ULTRASONOGRAPHY

for Diagnosis, Intervention, and Follow-up in Juvenile Idiopathic Arthritis

Louise Laurell

Institute of Clinical Sciences
at Sahlgrenska Academy
University of Gothenburg

The Sahlgrenska Academy

UNIVERSITY OF GOTHENBURG

ULTRASONOGRAPHY

for Diagnosis, Intervention, and Follow-up in Juvenile Idiopathic Arthritis

Louise Laurell

UNIVERSITY OF GOTHENBURG

Institute of Clinical Sciences
Department of Paediatrics
Sahlgrenska Academy
2011

http://hdl.handle.net/2077/26263

ISBN 978-91-628-8367-6

To Sigrid and all other children with juvenile idiopathic arthritis

CONTENTS

ORIGINAL ARTICLES

This thesis is based on the following articles, which will be referred to by their Roman numerals:

- Ultrasonography and color Doppler in juvenile idiopathic arthritis: diagnosis and follow-up of ultrasound-guided steroid injection in the ankle region. A descriptive interventional study.
  Louise Laurell, Michel Court-Payen, Susan Nielsen, Marek Zak, Mikael Boesen, Anders Fasth.
  Pediatric Rheumatology 2011, 9(4): 1–11.

- Ultrasonography and color Doppler of proximal gluteal enthesitis in juvenile idiopathic arthritis: a descriptive study.
  Louise Laurell, Michel Court-Payen, Susan Nielsen, Marek Zak, Carsten Thomsen, Maribel Miguel-Pérez, Anders Fasth.
  Pediatric Rheumatology 2011, 9(22): 1–13.

- Ultrasonography and color Doppler in juvenile idiopathic arthritis: diagnosis and follow-up of ultrasound-guided steroid injection in the wrist region. A descriptive interventional study.
  Louise Laurell, Michel Court-Payen, Susan Nielsen, Marek Zak, Anders Fasth.
  Submitted for publication.

- Comparison of ultrasonography with Doppler and MRI for assessment of disease activity in juvenile idiopathic arthritis: a pilot study.
  Louise Laurell, Michel Court-Payen, Susan Nielsen, Marek Zak, Mikael Boesen, Anders Fasth.
  Submitted for publication.

ABBREVIATIONS

ACR	American College of Rheumatology
ANA	antinuclear antibodies
CD	color Doppler
CR	conventional radiography
DMARD	disease-modifying drug
ERA	enthesitis-related arthritis
EULAR	European League Against Rheumatism
FS	fat suppression
HLA	human leukocyte antigen
Hz	hertz
IBD	inflammatory bowel disease
IL	interleukin
ILAR	International League of Associations for Rheumatology
JAS	juvenile ankylosing spondylitis
JCA	juvenile chronic arthritis
JIA	juvenile idiopathic arthritis
JPsA	juvenile psoriatic arthritis
JRA	juvenile rheumatoid arthritis
MCP	metacarpo-phalangeal
MRI	magnetic resonance imaging
MSUS	musculoskeletal ultrasound
NSAID	nonsteroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatology Clinical Trials
RA	rheumatoid arthritis
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Scoring
RF	rheumatoid factor
SpA	spondyloarthropathy
STIR	short tau inversion recovery
T1w	T1-weighted
T2w	T2-weighted
TMJ	temporomandibular joint
US	ultrasonography, ultrasound

INTRODUCTION

The term juvenile idiopathic arthritis (JIA) does not refer to a single disease, but rather encompasses all forms of arthritis that begin before the age of 16 years, persist for more than six weeks, and are of unknown etiology [1, 2]. JIA is the most common form of chronic rheumatic disease in childhood, and it causes extensive disability. In high-income countries, the annual incidence is about two to 20 children and the prevalence 16 to 150 cases per 100 000 children [2], and corresponding figures for the Nordic countries are 11 to 15 children and 86 children, respectively [3, 4]. Early therapeutic intervention and the use of new highly effective treatments have improved the outcome in many JIA patients, but have also increased the need for more precise methods for evaluating disease activity.

In adult rheumatology, numerous studies have established the important role of magnetic resonance imaging (MRI) and ultrasonography (US) in this context, and MRI is considered the reference standard for advanced imaging [119, 120]. Nevertheless, due to differences in disease characteristics and the unique features of the growing skeleton, the findings of studies in adults are not directly applicable to children and adolescents [17].

Imaging techniques such as US and MRI have not yet been fully evaluated and validated in pediatric rheumatology, and studies are still rare [5, 6].
This thesis is focused on application of Doppler-US for diagnosis, interventions, and follow-up in JIA.

BACKGROUND

Childhood arthritis: definition and evolution of classification

Chronic arthritis in children was first distinguished from adult arthritis by Mayer S. Diamantberger in his doctoral thesis in 1891 [7]. In 1897, the British physician George F. Still published a paper entitled "On a form of chronic joint disease in children", in which he stated the following:

The purpose of the present paper is to show that although the disease known as rheumatoid arthritis does undoubtedly occur in children, the disease which most commonly has been called rheumatoid arthritis in children differs both in its clinical aspect and in its morbid anatomy from the rheumatoid arthritis in adults; it presents, in fact, such marked differences as to suggest that it has a distinct pathology (Still, 1897, p. 47).

Since the time those observations were made, several publications have addressed the striking differences between chronic arthritis in childhood and rheumatoid arthritis (RA) in adults, and it is currently accepted that the former condition is distinct from the latter. It is also acknowledged that chronic childhood arthritis is a group of several distinct diseases that share a phenotype to varying degrees. Diagnosis of such pediatric arthritis is currently based on clinical assessment, without pathognomonic findings or objective confirmatory laboratory tests, and by exclusion of other diseases. Emerging clinical and laboratory findings have gradually improved our understanding of chronic childhood arthritis [8-10], which is now defined as a heterogeneous group of diseases characterized by chronic joint inflammation with the cardinal signs of inflammation: swelling, tenderness, warmth and concomitant limitation of motion, and with frequent extra-articular manifestations.

After Still published his article, and especially during the second half of the 20th century, various classifications of childhood chronic arthritis were proposed, revised, and dismissed. Over the last decades, primarily three different classifications have been suggested. Table 1 summarizes the evolution of classification in childhood arthritis.

Table 1. Evolution of classification in childhood arthritis

Subtype	Cumulated number of affected joints	Criteria		
		JRA[1] (1977)	**JCA**[2] (1977)	**JIA**[3] (1995)
Number of subtypes	n.a.	3	6+JRA[5]	7
Systemic	n.a.	yes	yes	yes
Oligoarticular[4]: persistent extended	≤ 4 > 4	n.a.	n.a.	yes
Pauciarticular[4]	≤ 4	yes	yes	n.a.
Polyarticular: RF-negative RF-positive	> 4	yes	yes JRA[5]	yes
Psoriatic	n.a.	n.a.	yes	yes
Enthesitis-related	n.a.	n.a.	n.a.	yes
Juvenile Anchylosing Spondylitis	n.a.	n.a.	yes	n.a.
IBD-associated arthritis	n.a.	n.a.	yes	n.a.
Undifferentiated arthritis	n.a.	n.a.	n.a.	yes

n.a. Non applicable

[1] ACR (American College of Rheumatology)

[2] EULAR (European League Against Rheumatism)

[3] ILAR (International League of Associations for Rheumatology)

[4] Oligo- and Pauci- are synonymous, meaning 'few'

[5] Polyarticular RF-positive patients are not included in the JCA classification, but regarded as a separate disease entity termed 'JRA'

In one, a definition of juvenile rheumatoid arthritis (JRA) was presented and revised in 1977 by the American College of Rheumatology (ACR). This describes JRA as an idiopathic arthritis with a minimum of six weeks duration in an individual under the age of 16 years. After six months duration, a certain type of onset can be established: systemic, pauciarticular (one to four joints affected), or polyarticular (more than four joints affected). The ACR criteria exclude juvenile ankylosing spondylitis (JAS), juvenile psoriatic arthritis (JPsA), and arthropathy associated with inflammatory bowel disease (IBD) [11].

In the second classification, which was also presented in 1977, the European League Against Rheumatism (EULAR) used the term juvenile chronic arthritis (JCA) to define an idiopathic condition lasting at least three months in an individual less than 16 years of age. The criteria for onset were listed as systemic, pauciarticular, and polyarticular. In order to encompass all forms of chronic inflammatory arthritides it also includes JAS, JPsA, and IBD, with substantial heterogeneity as a consequence. The EULAR designation JRA is used particularly for patients who are positive for polyarticular rheumatoid factor (RF), hence causing some confusion in relation to the definition of JRA given by the ACR [12]. Unlike the ACR criteria, the EULAR classification has not been validated.

The third and present classification was devised by the Pediatric Standing Committee of the International League of Associations for Rheumatology (ILAR) in 1995 [13, 14]. On the basis of clinical and laboratory features, and in an attempt to identify homogeneous and mutually exclusives categories, the ILAR grouped the different arthritides under the umbrella term juvenile idiopathic arthritis (JIA), and the criteria used were revised in 1997 and again in 2001 [13, 15]. JIA comprises idiopathic arthritides that last more than six weeks and appear before the age of 16 years [16]. Since only six weeks' duration of illness is required for diagnosis, the ILAR criteria bridge the gap between the JRA and JCA criteria [14]. The ILAR criteria cover both the onset and the course of the disease, and divide clinically distinguishable disease groups into seven subtypes. Importantly, the ILAR classification represents the first attempt to reach an international consensus in this area, aiming to facilitate comparison of scientific studies and collaboration. Table 2 summarizes the ILAR inclusion and exclusion criteria for the seven subtypes of JIA.

