) in healthy children'

This study was performed to describe the signal distribution at DWIBS in the normal developing lumbar spine and pelvic skeleton. Forty-two healthy children age 2 months to 16 years underwent an MR DWIBS-sequence of the abdomen and pelvis. Horizontal artefacts were seen in the lumbar spine and pelvic skeleton of 27 patients and the images of the lumbar spine were noisy, however all the scans were diagnostic. All children at all ages had restricted diffusion seen as high signal in the lumbar spine and pelvic skeleton. There was a tendency towards reduction of signal with advancing age, but there was also a wide difference between age-equivalent subjects. Three different age-specific patterns were seen in the lumbar spine. Children younger than 5 years of age had high signal centrally within the vertebral body. Children older than 10 years had high signal in the periphery of the vertebral body and children between 5-10 years had a mixed pattern. All growth plates of the pelvic skeleton demonstrated high signal and none of the subjects had high signal in the proximal femoral epiphyses. Twenty (48%) of the children had asymmetrical high signal in their pelvic skeleton, most frequently seen in the ischium and sacrum but also seen in the ileum and pubis.

There was good inter-observer agreement with a Cohen's Kappa coefficient of 0.58 for signal distribution and a Cohen's Kappa coefficient of 0.57 for asymmetry.



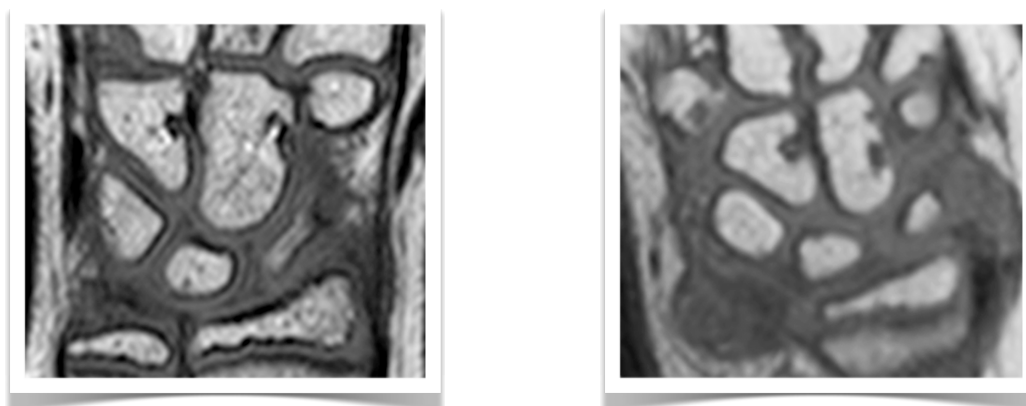
Fig 5. Example of restricted diffusion seen in a 5 year old (arrows). Asymmetrical signal is seen within the ilium. (The image is shown in black/white inversion).

7.4 Paper IV

'MRI of the wrist in juvenile idiopathic arthritis: erosions or normal variants –can we tell?'

This study was performed to compare the findings of bony depressions on MRI in healthy children and children with JIA in order to find true markers for disease. 78 children with JIA were selected for comparison with the cohort of 88 healthy children. Three of the MRIs from the healthy cohort could not be analysed in more than one plane, due to motion artefacts on the T1- sequences. The MRIs of 10 patients from the JIA-group showed no synovial enhancement, leaving 68 patients (52 girls) with JIA and 85 healthy patients (43 males) for analyses. Radiographs performed on the same children on the same day were used to compare the carpal length in the two cohorts.

No differences were seen in the number of bony depressions in the carpal bones between the two cohorts in any age group (group I: $p=0.953$, group II: $p=0.712$, group III: $p=0.940$, group IV: $p=0.836$). Exclusion of the children with disease duration less than 6 months did not change the significance. In the older children with JIA significantly more depressions were seen in the metacarpals, compared to the healthy children (Group III: $p=0.036$, Group IV: $p=0.011$). In age-groups I and II the difference was not significant (Group I: $p=0.404$, Group II: $p=0.612$). Even with no detectable difference in bony depressions of the carpal bones (as shown by MRI between the two cohorts), the length of the wrist measured from the radiographs, expressed by the Poznanski score, was significantly lower in children with JIA ($p<0.001$).



b) Fig 6. Examples of bony depressions in the hamate and capitate of a healthy 10-year old child (a) and a 8 year old child with JIA (b)

8.0 Discussion

8.1 Material and methods

8.1.1 Study design

All papers were cohort studies. A cohort study is one type of observational study. A cohort is a group of people with some common characteristics, invited to participate in the study based on these characteristics. An observational study contrasts an experimental study in that the data are collected and analyzed without being influenced by an experiment. Paper IV is a comparative observational study where the findings in two different cohorts are compared to describe possible differences. The studies are all cross sectional because the observations were done at only one point in time. The studies were prospective because the data were collected forwards from the beginning of the study.