Table 2. ILAR classification criteria, definitions and exclusions

Subtype	Definition	Exclusions
Systemic arthritis	Arthritis in one or more joints accompanied or preceded by fever of at least 2 weeks' duration that is documented to be quotidian for at least 3 days, and is also accompanied by one or more of the following: • Evanescent, nonfixed erythematous rash • Generalized lymph node enlargement • Hepatomegaly or splenomegaly • Serositis	1, 2, 3, 4
Oligoarthritis	Arthritis affecting one to four joints during the first 6 months of disease. Two subcategories are recognized: • Persistent oligoarthritis which affects no more than four joints throughout the disease course • Extended oligoarthritis which affects a cumulative total of five or more joints after the first 6 months of disease	1, 2, 3, 4, 5
Polyarthritis (RF-negative)	Arthritis affecting five or more joints during the first 6 months of disease; associated with a negative RF test.	1, 2, 3, 4, 5
Polyarthritis (RF-positive)	Arthritis affecting five or more joints during the first 6 months of disease; two or more positive RF tests at least 3 months apart during the first 6 months of disease	1, 2, 3, 5
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least two of the following: • Dactylitis • Nail pitting or onycholysis • Psoriasis in a first-degree relative	2, 3, 4, 5
Enthesitis-related arthritis	Arthritis and/or enthesitis with at least two of the following: • Sacroiliac joint tenderness and/or inflammatory lumbosacral pain • Presence of HLA-B27 antigen • Onset of arthritis in a boy > 6 years of age • Acute, symptomatic, anterior uveitis • History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative	1, 4, 5
Undifferentiated arthritis	Children with arthritis of unknown origin that persists for ≥ 6 weeks but • does not fulfill the criteria for any of the above categories, or • fulfills criteria for more than one of the above categories	

Some of the defined subtypes seem to identify homogenous disease entities, whereas others still include heterogeneous disorders [17, 18]. Furthermore, use of exclusion criteria that are strict but not always practical leads to a high proportion of unclassifiable cases that end up in a group called “undifferentiated arthritis”, and questions have been raised concerning the biological significance of the arbitrary cutoff points for age, the number of affected joints defining polyarticular versus oligoarticular disease, and duration of disease. Other problems found to be associated with the classification include the effects of heredity and enthesitis [14, 19, 20].

Considering the subtypes of JIA, those that are well characterized include systemic JIA, RF-positive polyarthritis, enthesitis-related arthritis (ERA), and oligoarthritis; those that are less well characterized are RF-negative polyarthritis and psoriatic arthritis.

Systemic JIA, like adult-onset Still’s disease, is characterized by prominent systemic features such as fever, rash, and serositis [2]. Pronounced activation of a patient’s innate immune system and the absence of any consistent association with autoantibodies or human leukocyte antigen (HLA) have led to the hypothesis that this type of disease is a polygenic autoinflammatory syndrome [21]. Findings of previous studies suggesting that interleukin-6 (IL-6) plays a major pathogenic role in systemic JIA have been substantiated by evidence of the effectiveness of treatment with tocilizumab, an anti-IL-6 receptor antibody [22, 23]. Moreover, the observation that treatment with anti-interleukin-1 can also be efficacious has led to the delineation of two subpopulations of systemic JIA: one that shows a pronounced, complete response to interleukin-1 (IL-1) blockade, and another that is resistant to IL-1 blockade or exhibits an intermediate response [24, 25]. The two populations also differ with respect to the number of joints that are affected and the neutrophil response: it is more likely that patients with fewer joints affected or with a higher neutrophil count will respond to anti-IL-1 treatment [17].

Patients with RF-positive polyarthritis represent 5% of all cases of JIA and are believed to be very similar to those suffering from adult RF-positive RA. There is also evidence that RF-positive polyarthritis is the only form of JIA that displays positive antibodies to cyclic citrullinated peptides [26]. The major

difference compared to the disease in adults is the impact on a growing skeleton, which generally leads to general growth retardation or to accelerated growth of affected joints.

Enthesitis-related arthritis (ERA) is a form of undifferentiated spondyloarthropathy (SpA) [27]. Most patients with ERA are HLA-B27 positive, and, within 10 years of onset, the disease progresses to include sacroiliac and spinal involvement in up to two-thirds of the affected children [28-30].

Although the subtype oligoarthritis as a whole is probably heterogeneous, in most cases it is a well-defined disease that is seen only in children [31]. Oligoarthritis occurs more often in girls, it has an early onset (before 6 years of age), and it shows consistent associations with HLA and characteristic asymmetric arthritis that affects mainly large joints. The patients have high concentrations of positive antinuclear antibodies (ANAs) and are at substantial risk of developing chronic iridocyclitis. According to the classification criteria for JIA, there are two categories of oligoarthritis: a persistent form in which the disease affects four joints or fewer, and an extended form in which more than four joints are affected after the first 6 months of disease [13]. However, patients who have either persistent or extended oligoarthritis and are positive for ANA have similar clinical characteristics (e.g., age at onset, sex ratio, asymmetry of articular involvement, and frequency of iridocyclitis), which suggests that these two categories of oligoarthritis actually represent different severities of the same disease [32, 33].

RF-negative polyarthritis comprises a heterogeneous group of JIA patients that can be divided into at least two subsets: one with disease that is similar to adult-onset RF-negative RA, characterized by symmetric synovitis of large and small joints, onset at school age, and the absence of ANA; and another that resembles oligoarthritis, apart from the number of joints affected during the first 6 months of disease.

If psoriatic arthritis is defined as involving the presence of arthritis and psoriasis or some psoriatic features, two disease entities exist: one of these belongs to the ERA category and is therefore, like adult psoriatic arthritis, a form of

spondyloarthropathy; the other is very similar to ANA-positive oligoarthritis, showing only small differences such as affecting small joints more often than large joints, a feature that might be attributable to psoriatic diathesis in the ANA-positive oligoarthritis phenotype [31, 34, 35]. Indeed, features of ANA-positive oligoarthritis are seen in most patients who meet the present classification criteria for psoriatic arthritis, which by definition exclude patients with enthesitis.

Thus the discussion that George Still initiated in 1896 concerning the definition of a disease entity in children is ongoing even today.

Clinical manifestations of JIA

The different subtypes of JIA are determined by the presence of articular and extra-articular manifestations, and, inasmuch as these signs evolve at different rates, it may take months before a definite diagnosis can be made. Not knowing the subtype does not preclude treatment, but it is necessary to be prepared to change the diagnosis as the illness progresses [36].

A striking symptom in children with JIA is pain, which the patients often describe as aching. A child may not complain of pain at rest, whereas pain can be elicited by both active and passive motion of a joint or palpation of muscle and tendon insertions. The way a child communicates such discomfort varies according to individual factors and to age. In the young child, it can be observed as increased irritability, tenderness or pain during motion or on palpation, holding a joint in a particular position, or refusing entirely to use a limb [37]. Disease damage to joints, muscles, and tendons may progress to severe disability and cause chronic pain, and thereby have a marked impact on the patients' psychosocial function [38, 39].

The majority of children with JIA have arthritis. The definition of "active arthritis" proposed by the ILAR is based on clinical findings of joint swelling or a limited range of joint mobility with pain or tenderness. The arthritic child is troubled by stiffness in the morning and after inactivity. Any joint may be affected, but more frequently the larger joints. The smaller joints in the hands and feet may be affected as well, especially in polyarticular-onset disease, and there can also be involvement of the temporomandibular joint (TMJ) and the cervical, thoracic, and lumbosacral joints [37].

Enthesitis is inflammation of the sites where tendons, ligaments, capsules, or fascia are attached to bone, and it is more common than usually assumed and may be difficult to differentiate clinically from arthritis [Paper II, 40, 41]. Enthesitis occurs in both the axial and peripheral skeleton, and is seen primarily in the JIA subtype ERA [13]. It arises more frequently in the weight-bearing lower limbs, as the calcaneal insertions of the Achilles tendon, the plantar fascia, different regions of the foot, the patella, and the greater trochanter, but also at other locations such as the ischial tuberosity and the iliac crest [42-47]. Clinical diagnosis of enthesitis is difficult, because it is based solely on palpable tenderness at insertion sites [48]. It should be noted that entheses that arise at superficial sites, such as the insertion of the Achilles tendon, can show soft tissue swelling, in contrast to those occurring at insertions of the plantar fascia and deep-seated sites such as the iliac crest [49-51]. The number of active entheses and affected joints at the onset of disease can predict future sacroiliitis [52]. Sacroiliitis may remain clinically unrecognized for quite some time, but once it has developed, treatment cannot always prevent disease progression [53-56]. These observations suggest that it is important to diagnose enthesitis at an early stage in order to be able to alter the course of this condition. Enthesitis represents the main impediment in JIA classification, because presence of this symptom assigns patients to more than one JIA subtype [19].

Other extra-articular manifestations that are common in JIA include uveitis, tenosynovitis, dactylitis, and occasionally also systemic involvement such as generalized lymph node enlargement, hepato- and splenomegaly, serositis, and fever. Additional important disease-associated manifestations are anemia, generalized and localized growth disturbances, osteopenia, osteoporosis, failure to thrive, facial and dental problems secondary to TMJ involvement, and renal amyloidosis. Moreover, in some cases pharmacological treatment induces systemic complications that can contribute to morbidity [36].