8.1.2 Cohorts

Two main cohorts were used in this thesis. One cohort consists of healthy children with no medical history of musculoskeletal disease, cancer, infection, current medication or recent skeletal trauma, the Tromsø cohort (TC). The images from this cohort were obtained exclusively for research purposes.

The other cohort consists of children diagnosed with JIA according to the ILAR-criteria, in one of three selected hospitals (GOS, NEM, OPG), the health-e-child cohort (HeCC). All children had clinical signs of wrist involvement. Standardised images were obtained according to a research protocol regardless of clinical indication for imaging.

The healthy cohort was used as a reference-group when comparing the findings in the two cohorts (paper IV).

The TC was balanced in regards to age and gender, whereas the HeCC consists of mainly girls and more of the individuals were from the older age groups. However, we found no associations between gender and the findings of bony depressions in the healthy children and the data were therefore pooled for analyses. When comparing the findings

of bony depressions in the two cohorts, we divided the children into four age groups to minimise the problem with different age distributions.

The HeCC was a selected group of JIA patients and was not balanced with regards to JIA-subtype, age or disease duration to reflect the general JIA-population. This is no epidemiological nor experimental study, and the clinical characteristics of HeCC is well described in the paper hence selection bias is not an issue within this cohort. However, the conclusions from the results may not be generalised for all children with JIA.

The children in the TC were invited via e-mails at the University Hospital North Norway (UNN) and on clip-boards at UNN and at the primary schools in Tromsø. Healthy volunteers tend to have a higher socioeconomic status than the average population, and many of the subjects were children of health workers, mainly doctors, nurses and radiographers, and from scientists at the University of Tromsø. Due to this possible selection bias the TC may not entirely reflect the normal population. There is an association between overweight and degree of physical activity and parental socioeconomic status in children [79]. We did not find any associations between our findings and level of activity in terms of sports-club membership, therefore selection bias with regards to activity level did not seem to be a problem. One motivation for healthy volunteers to participate may be fear or suspicion of disease and that they wanted this investigated through participation in a study. One family admitted that the mother was diagnosed with RA and that they thought this was a good opportunity to see if their son's hand was affected. We were not aware of similar motives in any other families. None of the subjects had any pain or symptoms of disease. This particular subject's MRI showed neither BMO nor fluid more than 2mm.

13% of the male and 7% of the female subjects were left-handed. In the average population approximately 10% are left-handed with 5 left-handed men per 4 women. Taking the relatively small sample size into consideration the handedness roughly reflects that of the normal population. We also found no associations between handedness and our findings.

8.1.3 MR-protocols

The MRIs of the HeCC were performed as part of a research protocol chosen by the initiators of the HeC-study. They include the core set of sequences recommended by the OMERACT-group for imaging in RA [56]. The protocol for the TC was chosen to mimic the spin echo T1-images and the fat saturated T2-images in the HeC-study, with some adjustments to facilitate research in healthy children.

Standardisation of multicentre MR-protocols is a challenge. The resultant MRI will always vary with the different machines and coils used for obtaining the image, even when using standardised protocols. The T1-images used for comparison with the TC were 3D- acquisitions, to enable reformatted images. For the TC we chose 2D-images with high resolution in the coronal plane. This is a faster technique and gave less motion-artefacts, which was important with non-sedated children. The images did not have entirely isotropic voxels, hence measurements could not have been performed in reformatted planes, but the images were sufficient for reformation to confirm the findings in the coronal plane.

Cortical bone returns low signal on all MR-sequences, contrasting the high signal from the fatty marrow on T1w-images. A chemical shift artefact producing a dark edge at the interface between fat and water was seen to some degree in the images. This may widen the dark zone and bias the imaged cortex [80]. This artefact only occurs in one direction (the phase-encoded direction) in the resultant MRI, and should be easily recognised. However, when the artefact was small it could have been difficult to differentiate from the overlying cortex [10] and potentially making the determination of a 'cortical breach' less accurate.

Different techniques of fat-saturation were used in the different hospitals to obtain the best, most homogenous fat-suppression. The resultant MRI is a product of signals with different intensities encoded to create an image. The highest signal received from a tissue will be coded as bright, and the other signal will be scaled related to this signal to form an image, regardless of the absolute signal intensity [81]. The different MR-protocols may result in different signal intensity of bone marrow and we do not know if, or to what degree this could affect the perception of BMO and possibly also presence and amount of joint fluid. Quantification of BMO could have been a solution to this problem,

but to date there are no validated methods for objective quantification of BMO on MRI of the paediatric wrist.

Rescaling could also have been a problem with the DWIBS-sequence. We did not have an external nor internal reference and all bright signal was interpreted as restricted diffusion, regardless of the degree of restriction. By choosing a high b-value of 1000, with three different diffusion gradient directions and sufficient background suppression, we saw that only areas of restricted diffusion returned high signal, and that T2-shine through effect was never a problem, because we did not observe any signal from areas with known fluid (like the gall bladder, renal collecting system or the bladder). The problem with using a high b-value as in our study could potentially be a low signal to noise-ratio within the images. Fortunately we found that all our images were diagnostic for the intended purpose.

8.1.4 Image reading

All images were read by two radiologists. In paper I,II and IV the image reading was performed in consensus and in paper III by two radiologists independently.

Consensus reading is a common method for image reading within radiology research. Consensus has an overall positive connotation, as it implies a common effort targeted towards agreement. Ideally, consensus is based upon active collaboration, rather than on passive compromising. However, consensus reading has been criticised because the observers will always retain a source of variability, hence both systematic and non-systematic errors may be obscured. Consensus interpretation does not reflect clinical practice but it is typically used in research, based on the assumption that a decision made in consensus is more accurate than an individual decision. In our setting where there is no established scoring system on MRI for disease in children with JIA, and no existing reference atlas of what to call normal standards, we needed to make a common agreement on what to call a bony depression in the healthy children, based on the OMERACT-criteria, in order to make a reference standard for image reading. In this setting a consensus reading may be justified and even the most applicable method for image interpretation [82]. In paper III we did an estimation of the amount and distribution of restricted diffusion. We did not intend to calculate the absolute amount of

restricted diffusion at a given age, but rather describe a trend in order to evaluate the usefulness of this technique as a screening method. The scoring system using quarterly intervals and presence/absence of asymmetry i.e. 'yes/no' gave good inter observer agreement.

One methodological problem in paper IV was the inability to blind the readers for whether the subjects were from the TC or HeCC. Different image protocols made it easy for the readers to differentiate the healthy from the children with JIA. We did not find a feasible way to avoid this recognition. We did however read the normal images twice, on two separate reading sessions, first by two observers (LS. Ording Müller, K. Rosendahl) and then six months later by one of the first observers and a third observer (LS.Ording Müller, P.Boavida) using a refined scoring system. There was no statistical difference in the number of depressions when comparing the two cohorts using either of the two scoring methods. This indicates consistency in the scoring methods.

8.1.5 Statistical analyses

Paper 1 and 2:

In these papers we wanted to assess the variance in bony depressions between age-groups. The variables were continuous. When comparing means in more than two groups, analyses of variance (ANOVA) is a preferred method, because using multiple two-sample t-tests would increase the chance of a type I -error. We used a one-way analysis of variance because we only wanted to look at one independent variable (age) on the dependent variable (bony depression). ANOVA only tells us the overall variance and therefore we performed post hoc analyses to assess the difference between the different age groups.

Chi square statistics is used to investigate whether distributions of categorical variables differ from one another within different groups when assessing associations. We therefore used chi- squared test to examine possible associations between bone depressions and handedness/sport club membership, and differences according to sex. Exact tests were used because of the small sample size.

Paper 3:

Simple Cohen's Kappa interobserver agreement coefficients of signal distribution and asymmetry were calculated to assess reliability of the scoring method. One could discuss whether a weighted kappa would be more appropriate in this case, because the aim was not to use this scoring system in a clinical setting, and we did not aim at finding the absolute relationship between age and signal. We only wanted to use the method to describe the tendency of change in signal with age, and one could argue that a weighted Kappa would be more appropriate. I would then have chosen a linear weighting. However, even the non-weighted kappa values were good. The relation between total scores and age was explored in a scatter plot. The distribution of scores in the different age groups was shown in a bar chart. There was a tendency towards a reduction of relative area of high signal within each bone with age, but also a widespread inter-individual variation. The aim of this study was not to be able to predict the amount of high signal at a given age, but to describe the findings in order to evaluate the usefulness of this sequence. Given the widespread inter-individual variation and the relative small sample size, statistical assessment of these relations was not considered justified, but the descriptive presentation of the findings were important as such.

Paper 4:

In this paper we wanted to compare the mean number of bony depressions in healthy children and children with Juvenile idiopathic arthritis. An independent t-test was used for this purpose, and standard deviations were given to show the variability in both groups. Independent t-tests are used to compare means on a continuous variable, when the variable is normally distributed (checked by a q-q-plot), there was homogeneity of variance (Assessed by Leven's test) and the two groups were independent of each other. The difference in distribution was presented in figures and with descriptive statistics (percentages).

8.2 Ethical considerations

Research on healthy individuals in general, and children in particular, forces us to make specific ethical considerations.