Treatment of JIA

Management of JIA is based on a combination of pharmacological interventions, physical and occupational therapy, and psychosocial support. Until a decade ago, very few randomized controlled trials focused on children with JIA, but this situation changed completely when the Food and Drug

Administration and the European Medicines Agency implemented what is called the “pediatric rule” [17]. According to this regulation, companies seeking to gain approval for any new treatment of a given disease in adults must also test the product in children, if there is a pediatric equivalent of the illness in question. The pediatric rule has opened the way for more targeted studies that are essential for the safety of pediatric patients, including those with JIA [57-59].

Pharmacological treatment of JIA is a challenge, because no single drug can cure the many variants of the disease. The aim of treatment is to control the inflammation that causes joint damage, impaired growth and development, long-term disability, and a secondary decrease in quality of life [2, 60]. In the past decade, great advances have been made in treatment regimens, which seems to have improved the long-term prognosis of the disease and alleviated some of the heavy burden it imposes on children, their parents, and society [61]. Table 3 presents a summary of the anti-inflammatory and immunomodulatory drugs that are currently used in treatment of JIA. In a majority of patients, nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment, because they suppress mediators of inflammation, reduce pain, and improve mobility. Intra-articular corticosteroid injections play an important part in the prevention of deformities [62, 63]. Systemic corticosteroids are administered orally or as intravenous pulse therapy, and are often used in systemic JIA. Among disease-modifying drugs (DMARDs), methotrexate has been chosen more frequently since the first reports of its use in JIA in 1986, and the most effective dose was proposed in a randomized trial [64, 65]. Research on the use of biological agents directed towards specific disease modulators has led to important improvements in the management of JIA in recent years [2]. These agents are used alone or in combination with methotrexate, and their effectiveness has had an impact on physicians’ expectations. The need for firm criteria for defining disease states has been raised [66-68]. In the future, it is likely that treatment strategies, including withdrawal of treatment when patients are in remission, will be guided not only by clinical data, but also by more objective measures such as imaging and normalization of biomarkers [69].

Table 3. Anti-inflammatory and immunomodulatory drugs used to treat children with JIA

Drug type	Mode of action
NSAID	Inhibit cyclo-oxygenase 1 and 2
Corticosteroid	Suppress inflammatory cytokine production
Methotrexate	Suppress inflammatory cytokine production, inhibits dihydrofolate reductase, inhibits lymphocyte proliferation at high doses
Anti-TNF alpha (*etanercept, adalimumab, infliximab, certolizumab pegol, golimumab*)	Blocks the action of TNF alpha (inflammation), T- and B-cell signaling and T-cell proliferation), both fusion protein and monoclonal antibodies
IL-1ra (*anakinra*)	A recombinant form of the natural receptor antagonist that blocks cellular signaling by IL-1 alpha and beta
Anti-IL-1 (*canakinumab*)	A humanized monoclonal antibody that blocks cell signaling of IL-1
Anti-sIL-6R (*tocilizumab*)	A humanized monoclonal antibody that blocks cell signaling by the complex of IL-6/IL-6R
T-cell costimulation modulator (*abatecept*)	A soluble human fusion protein that binds competitively to antigen CD80 or CDE86 and inhibits T-cell activation and downstream cytokines
Anti-CD20 (*rituximab*)	Chimeric monoclonal antibody against antigen CD20 receptors that lyses B-cells but not plasma cells

Based on: Pediatric Rheumatology in Clinical Practice, P. Woo, R.M. Laxer, D.D. Sherry; Springer-Verlag, London; 2007, p.17.

Follow-up of treatment efficacy and evolution of the criteria for disease remission

It is essential that the criteria for defining disease states are validated, clinically useful, and reliable when they are to be applied in monitoring of disease status in individual patients or as potential end points in clinical trials. New and effective therapies are now available that have the potential to eliminate JIA disease activity for extended periods, and this stresses the need for definitions of inactive as well as active disease. Clinical remission, with or without ongoing medication, is an important goal of all interventions [60, 70-73]. In the absence of a biological marker for active or inactive JIA, the aggregated judgments of experts are necessary to determine criteria for clinically inactive JIA [74]. At present, the validated criteria for defining clinically inactive disease in select categories of JIA are provisional and do not identify biologically inactive disease [66]. Furthermore, clinical examination cannot detect low levels of inflammation that can be demonstrated by US imaging [75-80]. Therefore, true remission in JIA, implying the absence of disease, cannot rely on clinical examination alone, but requires additional clinical laboratory data and imaging assessment.

The role of imaging in JIA

Conventional radiography

Conventional radiography (CR) has been, and still is, the central component of imaging in JIA, and it has also served as the basis for developing various systems used to score joint damage [81-86]. Assessment of structural damage by CR is a key outcome in studies of treatment efficacy in adult arthritis patients [6]. The imaging used to evaluate articular disorders in children differs from that applied in adults in several important aspects. The growing skeleton in young patients makes CR assessment of structural damage in JIA a challenge. The scoring systems designed for adults are not directly applicable, although certain other pediatric-targeted scoring systems have proven to be reliable and valid [87]. A limitation of CR, in addition to the radiation dose, is that it does not allow direct evaluation of inflammatory changes in soft tissues.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) provides detailed cross-sectional tomographic images of all aspects of rheumatic disease: synovial proliferation, joint and extra-articular fluid, cartilage damage, bone erosions and bone marrow edema [88-94]. Clinical musculoskeletal imaging uses chiefly three types of MRI sequences called spin echo, inversion recovery, and gradient echo. In general, T1-weighted (T1w) spin echo images best depict the anatomy, and use of paramagnetic intravenous MRI contrast agents can enhance visualization of inflamed structures. The thickened inflamed synovial membrane in synovitis appears hypointense on T1w images and is enhanced on T1w post-contrast images. Both enhanced synovitis and surrounding fat are hyperintense and thus can be difficult to differentiate. Nevertheless, good visualization of the synovial tissue can be achieved by using a technique called “fat suppression” (FS), which makes fat appear hypointense. Most tissues involved in an inflammatory process have a higher water content compared to normal tissues. Accordingly, T2-weighted (T2w) spin echo or short tau inversion recovery (STIR) sequences provide the best detection of disease, because the high hydrogen content causes the affected areas to appear bright [95, 96].

MRI, but not US, can visualize bone marrow edema, which is a key predictor of erosive joint damage in RA [97-100]. The edema is visualized by an increased signal in fat-suppressed T2w/STIR images due to the increased water content within trabecular bone [100, 101]. Bone marrow edema is either rare or absent in healthy adults, whereas MRI findings in healthy children have been reported to show physiological bone marrow edema at the iliac crest, in the wrist, and in the ankle region [Paper IV, 80, 102-105]. Consequently, it may be difficult to use MRI to detect pathological bone marrow edema in children and adolescents.

On MRI, an erosion is seen as a break in the cortical bone. Use of gradient echo sequences makes it possible to obtain high-quality 3D volume images in which the slice thickness can be reduced to sub-millimeter resolution, an advantage when investigating small structures such as minor bony erosions [96, 106]. Studies of adults with RA have demonstrated the significant prognostic value of MRI-detected bone erosions [107, 108]. Predicting prognosis in children with newly diagnosed JIA is of key importance, but thus far only a few MRI studies

of JIA have been conducted, all of which have used different methodologies [6, 90, 109-111].

The MRI-RA group of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) has devised a semi-quantitative scoring system for the assessment of inflammatory and joint damage abnormalities in RA, and has also suggested a core set of basic MRI sequences [112]. This system is called Rheumatoid Arthritis MRI Scoring (RAMRIS), and it may provide a standard also for forthcoming JIA studies [113].

The lack of validated MRI scales and standardized MRI protocols targeting children makes it difficult to draw firm conclusions regarding the value of MRI assessment in JIA [114, 115]. Furthermore, there are no long-term MRI studies of JIA, and the significance of MRI abnormalities over time is still unclear. Despite these limitations, the advances in MRI assessment of findings in JIA have strongly influenced current views on this disease [6]. MRI imaging has contributed greatly to strengthening the perceptions that synovitis is the primary inflammatory focus of JIA, that synovitis is associated with damage, and that patients in apparent clinical remission may still have persistent synovitis [6].

Current treatment strategies in JIA aim to achieve early suppression of inflammation in order to prevent erosive disease. CR mainly detects structural damage, and thus, in this context, other more subtle imaging methods are needed that can discern the slightest traces of early joint changes. Alternative imaging techniques that will play an important role in this evolution include US and MRI.

Musculoskeletal ultrasound (MSUS) has emerged as an indispensible tool for physicians involved in musculoskeletal medicine, and lately it has become more attractive to pediatric rheumatologists as well. In this regard, recent reports have described parity and even superiority of US in comparison with physical examination and other imaging modalities. US is suitable for examining children of all ages, and, compared with other imaging modalities, it offers the benefits of being mobile, immediately accessible at bedside, easy to combine with clinical assessment (interactivity), non-invasive, and cheaper. With proper training, any clinician can perform US examinations, making the technique

readily available at point of care [116, 117]. Moreover, multiple locations can be assessed during the same session, and repetitive follow-up examinations are easily performed.

Numerous studies have established the important role of MRI and US in investigation of disease activity in adult rheumatology, and MRI is considered the reference standard for advanced imaging in that context [118-120]. However, in pediatric rheumatology, MRI and US have not been fully evaluated, and studies are still rare [5, 6, 93, 121-124]. Due to differences in disease characteristics between adult and pediatric rheumatology, and the unique features of the growing skeleton, the results of studies of adults are not directly applicable to children or adolescents [17].