The Norwegian law that regulates medical research 'Helseforskningsloven' § 18 states that in all medical research the disadvantage or risk from participation in a research project must be insignificant. We know that the use of ionising radiation may be harmful, particularly in children [83]. For stochastic effects of the radiation, there is no threshold dose below which it is absolutely certain that an adverse effect cannot occur. However, the radiation dose to each research subject only equalled approximately 5 days of background radiation and statistically there is no increased risk of medical adverse effects from this exposure. MR-investigations do not include ionising radiation but the images are obtained in a strong magnetic field (1.5T). Some claim that we do not know the full truth about potential effects on human tissue from the magnet and in a small pilot study evidence of genomic changes in human tissue after exposure to the strong magnetic field was found [84]. Still, no research has been able to find any long-term adverse effects in humans or foetuses after the first trimester in utero. One other strong principle in medical research is that all participation must be voluntarily recruited ('Helsepersonelloven §18b) and that informed consent must be obtained. Formally, in children under 16 years, the parents give the consent for their child to participate. Still the child must be adequately informed and not be forced nor feel any pressure to participate. We made information sheets with information adjusted to the child's age (see appendix) and gave all subjects the opportunity to look at the MR-magnet before the examination. It may be challenging to determine whether a child is adequately informed and the researchers are responsible to make sure the child does not feel obliged to undergo an investigation, in order to satisfy their parents, carer or the health worker. To avoid this one of the responsible researchers was present during all examinations to ensure that no pressure was put on the child. A parent or carer was also present during the examination. We emphasized that it was entirely up to the child to stop the investigation at any time, before or during the uptake, if desired. In research on healthy volunteers there is always a risk of incidental findings and there should be a system in place to detect and handle such findings [85, 86]. In our project the primary investigators (LS Ording Müller, D Avenarius) assessed all the images immediately after they were

performed. The parents should ideally be made aware of the possibility of incidental findings before consenting to participate. They were also made aware of the limitations to the study to make sure nobody took participation in the study as an opportunity to investigate a possible medical issue, like the family with a mother diagnosed with RA. One of our subjects had marked BMO in the distal radius in a pattern that would have been interpreted as a fracture in a child with symptoms. He admitted to have had an extension trauma to his wrist when playing football but had very few symptoms. The problem was that no normal standards were yet established and we found it difficult to determine whether this was pathological, and needed treatment or not. We referred the child to the orthopaedic surgeon who applied plaster cast just to 'make sure' knowing that this treatment is nearly harmless to the child. No other incidental findings were picked up. The law for medical research 'Helseforskningsloven §18c' states that the research should be beneficial for the research 'object' itself or for other individuals with similar age-specific illness or disease. Investigations done on the TC were performed only for research purposes and were not indicated for medical reasons. Therefore any potential risk from undergoing the investigations could not be weighed up against some diagnostic benefits for each individual, but the spontaneous feedback we received from most parents was that they felt that this was a useful experience for their child, in case they would need a diagnostic MRI in the future. The 'Helsinki declaration' states that in research on a disadvantaged or vulnerable population, which includes children there must be "...reasonable likelihood that the community stands to benefit from the results of the research." In research on healthy individuals there is a utilitarian attitude to benefit, where the advantages to the society from the research is of most importance. There is an urgent need for normal references for interpretation of paediatric MRI. Risk assessment was carefully performed and the project was approved by the regional ethical committee (REC). The benefits of this project were considered to outweigh the potential risks of participation.

8.3 Results

This thesis addresses two general aims. The first is to describe the presence of signs on MRI, previously thought to be markers of disease, in healthy children. The second was to compare findings in healthy children with children with JIA in order to find markers for true disease.

In total, 96 healthy children underwent; either a lumbar and pelvic DWIBS-sequence (8 subjects), a wrist MRI (54 subjects) or both (34 subjects). The studies are prospective and the images were performed exclusively for research purposes. No similar studies on MRI of healthy children have previously been described.

8.3.1 Bony depressions

Bony depressions at the wrist that, according to the OMERACT-criteria could have been defined as 'erosions', were seen as a normal finding on MRI in healthy children. This is supported by a Finnish study where bony depressions resembling erosions also were seen in healthy adults [87], although less frequently than seen in our study. The differences could, in part, be due to different magnet strengths and protocols, but could also be due to different definitions of 'bony depression' in the two studies. However, we also found bony depressions at the wrist as a normal finding in children on radiographs, although much less frequently than seen on MRI. These findings contrast the study in adults, where bony depressions were rarely seen on radiographs of the carpal bones [87]. This indicates that the surface of the growing carpal bones is more irregular than in adults. MRI showed bony depressions of the carpal bones ten times more frequently and with better resolution than radiographs. Previous studies support cross sectional imaging as superior to radiographs in sensitivity to erosions, hence normal surface irregularities are also more easily depicted on MRI [47, 88]. Heavy mineralised cortical bone is easily depicted on radiographs, creating a smooth bony surface of the bone in the two-dimensional image. On MRI cortical bone returns very low signal due to lack of water molecules available to precess [10, 80]. This make normal surface irregularities at the chondro-osseous junction, ligament insertions and grooves for crossing vessels appear as irregularities or 'holes' at the bony surface on T1 weighted MRI. New imaging