Ultrasonography (US)

Basic physics in US

Ultrasound is defined as soundwaves with a frequency above that which humans can hear, or more than 20 kHz. When ultrasound meets interfaces between different tissues, it is partly reflected and partly transmitted. Two factors influence the reflectivity: the acoustic impedance of the medium and the angle of incidence of the sound beam. Reflection is maximal when the beam is perpendicular to the interface. If the angle of incidence is different from 90°, there is also a refraction (change of direction) of the sound beam. US transducers generate US pulses and also receive the returning echoes. High-frequency transducers (12–20 MHz) ensure good image resolution, albeit at the expense of tissue penetration, and hence they are suitable for examining superficial structures such as most musculoskeletal components. By comparison, low-frequency transducers provide better penetration, but at the expense of image resolution, and thus they are used to examine deeper structures. In short, the choice of transducer represents a compromise between resolution and penetration.

Gray-scale US

US images are displayed by “brightness-modulation” (B-mode) using a gray-scale. The pixels (picture elements) forming the image are created by the reflected US waves of the investigated tissues. As the US pulse travels through the tissues, echoes are generated at interfaces between tissues with different

acoustic properties. The intensity of the echoes defines the gray-scale of the US images and is described as being anechoic, hypoechoic, isoechoic, or hyperechoic (Figure 1):

- anechoic: no internal echoes
- hypoechoic: brightness of echoes decreased relative to an adjacent structure
- isoechoic: echogenicity the same as that of an adjacent structure
- hyperechoic: increased brightness of its echoes, relative to an adjacent structure

A structure that is anechoic will appear black; this applies to most fluid collections, although fluids containing varying degrees of reflective material may be echogenic (hypoechoic, isoechoic, or hyperechoic). Connective tissue, tendons, synovial tissue, debris, and other structures are seen in varying shades of gray. Interfaces with a very high degree of reflection appear bright (white and hyperechoic), and this is characteristic of bone surfaces and air-filled areas. Gray-scale US gives valuable information about the morphology of an investigated area, and it allows dynamic investigation of joints and tendons in real-time.

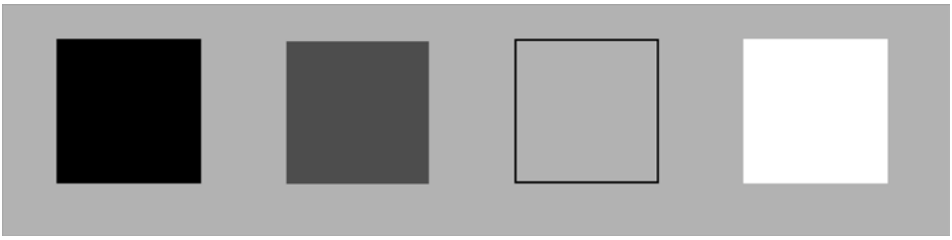

Figure 1. The gray-scale of US images is described as anechoic, hypoechoic, isoechoic, and hyperechoic, relative to an adjacent structure.

Doppler-US

The Doppler effect is a change in wavelength resulting from motion of a sound source, receiver, or reflector. Since the transducer is a stationary source and receiver, the Doppler effect in US arises when an emitted signal is backscattered by moving blood cells. The Doppler signal is displayed as colored pixels superimposed on the US images, encoding either for shifts of frequency (color Doppler, CD) or amplitudes of the Doppler signals (power Doppler). The power

Doppler mode is more sensitive than the CD mode, but it does not provide information on direction or velocity of flow. The main limitations of Doppler-US techniques are determined by the choice of equipment, the lack of standardization of the examination technique, the reproducibility and the experience of the examiner [125-127].

Contrast agents in US

Contrast agents in the form of microbubbles are used in US to enhance scattering properties of blood. The use of contrast agents in MSUS is still experimental, and no intravenous contrast media are registered for use in children.

Musculoskeletal US in pediatrics

Examination technique

US of the musculoskeletal system has no contraindications, and it does not require any preparation of the patient. A high-frequency linear array transducer must be used. The structures of interest (e.g., tendons, ligaments, muscles, and menisci) should always be examined perpendicularly to provide strong reflections and good visualization of the anatomical details, which also makes it possible to differentiate true hypoechoic pathology from anisotropic artifacts [128, 130]. The contralateral limb should always be assessed as a reference, keeping in mind that pathological findings may be bilateral. Of course, US allows direct interaction with the patient and immediate comparison of imaging and clinical assessments. Compression with the transducer, referred to as sonopalpation, may provide information about the correct nature of a structure, for example, differentiation between fluid and soft tissue. It can be essential to apply as little pressure as possible in order to visualize certain pathological findings in superficial soft tissues, such as effusion in bursitis and tenosynovitis, or tissue vascularization on Doppler examination. Dynamic examination during active or passive mobilization of the soft tissues may facilitate recognition of anatomical structures and localization of pathological changes [129-131].

US is easy to perform on children of all ages, because agitation of the patient is rarely a problem. The time factor is also important in dealing with young children. Only a relatively short amount of time is required to examine each

anatomical structure, and thus it is a simple matter to assess multiple locations during a single session. US images are analyzed in real time, and therefore the information that is acquired can be used directly to adjust the clinical assessment, an aspect that may be particularly useful if there are few verbal complaints (e.g., in infants) [116]. The advantages and disadvantages of MSUS imaging in children are summarized in Table 4.

Table 4. Advantages and disadvantages of musculoskeletal US imaging in children

Advantages
Non-invasive: no ionizing radiation, no need for sedation or general anesthesia, no intra-venous contrast
No complications, no contraindications
Ability to visualize both soft tissues (inflammatory changes) and bone surfaces (destructive disease manifestations)
Multiregional: possible to examine several joint regions in one session
Potential for guiding interventions (i.e. intra-articular steroid injections)
Unsurpassed resolution of superficial musculoskeletal structures
Interactivity with clinical assessment, dynamic tests
Well tolerated by children of all ages, agitation rarely a problem
Results available in real-time
Relatively short examination time
Repeatability (follow-up)
Bedside availability
Widely available (all hospitals)
Relatively low cost
Disadvantages
Long learning curve
Operator dependence (acquisition and interpretation of images) - like MRI
Incomplete examination: acoustic shadowing from overlying bones, unable to image bone; air, fat and fibrosis may alter images
Lack of overview (but with possibility to obtain ‘panoramic view images’)
Limited normative data on children
Doppler-US not validated for use in children, difficult to standardize and make objective measurements
Difficult to standardize for clinical trials
Machine dependence - like MRI
Less objective documentation

Investigation of healthy children

The cartilaginous ends of long bones are responsible for the enchondral ossification that occurs during growth in childhood [132]. Therefore, children have a large amount of cartilage tissue, whereas adults have only a thin layer of avascular articular cartilage, and this has implications for interpretation of MSUS images [128]. The ends of the bones comprise three zones called the epiphysis, the metaphysis, and the physis [133, 134]. At birth, the epiphysis is completely cartilaginous, except at the distal end of the femur. Over time, one or several epiphyseal ossification centers appear and enlarge until the entire epiphysis has been ossified, with the exception of the thin layer of articular cartilage. Thus, during childhood, there are three vascular systems in the long bones: the epiphyseal, the metaphyseal/intramedullary, and the periosteal blood supply [132, 135, 136]. When a growing child is examined by Doppler-US, any juxta-articular flow must be thoroughly analyzed, because the Doppler signal can represent either normal cartilaginous vascularization or synovial hyperemia indicating inflammation [128]. In adulthood, the articular cartilage of the epiphysis is avascular, and any juxta-articular Doppler flow suggests inflammation. Consequently, it is important to have knowledge of the normal appearance of each joint at different developmental stages in order to avoid diagnostic errors when performing US examinations in growing subjects [128, 137, 138].

Sonographic reference values have not been established for most pediatric joints, and there is no consensus regarding what constitutes “normal” gray-scale and Doppler findings at the single-joint level in children or adults [125]. In children, the infant hip is the best described, because US is an established method for evaluating hip dysplasia and other hip disorders [139-146]. US assessment of cartilage thickness in some large and small joints of healthy children was recently validated by comparison with MRI findings, which has led to proposal of age- and sex-related reference intervals [147-149].

The role of US in pediatric rheumatology

Two major factors have resulted in increased interest in using MSUS in JIA: (1) the evolution of high-frequency linear transducers that depict superficial musculoskeletal structures with unsurpassed resolution [128]; (2) the need for imaging techniques that can detect the slightest traces of soft tissue inflammation. Only a few studies so far have investigated both gray-scale and Doppler assessments of children with JIA [Papers I, II, III and IV, 77, 150-153, 177, 178, 182, 220].

In daily clinical practice, the diagnosis of "active arthritis" in JIA is based primarily on clinical evaluation. However, it is often difficult to clinically determine whether a perceived joint swelling is secondary to synovitis with joint effusion or is due to soft tissue edema and/or tenosynovitis [Papers I and III, 41, 91, 154]. Similarly, pain and limitation of mobility in a joint are not always the result of active arthritis. In JIA, it is a particularly complex task to clinically assess disease activity in the small joints of the hand [155].
US assessment of disease activity has been proven to be more informative than clinical examination in JIA. Subclinical synovitis is frequently detected by US, particularly in the hands and feet [40, 153, 154, 156]. A recent study of JIA patients with a clinical history of unilateral wrist involvement showed that 50% of previously unaffected wrists had abnormal gray-scale findings but no Doppler signals, which indicates that the primary clinical assessment falsely described the disease involvement as unilateral [77]. Gray-scale abnormalities of this kind are not present in healthy children [Paper IV, 77, 157]. US can also detect subclinical enthesitis in JIA, as demonstrated in another recent investigation, in which Doppler-US revealed enthesitis in 50% of clinically normal entheses [151].

The issue of subclinical disease may be particularly relevant in JIA. In the current ILAR classification, oligoarthritis versus polyarthritis is defined by the number of affected joints in children with JIA. Active disease in at least five joints is a prerequisite for the diagnosis of polyarticular JIA, which in turn is a requirement for inclusion in clinical trials of second-line or biological agents [6, 65, 73, 123, 158]. Thus, when disease activity is based solely on clinical findings, a substantial number of children may be wrongly classified as having extended oligoarticular or polyarticular disease on the basis of joint

involvement, when they in fact have oligoarticular disease with tenosynovitis [41]. It can be concluded that, in the future, US identification of subclinical disease in JIA will have a marked impact on diagnosis and choice of therapy, and potentially also on classification of the subtypes of this disease [5, 19].

Detection of disease activity by US

Synovial hypertrophy with hyperemia, joint effusion, tenosynovitis, enthesitis, and bone erosions are MRI findings that reflect the pathology of JIA. The corresponding US signs include the following: non-compressible hypoechoic synovial hypertrophy; compressible hypoechoic/anechoic joint effusion; hypoechoic/anechoic tissue within the tendon sheath; hypoechoic and/or thickened tendons, ligaments, capsules or fasciae on bony insertions; erosions seen as localized cortical defects. In addition, the Doppler technique is used to detect hyperemia. Definitions of JIA pathology vary in different US studies. In our investigations, we defined US synovitis/tenosynovitis as synovial hypertrophy with or without synovial vascularization, and with or without effusion [159, 234]. Table 5, summarizes the pathology of JIA and the corresponding OMERACT 7 definitions of US signs of the disease [159].

Table 5. Definitions of musculoskeletal US findings in JIA pathology

JIA pathology	Definitions for US pathology (OMERACT 7)
Synovial hypertrophy	Abnormal hypoechoic (relative to subdermal fat, but may be isoechoic or hyperechoic) intra-articular tissue that is non- displaceable and poorly compressible, and may exhibit a Doppler signal
Joint effusion	Abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular material that is displaceable and compressible, but does not exhibit Doppler signal
Tenosynovitis	Hypoechoic or anechoic thickened tissue with or without fluid in the tendon sheath that is seen in two perpendicular planes and may exhibit a Doppler signal
Enthesitis	Abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes such as enthesophytes, erosions, or irregularity
Bone erosion	Discontinuity of the bone surface visible in two perpendicular planes

Based on: Musculoskeletal ultrasound including definitions for ultrasonographic pathology, R. J. Wakefield, et al.; J Rheumatol; 2005, 32, 12, p. 2485-7.

Synovial thickening

The synovial membrane is a thin layer of soft tissue that lines joint cavities, tendon sheaths, and bursae, and it is the location of the primary inflammation that occurs in arthritis. Such inflammation is characterized by hypertrophy and edema that are caused by proliferation of the capillaries and postcapillary venules and by an increase in perfusion [160]. US is a sensitive method for detecting synovial thickening and synovial cysts [161], and it shows synovial hypertrophy as a solid, non-compressible, abnormally thickened hypoechoic

tissue associated with joint lines or surrounding tendons [159, 162]. It is more challenging to assess synovial hypertrophy in younger children than in adolescents and adults, despite a better image quality in children due to less fat and fibrosis and more cartilaginous joints. In children, the synovial tissue is difficult to distinguish from the hypoechoic cartilage of the epiphyses. Doppler examination is generally not a solution to this problem, since vascularization can be present in both hypertrophic synovial membranes and in cartilaginous epiphyses during growth. Therefore, to avoid diagnostic errors, it is important to have good knowledge of the normal US appearance of each joint at different stages of development, and it is also imperative to use a meticulous scanning technique that allows clear interpretation of possible anisotropic artifacts [128, 130]. For the most part, it is easier to differentiate synovial tissue from effusion. Effusion is often anechoic or more hypoechoic than synovial tissue, and it can be mobilized by compression with the transducer; by comparison, synovial tissue is solid and non-compressible [163].
A semi-quantitative system for grading pathological gray-scale findings is used most frequently in adult rheumatology, but no such system has been validated in JIA [164].

Effusion

Physiological joint effusion is common in children. Notably, in a recent MRI study, the wrists of healthy children were found to contain fluid in relatively large amounts that have previously been considered to be pathological in adults [104, 165]. Even in a large and easily palpable joint such as the knee, sonography is more sensitive than CR or clinical examination for detecting effusion [161, 166]. US can detect volumes as small as one milliliter, and interobserver agreement of 79% was found in an analysis of effusion in joints of the hands and feet [167]. As mentioned above, sonopalpation entails compression with the transducer, and it is useful for distinguishing effusion from synovial proliferation. In a prospective study, it was found that US detection of a knee effusion in JIA was highly correlated with clinical disease activity, although the correlation was lower for the hip, probably because that joint is less accessible to clinical investigation [168]. In our research [Paper IV], the only finding of potential pathological significance in healthy controls was effusion demonstrated by both US and MRI.

Synovial perfusion

When using gray-scale US, it can be difficult to differentiate between active synovitis and inactive synovial thickening, because both may appear as non-specific hypoechoic synovial hypertrophy. Doppler-US techniques depict the increased vascularity of the hypertrophied synovium, and they are considered to be superior in distinguishing between active and inactive synovial thickening [169-175]. It has been shown that the Doppler signal is correlated with clinical and laboratory data, MRI results, and histology, and it also reflects disease activity in adult RA [173, 175, 176]. Furthermore, investigations of JIA have demonstrated that the Doppler signal is correlated with clinical activity and with serum levels of IL-6 [150, 152, 177-179]. Various systems using quantitative or semi-quantitative methods have been proposed to evaluate synovial Doppler flow in adults, but none of those techniques have been validated in JIA [125, 164, 173]. Our group did not detect any Doppler flow in healthy children [Paper IV], which agrees with a recent US study in which the Doppler signal was found to be absent in healthy controls, and any presence of Doppler flow was significantly associated with clinical synovitis in JIA [150]. In a growing child, juxta-articular Doppler flow can represent either the well-vascularized cartilage of the epiphysis or synovial hyperemia reflecting disease activity, which underlines that it is necessary for the investigator to have good anatomical knowledge of the area that is examined. In two of our studies [Papers I and III], Doppler flow was detected in 88–91% of clinically affected joints that exhibited synovial hypertrophy on gray-scale US. That observation concurs with other investigations in which hyperemia was found in 93% of symptomatic MCP joints and 77% of symptomatic knees in JIA patients [177, 178].

The use of ultrasound intravenous contrast media in Doppler-US to diagnose inflammatory joint disease has not yet been validated in either adults or children [180-182].

Enthesitis and tenosynovitis

Enthesitis is defined as inflammation of the sites where tendons, ligaments, capsules, or fascia are attached to bone. Conventional radiography visualizes mainly the bony parts of an enthesis (i.e., calcifications, enthesophytes, and bony erosions) and thus reveals only the late stages of disease [183]. MRI or US can demonstrate the early soft tissue signs of inflammatory enthesitis in adult SpA and in JIA [Paper II, 151, 184-187].

The OMERACT 7 definition of US signs of enthesitis stipulates an abnormally hypoechoic and/or thickened tendon or ligament at its bony attachment seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes (Table 4) [159]. Other recognized US signs of enthesitis include focal or diffuse loss of normal tendon or ligament fibrillar structure, effusion, intratendinous or intraligamentous calcifications, bone erosions, enthesophytes, and associated abnormalities of adjacent bursae [188, 189].

US is more sensitive than clinical assessment for diagnosing enthesitis in adult SpA patients and in JIA, and Doppler-US has been shown to be a sensitive method for detecting abnormal blood flow in and around peripheral entheses [151, 188-196].

The US appearance of tenosynovitis is the same in patients of all ages, showing effusion and/or synovial hypertrophy in a tendon sheath. Recent JIA studies have demonstrated that tenosynovitis in swollen ankles is detected by US more often than previously assumed [Paper I, 40, 41].

Cartilage thinning and erosions

On US, the articular cartilage is normally seen as a hypoechoic structure creating a smooth outline of the bone surfaces. Age- and sex-related reference intervals for US measurements of cartilage thickness in children have been proposed and validated by comparison with MRI results [147-149]. Some early US studies of JIA patients have reported cartilaginous changes involving early thickening or late thinning with blurred surfaces [161, 197, 198].

Bony erosions

A relevant proportion of any JIA patients who do not receive treatment will develop progressive joint destruction and serious physical disability [121]. The occurrence of erosions early in the course of this disease is associated with a higher risk of progressive JIA, and is an indicator of poor long-term outcome [199, 200]. In both RA and JIA, US is equal or superior to CR in detecting cortical erosions in areas that are accessible to the soundwaves. Notably, US has been found to be comparable to MRI in some studies but not in others, and this discrepancy might also be related to whether the investigated sites were accessible to US examination [121, 201-204].

US-guided steroid injections

Steroid injections constitute an important form of treatment in JIA [62, 63], and the clinical effect that is achieved depends on accurate placement of the steroid in the diseased compartment. In adult rheumatology, it has been shown that up to 50–70% of palpation-guided joint injections are placed incorrectly [205-207]. Imaging guidance can significantly improve the accuracy, and US is the best available technique for this purpose [128, 206, 208-212, 223-225]. US guidance may be static or dynamic. With static guidance, the structure of interest is identified, and the angle required by the needle is noted, with the point of entry marked on the skin. In dynamic procedures, US visualizes the needle in real time, which provides more accurate guidance and is generally preferred by experienced users [116]. A number of studies have shown that imaging-guided injections provide results superior to those obtained with palpation-guided injections, and these observations were made in adults with arthritis/osteoarthritis in large and small joints, and in children with arthritis in the ankle region (Figure 2) [206, 213-215, 227].