modalities with better inherent spatial and contrast resolution may reveal details of the anatomy that previously not have been encountered for in image interpretation. The inter-metacarpal ligaments, seen in profile on the MRI, were frequently also seen on the radiographs and are therefore well known as normal variants. However, the grooves seen at the ligament insertions were in part large and irregular on MRI, which can make the differentiation between a normal variant and a true erosion difficult. In 50% of the children we noticed a bony depression at the dorsal aspect of the bases of the 2nd metacarpal. This depression most likely represents the insertion of two small ligaments [89]. This was never seen on radiographs, and could easily have been misinterpreted as erosions at the joint surface when seen on an MRI of a child with JIA.

8.3.2 Bone marrow oedema

Signal change suggestive of BMO was seen in a surprisingly high number i.e. 54% of the healthy children. BMO is regarded as a pathological finding in adults and is suggested as the most specific finding of RA at the wrist [90]. BMO is a non-specific expression on MRI and only refers to a finding with specific signal characteristics [57] regardless of the histological characteristics of the tissue. It is not unlikely that the 'BMO' seen in healthy children represents a different entity than the 'BMO' caused by inflammation. Presence of haematopoietic marrow may be one cause of BMO on MRI. This seems less likely to be the explanation for the signal changes seen in the TC because epiphyseal marrow conversion occurs within 6 months of the radiological appearance of the ossification centre and, as such, should be complete within the capitate and the hamate (two of the most commonly involved bones) by 1 year of age[91]. Reconversion of fatty to red marrow which is a physiological process to meet the body's need for red blood cells, as a reaction to stress, also seem unlikely because this will typically occur from centrally to peripherally, and because all of the children in this cohort were healthy. We know that stress injuries may cause BMO on MRI. These signal changes are most likely due to haemorrhage and hyperaemia from micro fractures [92]. One could speculate whether the BMO in healthy children is caused by normal physiological reactions, like hyperaemia, to shear stress forces applied to the elastic, growing knuckle during normal daily activity. The problem is that the BMO-signal caused by physiological processes is indistinguishable from BMO-signal caused by inflammation on standard fat suppressed

T2-sequences, and interpreting BMO as a sign of inflammation of the bone in JIA may lead to overestimation of disease activity and severity.

8.3.3 Joint fluid

Joint fluid was seen in at least one of the radioulnar, radiocarpal, carpometacarpal, and proximal metacarpal joints in all the healthy children. A thin, laminar layer of joint fluid is present in all normal joints and is frequently seen on MRI. Surprisingly joint fluid more than 2mm was seen in almost 50% of the children in at least one joint, most frequently seen in the first carpometacarpal joint and the scaphoid/trapezoid joint. This amount of fluid at the wrist has been defined as pathological in adults [57]. We also found fluid in the piso-triquetral recess in half of the children, a finding that previously has been described as a marker of carpal synovitis [93]. In a paper by Fredricson et al. fluid collections were found on MRI of the wrist in 80% of asymptomatic elite gymnasts [94]. Increased joint fluid production may be a physiological reaction to active use of the wrist joints and not necessarily a sign of pathology.

8.3.4 Restricted diffusion

Restricted diffusion was seen in all the healthy subjects with a tendency towards reduced signal with advancing age. We do not know exactly what the areas of restricted diffusion represent but because we see a reduced signal in the older age groups, it is likely to be the cellular red marrow within the axial skeleton and proximal femur that accounts for some of the signal. Also growth zones with high cellularity showed restricted diffusion in the cohort of healthy children. Diffusion weighted imaging is increasingly used in oncology imaging, both for tumour characterization, but also in screening and follow-up of skeletal metastases [77, 95]. DWI has also shown promising results in detection of early inflammation [96]. Clinical assessment of children may be challenging, particularly in diseases where the pathology may be multifocal like in JIA. We are continuously seeking safe, efficient and sensitive methods that could facilitate the diagnosis of multifocal JIA or other inflammatory diseases like e.g. chronic multifocal osteomyelitis (CRMO).

Whole body DWI could potentially have been such a method but the findings of restricted diffusion in healthy indicates that this method is probably too inaccurate. The DWIBS-sequence is unable to differentiate the physiological causes from the pathological causes of restricted diffusion. One of the limitations to this study was that we only had one MR-sequence, the DWIBS. In clinical practice this would not be the case and we would often have other, complementary sequences to compare with, which could increase the specificity of the findings. However, as a screening tool for skeletal pathology in children the DWIBS may lead to over-diagnosing of disease.