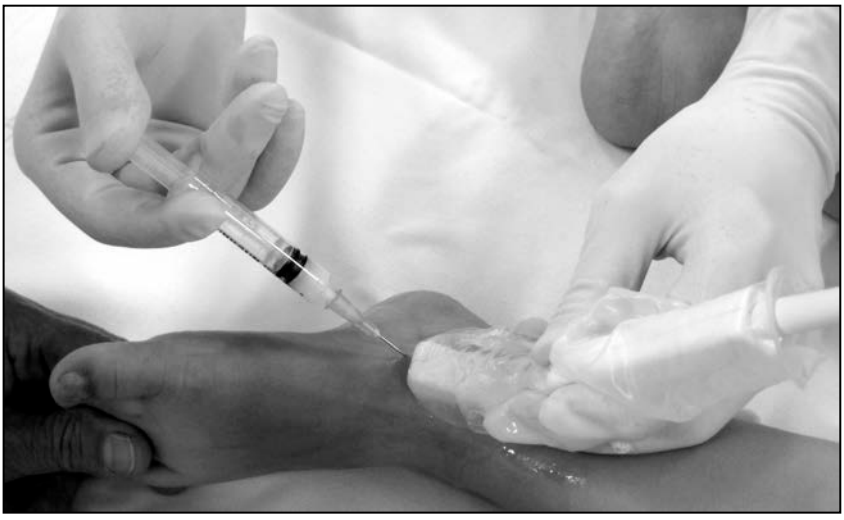

Figure 2. US-guided steroid injection of the talo-crural joint. The needle is inserted obliquely into the antero-medial recess of the joint (longitudinal US plane).

In JIA patients with wrist swelling, it is common clinical practice to perform palpation-guided injections in the radio-carpal joint, whereas injection of the

midcarpal joints or tendon sheaths is done less frequently. When clinical ankle swelling is present, a palpation-guided injection is usually given in the talo-crural joint, and less often in the subtalar joints or tendon sheaths; which might explain the poor outcome of steroid injections in ankle disease in JIA [153, 215, 216, 227].

Subcutaneous atrophy due to extravasation of steroid is a well-recognized adverse effect of intra-articular steroid injections, and it occurs most likely in small or complex joints such as the wrist or ankle in children under 4 years of age, or when a larger volume is injected [217, 218]. Employing US guidance makes it easier to ensure that the needle tip is correctly positioned before injecting the drug, which potentially minimizes the risk of extravasation of steroid into the subcutaneous tissue.

US follow-up of treatment efficacy and disease remission

Follow-up of treatment in arthritis patients is based on clinical examination and/or imaging. Repetitive follow-up examinations with US is attractive because it is non-invasive and lacks ionizing radiation [116].
US follow-up of treatment efficacy in JIA have reported that gray-scale US was sensitive enough to detect decreases in joint effusion and synovial hypertrophy in knees treated with NSAIDs, DMARDs, or oral or intra-muscular steroids, and in knees and hips after intra-articular steroid injection [142, 197, 198, 219]. The rate of decrease was faster for effusion than for synovial hypertrophy [197, 198].

US with Doppler is widely used for follow-up in adult rheumatology, whereas there are only four corresponding studies of JIA, in which the technique was used to evaluate treatment efficacy after steroid injections in the ankle region, wrist region or in knee synovitis after systemic corticosteroids and NSAIDs [Papers I and III, 178, 220].

Several investigations have established that MRI and US can improve the accuracy of remission measurement in RA [75, 78, 221]. Irrespective of the clinical or laboratory criteria applied to determine remission, the majority of the

RA patients in those studies continued to exhibit signs of active inflammation. Even in RA patients with clinically asymptomatic joints, MRI showed that 96% had synovitis and 46% had bone marrow edema, and US indicated that 73% had synovial hypertrophy and 43% an increased Doppler signal [80]. In DMARD-treated RA patients, it has been observed that such low-grade inflammation predicts subsequent radiographic deterioration [75, 76].

In JIA, it is possible today to induce permanent remission in an increasing proportion of affected children, but this cannot be reliably demonstrated by clinical examination alone [2, 5, 77]. In that context, Doppler-US has been found to reveal ongoing inflammation in the wrist and ankle joints of some JIA patients who meet the current clinical criteria for remission; there was complete concordance of the clinical and US assessments of the knee joint in that study, whereas it was judged that US assessment was particularly beneficial for the wrist and ankle regions [77]. Thus, inasmuch as clinical criteria cannot exclude disease activity, it seems that the current remission criteria are more appropriate for defining low disease activity. In short, it appears that determination of true remission cannot rely solely on clinical examination, but requires repetitive imaging to confirm the absence of subclinical inflammation [77].

AIMS OF THE PRESENT STUDIES

The objective of the present project was to evaluate Doppler-US in the clinical setting of pediatric rheumatology, with the goal of contributing information to a growing knowledge base for the benefit of children with juvenile idiopathic arthritis.
The specific aims were as follows:

- To assess the ability of gray-scale US and Doppler to determine the exact anatomical location of inflamed structures in clinically affected ankle and wrist regions in JIA [Papers I and III]
- To evaluate US guidance of steroid injections in JIA [Papers I and III]
- To investigate the use of Doppler-US for follow-up of steroid injections in JIA [Papers I and III]
- To assess use of Doppler-US and MRI for diagnosis of gluteal enthesitis in JIA [Paper II]
- To compare Doppler-US and MRI applied to evaluate symptomatic joints in JIA patients, and to compare the results with those obtained in healthy age- and sex-matched controls [Paper IV]

SUMMARY OF THE RESULTS

Paper I

Ultrasonography and color Doppler in juvenile idiopathic arthritis: diagnosis and follow-up of ultrasound-guided steroid injection in the ankle region. A descriptive interventional study.

The purpose of the study reported in Paper I was to investigate US imaging of the ankle region in children with JIA, considering the usefulness of this technique for detection of synovial hypertrophy and hyperemia, guidance of steroid injections, and assessment of treatment efficacy. Forty ankle regions in 30 JIA patients with clinically active arthritis were investigated by Doppler-US. All patients underwent Doppler-US assessment before (week 0) and 4 weeks after US-guided steroid injection. Gray-scale US was performed to detect structural abnormalities, and CD was conducted to identify hyperemia. For each of the compartments, the presence/absence of the following US signs of disease were registered: (1) non-compressible hypoechoic synovial hypertrophy; (2) compressible anechoic/hypoechoic joint effusion; (3) bone erosion defined as a localized hyperechoic cortical defect seen in both the longitudinal and transverse planes. Synovial hyperemia was assessed by giving CD flow a semiquantitative grade of 0, 1, 2, or 3, where grades 1–3 were considered pathological signs of hyperemia. US synovitis/tenosynovitis was defined as synovial hypertrophy with or without synovial vascularization, and with or without effusion.

At week 0, Doppler-US detected synovial hypertrophy, effusion, and/or hyperemia in 121 compartments (70 joints, 50 tendon sheaths, and one ganglion cyst). Synovial hypertrophy was found in 78% of the talo-crural joints. An isolated talo-crural synovial hypertrophy was found in only three ankles. The compartments most frequently involved in association with the talo-crural joint were the posterior subtalar joints and tendon sheaths. Synovial hypertrophy was detected in 65% of the posterior subtalar joints, 30% of the midfoot joints, and 18% of the tendon sheaths examined. Involvement of multiple tendons was noted in twelve ankles and isolated tenosynovitis, without any joint

involvement, in four ankles. Effusion was detected in 40% and CD flow in 89% of the involved compartments. Bone erosions were found in three ankles.
US-guided steroid injection was performed in 85 of the 121 diseased compartments. Twelve ankles received one injection and 28 multiple injections (two to three compartments in 25 ankles and four to five compartments in three ankles).
At 4-week follow-up, synovial hypertrophy in talo-crural joints was normalized or decreased in 87%, and the mean synovial thickness of the talo-crural joint (measurements on four separate locations) showed a significant decrease ($p < 0.001$, paired t-test). Normalization of synovial hypertrophy was noted in 93% of the other injected compartments. Doppler flow had disappeared completely in 89% of all injected compartments, had decreased in eight, and it was unaffected in one compartment (a talo-crural joint). Results were equally good for non-injected diseased compartments at most anatomical sites, except for the posterior subtalar joints.

In conclusion, US enabled exact anatomical localization of synovial inflammation in the ankle region of JIA patients. The talo-crural joint was not always involved, and disease was frequently found in compartments that are generally difficult to evaluate clinically. US enabled precise guidance of steroid injections, and it proved to be valuable in follow-up examinations. Normalization or a decrease in synovial hypertrophy and hyperemia was achieved in most cases, which supports the notion that US is an important tool for management of ankle involvement in JIA.

Paper II

Ultrasonography and color Doppler of proximal gluteal enthesitis in juvenile idiopathic arthritis: a descriptive study.

In this investigation [Paper II], we evaluated the usefulness of US for diagnosis of enthesitis in JIA. Thirty-eight consecutive patients with focal, palpable tenderness of the gluteus medius insertion on the posterior iliac crest (n = 76) were included, and Doppler-US examination and contrast-enhanced MRI were performed on all these children. Thirty-eight healthy age- and sex-matched controls were also assessed clinically for tenderness on palpation of the posterior iliac crest and by Doppler-US. In each patient, an US scan was obtained to search for possible hypoechoic thickening of the fascia, hypoechoic areas in the gluteus medius muscle insertion, or irregularities of the bony surface. The thickness of the muscle insertion was measured, and hypoechoic changes were graded from 0 to 3, where grades 1–3 were considered pathological signs of enthesopathy. CD examinations were done on all subjects to determine the presence or absence of hyperemia. MRI examinations of the patients were performed to search for sacroiliitis, subchondral edema and synovial, or subchondral contrast enhancement in the sacroiliac joints, and for bone edema in the iliac crest. The insertion of the gluteal fascia and muscle were also examined for contrast enhancement.

US examination of the healthy controls revealed normal posterior iliac crests bilaterally (n = 76), and CD showed no vascularization in any of the gluteus medius insertions.

US examinations of the 76 proximal gluteus medius insertions of the patients revealed various pathological hypoechoic changes in 53%. The changes were of grades 1, 2, and 3 in 13%, 20%, and 67% of the crests, respectively. The entheses in JIA patients were significantly thicker compared to those in healthy controls ($p < 0.003$ left side, $p < 0.001$ right side). There was no significant difference in thickness between the left and right sides in individual subjects. CD detected signs of hyperemia in 37% of iliac crests. Furthermore, there were no apparent irregularities of the bony surfaces in any of the subjects. There was a considerable time span between the MRI and US examinations (median 4

weeks, range 29 weeks), and only four patients had US and MRI scans in the same week.
MRI detected signs of enthesitis in 16% of the iliac crests and pathological iliac crest bone edema in 8%. In the 25 patients examined by contrast-enhanced MRI, 6/50 (12%) of their iliac crests showed enhancement in the fascial and/or muscular insertion. In one of the six crests that exhibited contrast enhancement on MRI, hyperemia was also detected on CD. Bone edema and contrast enhancement never occurred in the same iliac crest. MRI indicated sacroiliitis in 16 of the patients (28 sacroiliac joints), and, in 10 of those subjects (14 sacroiliac joints), US detected enthesitis at the iliac crest.

In conclusion, US examination of 38 patients with JIA showed that the 76 symptomatic gluteus medius insertions were thicker than the corresponding asymptomatic insertions in the healthy controls, and they were hypoechoic (indicating enthesitis) in about half of the patients. The US findings in some of the patients may have indicated chronic, inactive disease, because there was limited Doppler flow and MRI contrast enhancement. The observations made in this study suggest that using US as an adjunct to clinical examination can improve assessment of enthesitis in JIA.

Paper III

Ultrasonography and color Doppler in juvenile idiopathic arthritis: diagnosis and follow-up of ultrasound-guided steroid injection in the wrist region. A descriptive interventional study.

In the study described in this paper [Paper III] we evaluated US examination of the wrist region in JIA patients, considering the usefulness of this method for detection of synovial hypertrophy and hyperemia, guidance of steroid injection, and assessment of treatment efficacy. In 11 patients, 15 wrists with clinically active arthritis were examined by US and CD before and 1 and 4 weeks after US-guided steroid injection. Gray-scale US was performed to detect structural abnormalities, and CD was done to identify hyperemia. The presence/absence of the following US signs of disease were registered for each of the compartments: (1) non-compressible hypoechoic synovial hypertrophy, (2) compressible anechoic/hypoechoic joint effusion, and (3) bone erosion defined as a localized hyperechoic cortical defect seen in both the longitudinal and transverse planes. Hyperemia was defined as any presence of synovial vascularization as revealed by CD examination. US synovitis/tenosynovitis was defined as synovial hypertrophy with or without synovial vascularization, and with or without effusion. The dorsal synovial recesses of the radio-carpal and midcarpal joints visualized by US were defined as normal if they were thin or impossible to visualize, and as hypertrophic if they were thick or rounded.

Before injection (week 0), synovitis was found in 13 (87%) of the radio-carpal joints and eight (53%) of the midcarpal joints. The compartments involved in association with the radio-carpal joint included the midcarpal joint (five wrists), tendon sheaths (two wrists), and both the midcarpal joint and tendon sheaths (one wrist). In two wrists, synovial hypertrophy was detected only in the midcarpal joint and tendon sheaths. Tenosynovitis was found in five of the 15 wrists (33%). Doppler-US examination of all 135 tendon sheaths revealed synovial hypertrophy in 18 (13%) and hyperemia in 16 (12%). No patients had tenosynovitis without radio-carpal or midcarpal involvement. CD examination showed synovial hyperemia in 23 of the 26 diseased compartments (88%). Effusion was detected in two of the 21 inflamed joint compartments and in five of the 20 diseased tendon sheaths. Involvement of multiple compartments was

observed in 10 of the 15 wrists, and only five wrists showed isolated radio-carpal involvement. Bone erosions were found in only one wrist.
US-guided steroid injection was performed in 21 of the 26 diseased compartments.
After 1 week, normalization of synovial hypertrophy was noted in 57% of the injected compartments, and normalization of hyperemia was seen in 86%; corresponding rates after 4 weeks were 86% and 90%, respectively.
After 4 weeks, Doppler-US demonstrated persistent synovitis in injected compartments in two wrists: one of these involved synovial hypertrophy without hyperemia in the radio-carpal joint, and the other entailed synovial hypertrophy with hyperemia in the radio-carpal and midcarpal joints of the same wrist. At the 4-week US follow-up of non-injected compartments, only one joint (midcarpal) exhibited residual synovial hypertrophy and hyperemia.

In conclusion, US enabled exact anatomical location of synovial inflammation in compartments that are known to be difficult to evaluate clinically; it allowed exact guidance of injections; and it proved to be valuable for follow-up examinations. Normalization of synovitis was achieved in most cases, which indicates that US is an important tool for management of wrist involvement in JIA.

Paper IV

Comparison of ultrasonography with Doppler and MRI for assessment of disease activity in juvenile idiopathic arthritis: a pilot study.

The aim of the study reported in Paper IV was to compare MRI with Doppler-US for assessment of disease activity in JIA, and to compare the results with those obtained in healthy controls. In 10 patients, 11 arthritic joints (six wrists, three knees, two ankles) were assessed by Doppler-US and by MRI. Four different anatomical areas were assessed in the knee, ankle, and wrist, respectively. The same imaging modalities were used to evaluate eight joints (three wrists, three knees, two ankles) in six healthy age- and sex-matched controls, except that MRI contrast media was administered only to patients. In both patients and controls, the US results were compared with the MRI findings. For each of the compartments, the presence/absence of the following US signs of disease were registered: (1) non-compressible hypoechoic synovial hypertrophy, (2) compressible anechoic/hypoechoic joint effusion, and (3) bone erosion defined as a localized hyperechoic cortical defect seen in both the longitudinal and transverse planes. Hyperemia was defined as any presence of synovial vascularization as revealed by CD examination. US synovitis/tenosynovitis was defined as synovial hypertrophy with or without synovial vascularization, and with or without effusion.

All MRI examinations of wrists were scored using the OMERACT RAMRIS including the stipulated definitions of pathology, and knee and ankle MRIs were scored by applying an adjusted RAMRIS system. Synovitis was determined as above-normal post-gadolinium enhancement with a thickness greater than the width of the normal synovium (compared with T1w images) in scans obtained after intravenous administration of gadolinium contrast. Bone marrow edema was described as a lesion located within the trabecular bone and displaying ill-defined margins and signal characteristics consistent with increased water content on the STIR or FS T2w images. Bone erosion was designated as a sharply marginated bone lesion showing correct juxta-articular localization and typical signal characteristics, and visible in two planes with a cortical break in at least one plane.

The median time span between the US and MRI examinations was 1 week (range 0–7 weeks). US detected synovial hypertrophy in 22 areas of 11 joints, 86% of which had synovial hyperemia, and MRI revealed synovitis in 36 areas of the same 11 joints. Erosions were identified by US in two areas of two joints and by MRI in six areas of four joints. Effusion was shown by US in nine areas of six joints and by MRI in 17 areas of five joints. MRI detected juxta-articular bone marrow edema in 16 areas of eight joints.
All US and MRI examinations of healthy controls were performed on the same day. A slight effusion was detected in eight areas of five joints by US and in 14 areas of six joints by MRI. Furthermore, MRI revealed multiple and patchy, non-specific heterogeneous marrow signal changes on STIR images in five joints of four control subjects.

In conclusion, this study yielded results indicating that both MRI and US can provide valuable imaging data on disease activity in various joints of children with JIA. The two imaging modalities seem to complement each other, and they give partly different information on the patients who are assessed. However, it should be pointed out that this research represents a pilot study, and thus our results need to be confirmed in a larger prospective clinical investigation.

ETHICAL CONSIDERATIONS

The studies presented in this thesis were conducted in accordance with the international principles of research ethics outlined in the World Medical Association's Declaration of Helsinki (2004), and they were approved by the Regional Ethics Committees of Lund University, Sweden, and Copenhagen, Denmark. All parents gave informed consent for their children to participate, and oral consent was obtained from the children themselves. The US modality is patient-friendly in that diagnostic use is not associated with any known risks, and there are no contraindications. US examinations are easy and fast for the patient, and thus repeated follow-up assessments are experienced as convenient and agreeable.

MRI does not involve ionizing radiation. In our studies, MRI contrast agent was administered to patients but not controls, and dermal anesthetic cream was applied in all patients to prevent local procedural pain. General MRI safety precautions were taken as stipulated by the MRI departments, including the use of standardized checklists.