8.3.5 Comparison of bony depressions in healthy children and children with JIA

A subset of 78 age-equivalent patients with wrist-involvement from the HeCC was selected for comparison with the TCw, 68 of which had synovial enhancement on MRI hence included in the study. The study was prospective and the images were performed as part of a research protocol.

We found no significant difference in the number of bony depressions in the carpal bones between the TCw and the HeCC at any age group. The significant difference in the Poznanski score shows us that there is a difference between the groups, but that traditional scoring systems are unable to accurately detect the differences. Some sites were commonly involved in both groups and they are thought to represent the insertion of ligaments or crossing vessels. Knowledge of the normal anatomy of the carpal bones is crucial when interpreting the rheumatic wrist and pitfalls in scoring of MRI have previously been published for the wrist in adults [97, 98]. In the children with JIA, true erosions seemed to evolve from the normal anatomical grooves within the bone. This could be case because the peri-ligamentous areas are thought to be predilection sites for erosions [99]. The size of the bony depressions was not taken into account in our scoring, and maybe an accurate method for measuring the size of the depressions would reveal differences between the groups. However, we saw that the depressions vary in size in both healthy children and children with JIA and to determine the 'cut off' for when a depression becomes an erosion may still be difficult. It is also shown that measuring the size of the erosions may be difficult, especially in small bones and that the accuracy of the measuring tools will vary with different protocols used, and will particularly be

influenced by the degree of chemical shift artefacts within the image [100]. Even though certain areas were commonly involved in both healthy children and children with JIA, some of which have previously been described as normal variants in adults, bony depressions were also commonly seen in other, more random, locations in the carpal bones in both cohorts. This indicates that the surface of the growing carpal bones is more irregular than in adults, making the determination of erosions even more difficult in children. One approach to determine the size of an erosion is to predict the total volume loss of the affected bone. This method is advised by the OMERACT-RAMRIS criteria, using a ten-scale system (0-10, where 10 is 90-100% volume loss)[78] and later modified for the use in children where the carpal bones are smaller using a 4-scale system (1-4, where 4 is 75-100% volume loss) [65]. An extensive work on validating a semi- quantitative scoring system using both 0-4 scale and 0-10 scale shows that the results for inter-observer variability and aggregate scores in particular, are moderate to poor and it's use as a sensitive tool for assessing progressive disease in JIA is questionable [75].

The size of the wrist was smaller in the children with JIA compared to the healthy children, shown by the significantly lower Poznanski score in the HeCC. Similar findings were described by Poznanski in the original paper from 1978 where the Poznanski-score was introduced [42]. The carpal bones in children are in part cartilaginous, particularly in the younger age groups [101]. The relatively smaller wrist in the children with JIA could be due to cartilage destruction, bony destruction or growth disturbances [102-104]. When looking at some of the MRIs of the JIA patients we felt that the wrist was generally small with edgy carpal bones and possible loss of cartilage. However, when studying the surface irregularities of each single carpal bone and metacarpal bases we were still often unable to label any of the bony depression as erosions and not normal surface irregularities.

There were some differences in the distribution of bony depressions between the two cohorts, where bony depressions in some areas were exclusively seen in the children with JIA. This was particularly the case for the joint surfaces of the CMC-joints. In 6 carpal bones from 5 of the JIA- patients, surface irregularities were seen around the whole circumference of a bone. These features were never seen in the healthy children and are more likely to represent true pathology. The maximum number of bony depression was higher in the children from the HeCC. Four children with JIA exceeded the maximum

number of bony depressions seen in the TCw. This indicates that more extreme features of bony destruction may be seen in children but the early signs of erosions may be difficult to differentiate from normal findings.

Bony depressions were seen more frequently in the metacarpal bases in the older children with JIA compared to their age-equivalent healthy subjects. This could in part be due to different distribution of JIA-subtypes between the age groups. However, the differences were not seen for the carpal bones indicating that the normal bony surface is less irregular in the metacarpals compared to the carpal bones. One could also speculate that the pattern of bony destruction may be different in tubular- and round bones.

8.4 Epistemological considerations

The results from this thesis highlight important epistemological issues in radiology in general and in paediatric radiology in particular. In the article 'What's the evidence', B.P. Wood addresses some difficulties in radiology research [105]:

'Our specialty is characterized by a variety of opinions and techniques, which constitute rational approaches to diagnostic medical imaging. Interpretations of the results and observations at imaging vary. The design and steps of a diagnostic study method also vary according to the equipment, experience of the radiologist, and question to be addressed. The great diversity of disease entities to be addressed also adds opportunity for controversy. Radiologists interpret visual information, which is categorized by pattern and which is matched with information and concepts that reside as schemas within the long-term memory.'

This highlights some of the challenges we face when creating scientific evidence in radiology. One problem is to create a scoring system that can easily be adapted by different radiologists and applied to all images of the same category regardless of different equipment and imaging protocols being used. This is one of the 'inherent errors' of radiology research because we most often have to translate visual information into numbers. Even detailed definitions, like the OMERACT-criteria for pathology, give room for interpretation and there is no guarantee that two different radiologists interpret the definitions equally. Automatic imaging interpretation systems may improve these

inaccuracies, but the different imaging protocols and machines used to create an image will always be a source of possible error. Another problem is to find universally accepted interpretations of the imaging findings. The definitions of pathology used in radiology research must reflect the actual pathological process we intend to depict. Radiology is a rapidly expanding medical science. The interpretation of new imaging techniques is often based on our previous experience and knowledge from other imaging modalities, or similar techniques used on different body-parts or age groups. This is particularly the case for paediatric radiology where imaging techniques initially are tested on adult patients, before they are applied to the paediatric population. Definitions from 'adult radiology' are therefore often adapted for use in children. However we need to seek evidence of how our imaging findings fit into the clinical context, as Wood writes:

'The tools of evidence we now seek serve as an expanding scheme into which our tools of pathophysiology and clinical decision making experience fit'. [105]

Thornbury and Fryback describe radiological evidence in the light of how our findings contribute to the diagnostic efficacy [106]. They introduce a hierarchical system where the usefulness or 'efficacy' of evidence in radiology is evaluated at different levels (Fig 7). Efficacy at the lower level is a prerequisite for efficacy at a higher level. However, higher efficacy at a low level does not guarantee high diagnostic efficacy at a higher level. E.g. good image quality and feasible image acquisitions or even reproducible scoring systems do not guarantee that a test will improve patient outcome.

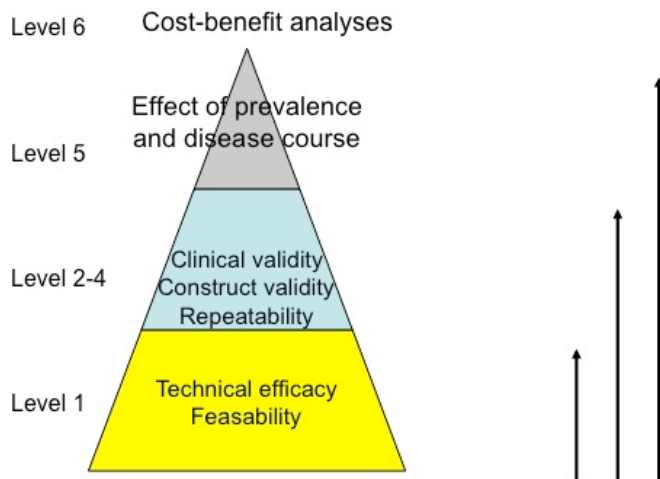


Fig 7. Thornbury and Fryback's levels of diagnostic efficacy for radiological investigations

The results from this thesis suggest that some of the published 'evidence' in imaging of JIA is based on inaccurate definitions of pathology [11, 47, 65, 107]. Clinical-and construct validity or the effect on the disease course may not have been evaluated hence these inaccuracies were not appreciated.

8.5 Clinical implications and future directions

The main challenge in future work on scoring system on MRI for children with JIA will be to find methods to differentiate normal variants from true pathology. Comparison of BMO and joint fluid distribution between healthy children and children with JIA, may be useful to find possible differences that may facilitate image interpretation of true pathology. The term 'bone marrow oedema' is non-specific and only refers to the signal characteristics on classic MRI-sequences. A study by Zanetti et al shows that the BMO in osteoarthritic knees in adults contain surprisingly little oedema [108]. There is ongoing research on methods for quantification and characterisation of BMO-lesions, particularly on 3Tesla-MRI [109]. These methods may allow us to better understand the pathophysiology of BMO and may be useful in differentiating the BMO-like signal seen in healthy individuals from the BMO caused by inflammation. Contrast enhancement pattern of the BMO could possibly be different in healthy subjects and subjects with JIA. Contrast enhanced MRI, particularly dynamic contrast imaging, could play a potential

future role in characterising BMO [110]. Due to ethical considerations contrast was not administered to the healthy subjects.

An atlas of normal variants on MRI with normal ranges of carpal bone size and age-specific ratios of bone and cartilage may be helpful in differentiating normal surface irregularities of the carpal bones from erosions. The development of new hardware and software has broadened the clinical applications of 3 Tesla MRI. In the evaluation of the wrist, 3 Tesla MR-systems offer more advanced capabilities and higher diagnostic accuracy than lower-field-strength systems [111, 112]. Hopefully a more detailed knowledge of the anatomy of the small bones on MRI may facilitate an improved definition of bony destruction in the paediatric skeleton. There is reason to believe that bony destruction in JIA is a consequence of overlaying cartilage destruction. Methods for detection of changes in the cartilage may be a more accurate method for assessment of early signs of destructive disease, particularly in children where the proportion of cartilage compared to bone is bigger than in adults. Several new MRI-techniques sensitive for changes in cartilage have emerged over the last years. Assessment of cartilage on MRI is an area of active investigation and may in the future give new insight into new, more accurate methods for detection of early destructive change on MRI [67]. Different patterns of contrast enhancement could potentially have enabled us to distinguish between normal variants and true erosions. A study in patients with RA suggest that true erosions are more likely to show contrast enhancement on post Gd-scans [113]. Until we develop validated methods for early detection of bony destruction on MRI, a baseline study with subsequent follow-up imaging could be advised to potentially increase the diagnostic accuracy of bony destruction on MRI. To date, the best validated method for assessment of bony involvement of JIA remains plain radiography.

The DWIBS-sequence was developed as a non-specific screening method for skeletal pathology, particularly for use in oncology [72]. The method does not allow quantification of the restricted diffusion. More specific diffusion weighted methods, using quantitative measures of diffusion, like ADC-values, may distinguish between different causes of restricted diffusion in the skeleton [114]. If diffusion weighted imaging ought to be used in screening for skeletal pathology in children normal standards for the amount of restricted diffusion must be established. Until then it does not seem expedient to use DWI as a screening tool for skeletal pathology in children.

8.6 Strengths and limitations

The strengths of our studies are the prospective design, the standardized state-of-the-art imaging protocols used and the high numbers of children included. All children from the TC were healthy and without any symptoms or medication at the time of the examinations. All but two were Caucasian. All the children in the HeCC were recruited by dedicated members of the HeC-research group, using the same inclusion- and exclusion criteria.

One limitation of consensus-reading is the tendency to obtain subjective scores and the inability to perform tests of interobserver variability. However the scoring criteria were well defined and we experienced little disagreement during the scoring sessions. Different protocols used in the different centres could be a source of error. Meticulous work was performed to minimise the differences, but when using different MR-machines and coils there will always be small differences in the resultant MRI images and data. The OMERACT-criteria are created as general scoring criteria for multicenter use, hence problems with different protocols was most likely taken into consideration when making the scoring criteria. During the work with the thesis we refined our scoring system to perfectly match the OMERACT-criteria and to minimise the problems inherent within the different protocols. We found no significant difference in the mean number of depressions at any age when comparing the scores from the first session with the second. The HeCC was not balanced with regards to sex and age. We however found no association with our findings when sex and data were pooled for analyses. Comparison of TCw and HeCC was done age group by age group in order to minimise the age difference in the two cohorts. The major limitation was the inability to blind the readers for the healthy/JIA-status of the subjects. This would probably have been a bigger problem if we had found major differences in the absolute numbers of bony depressions between the two groups. It seems unlikely that bias from knowing if the child was healthy or suffering from JIA could have had major influence on the results.

9.0 Conclusions

- Bony depressions resembling erosions at the wrist are frequently seen on MRI in healthy children.
- Bony depressions, with or without sclerosis, may occasionally be seen on radiographs of the wrist in healthy children.
- The number of bony depressions seen on MRI increase with advancing age. No association with age was seen for the depressions detected on radiographs.
- Bone marrow oedema is a common finding within the carpal bones, proximal metacarpals and distal radius/ulna on MRI and was seen in 53.6 % of the healthy children.
- Joint fluid in the radioulnar, radiocarpal, carpal and carpometacarpal joints is a normal finding and more than half of the children showed more than 2mm fluid in at least one joint.
- Restricted diffusion in the lumbar spine and pelvic skeleton is normal in healthy children, even in an asymmetrical pattern,
- No difference in number of bony depressions in the carpal bones was seen between children with JIA and healthy children at any age group.
- The wrist is generally smaller in children with JIA.
- In some areas of the wrist bony depressions were exclusively seen in children with JIA.
- Confluent bony depressions around the circumference of a carpal bone was only seen in children with JIA.
- Some MRI features were seen only in children with JIA hence more likely to represent true pathology.

In summary, this work shows that definitions of pathology on MRI based on and extrapolated from findings from the adult population cannot automatically be used when interpreting images in children. Traditional MR-sequences are inaccurate in differentiating true erosions from normal findings of bony depressions, unless they appear in certain specific locations. Establishment of age-specific normal standards and proper validation of MR-techniques used to diagnose and follow-up paediatric diseases is crucial for the accuracy of image interpretation.

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