With the exception of the US and MRI examinations, the patients enrolled in the studies were not subjected to any interventions other than those that would have been indicated by local clinical practice, and they were prescribed the same treatment as they would have received if they had not participated in the studies. According to local practice, triamcinolone acetonide was used for all US-guided injections, and to prevent procedural pain all injections were performed under general anesthesia in patients of pre-school age and with nitrous oxide-oxygen analgesia in patients of school age.

As a consequence of the knowledge gained in this research project, Doppler-US has been implemented in daily clinical practice at the local pediatric rheumatology unit in order to benefit the patients.

GENERAL DISCUSSION

Detection of the exact anatomical location of inflamed structures in JIA (Papers I, II, III)

According to recent investigations in children, clinical examination alone is inadequate to identify structures involved in JIA, and US is more sensitive for detection of active arthritis and enthesitis [40, 151, 153, 154, 156]. Our studies were descriptive in nature and thus were not designed to compare the results of clinical and US assessments. Two of our investigations [Papers I and III] focused on the ankle and the wrist, joints that are often involved in JIA and which are anatomically complex and difficult to evaluate clinically [40, 41, 77, 155]. Our results show the intricate distribution of synovial involvement in multiple joints and tendon sheaths, and also demonstrate the frequent involvement of multiple compartments.

In JIA, the pain caused by inflammatory enthesitis can be severe, disabling, and persistent but due to diagnostic uncertainty, this is not always recognized and hence not treated appropriately [28, 151, 184]. The study described in Paper II is the first to assess US and MRI examinations of JIA patients performed to detect enthesitis in a small and deep-seated insertion, a situation in which it is very difficult to make a clinical diagnosis and hence imaging would be highly valuable. Our findings of a significantly thicker gluteus medius insertion in patients than in controls, and insertions that were hypoechoic (enthesitis) in about half of the patients, indicate that US is a useful adjunct to clinical examination in the assessment of enthesitis [159].

US guidance of steroid injections in JIA (Papers I, III)

Steroid injections constitute a major form of treatment in JIA, and this method can be significantly improved by use of guided injection, particularly with US [62, 63, 206, 222-225]. To treat ankle swelling in JIA, it is common clinical practice to perform a palpation-guided injection in the talo-crural joint, whereas injection in the subtalar joint or tendon sheaths is done less often, which might explain the poor outcome of steroid injections in ankle disease in JIA [41, 153, 215, 216, 226]. In the study reported in Paper I, US showed no involvement of

the talo-crural joint in 22% of cases, and it revealed involvement of other compartments in association with the talo-crural joint in 70%. Accordingly, for a great majority of the ankles, giving a palpation-guided injection only in the talo-crural joint would probably not have provided optimal results. In the same study, the posterior subtalar joint was the second most frequently involved compartment (65% of cases), and in children it is very difficult to inject that joint without imaging guidance [215, 218, 227]. Our follow-up of non-injected compartments showed that the overall results were good at most anatomical sites, with the exception of the five posterior subtalar joints. In these joints normalization or regression was achieved at only 60% of the locations, indicating the importance of local steroid injections of inflamed posterior subtalar joints. In the investigation presented in Paper III, Doppler-US depicted frequent involvement of the radio-carpal and midcarpal joints (in 87% and 53% of joints, respectively), and diseased tendon sheaths were found in one third of the symptomatic wrists. In JIA patients with wrist swelling, it is common practice to perform a palpation-guided injection in the radio-carpal joint, whereas injection of the midcarpal joints or tendon sheaths is performed less often [216, 228]. In two of our studies [Papers I and III], US guidance of injections in the ankle and wrist regions enabled real-time visualization of the entire procedure and exact placement of the steroid in the diseased compartments. In most of the patients treated in that manner, normalization or regression of synovial hypertrophy and hyperemia was achieved, and there was a low rate of subcutaneous atrophy.

The role of imaging in follow-up of treatment effects in JIA (Papers I, III)

Repetitive follow-up examinations with US is attractive because it is non-invasive and lacks ionizing radiation [116].

US with Doppler is widely used for follow-up in adult rheumatology, but no previous investigations have scrutinized Doppler-US for follow-up of treatment efficacy after steroid injections in JIA [229-231]. In short, it appears that determination of true remission cannot rely solely on clinical examination, but requires repetitive imaging to confirm the absence of subclinical inflammation [77].

Here, Doppler-US follow-up was performed in the ankle region 4 weeks after US-guided injection [Paper I] and in the wrist region 1 and 4 weeks after injection [Paper III]. Treatment effects were more rapid in tendon sheaths than in joints. Normalization of synovial hyperemia and synovial hypertrophy were often coincidental in the tendons, whereas the joints exhibited more rapid normalization of hyperemia than of synovial hypertrophy [231, 232]. At follow-up, in two of our studies [Papers I and III], we found that results were equally good for non-injected diseased compartments at most anatomical sites, with the exception of the posterior subtalar joints in the ankles, and one midcarpal joint in the wrist. Of the 50 involved tendon sheaths in ankles, 29 were not injected, but there was a total normalization of synovitis in all but one, indicating that it might suffice to use selective steroid injections of affected tendon sheaths in this region.

Repeated US assessments were well tolerated by the children and easy to incorporate into clinical assessments, and Doppler-US proved to be valuable for evaluation of treatment effects [116].

The role of MRI and Doppler-US in JIA (Paper IV)

The study reported in paper IV showed that, like MRI, US was valuable for assessment of disease activity and damage, and these two modalities appeared to be complementary and gave partly different information on the patients who were examined [118-120].

In Paper IV, the only finding of potential pathological significance in healthy controls was effusion demonstrated by both US and MRI. The positioning of joints differed slightly between the MRI and US examinations, which might have influenced the distribution of effusion within the joints we analyzed. Physiological joint effusion is common in children. Indeed, a recent MRI study detected fluid in the wrists of children at a relatively large volume that has previously been considered to be pathological in adults [104, 165].

Importantly, MRI, but not US, can visualize bone marrow edema, a key predictor of erosive disease in RA [97-100]. In our pilot study [Paper IV], MRI revealed signs of juxta-articular bone marrow edema in six of the 10 JIA patients, but also in five joints of four control subjects (wrists and ankles). Our observation concurs with other investigations in which MRI in healthy children have been reported to show physiological bone marrow edema at the iliac crest,

in the wrist, and in the ankle region [102-105]. Consequently, it may be difficult to use MRI to detect pathological bone marrow edema in children and adolescents [104].

In our study [Paper IV] MRI proved to be the best method for identifying erosions in JIA patients, which agrees with the results of previous studies of patients suffering from rheumatoid arthritis (RA) or JIA [121, 203]. Three of the four joints in which MRI detected erosions were wrists, and in two of those the erosions were located mainly on the capitate and lunate bones, in areas that are not accessible to US. However, these areas are also difficult to evaluate with MRI and, due to their anatomic peculiarities, they are associated with an intrinsically higher risk of being scored as false positive [233].

In pediatric patients, US offers these advantages over MRI: it does not require sedation or general anesthesia (which facilitates repeated examinations for follow-up); it is quickly accessible bedside; it is easy to combine with clinical evaluation [6, 164]. US images are analyzed in real time at the point of care, and the information obtained can be used directly to focus and improve the accuracy of the clinical assessment [116, 234]. Agitation of the patient is rarely a problem, and young children can be seated on a parent's lap or play while being examined [128]. The time required for examination is relatively short, and multiple locations can be assessed during a single session [162, 235]. Furthermore, in the hands of an experienced US examiner, a high-frequency US transducer can provide unsurpassed resolution of the superficial musculoskeletal structures [6].

By comparison, MRI offers the advantages of providing an overview and detecting pathology in deeper locations that are not accessible to US, such as the intercarpal spaces and the bone marrow [109]. The main disadvantages of MRI are the often poor availability, the lack of mobility, that it cannot be integrated with the clinical assessment, and that it requires sedation when used on young children, an age group with a high prevalence of JIA [236]. The investment, maintenance, and operating costs of the required equipment are also considerably higher for MRI than for US.

In conclusion, US seems to provide useful imaging information that can make it a suitable option in many, in both daily clinical practice and research studies in the field of pediatric rheumatology.

CONCLUSIONS

Based on the results presented in this doctoral thesis, the following can be concluded about the use of US in pediatric rheumatology:

- It enables identification of the exact anatomical location of inflammation in accessible joints and compartments
- It improves assessment of synovitis and enthesitis
- It allows exact guidance of steroid injections
- It is valuable for repeated monitoring of treatment efficacy
- It is readily available at point of care and complementary to MRI for assessment of disease activity and damage

FUTURE PERSPECTIVES

At point of care, it is likely that US will play a significant role in the assessment of disease activity in children with JIA, as it already does in adult rheumatology. Clinical examination, clinical laboratory criteria, and imaging investigation will be used together to confirm, or reject, the presence of inflammation and damage in JIA, and US will be of increasing importance in that context. Other imaging modalities that may be of interest are fusion of US, or of positron emission tomography (PET), together with MRI or computed tomography (CT), and fluorescence optical imaging.

We believe that US guidance of steroid injections, especially in anatomically complex areas, will soon be performed routinely, and that MRI and US will be common practice in disease evaluation, and that the two imaging modalities will complement each other.

Even if a large part of the knowledge obtained in US studies in adult rheumatology might be applied to children as well, this imaging technique must be further validated in all fields of pediatric rheumatology. Radiologists and pediatric rheumatologists need to work in close collaboration to establish reference values for all US aspects of various joints and tendons in children at different stages of development.

Multicenter studies are desirable to validate the US-Doppler technique for short- and long-term follow-up of children with JIA, in order to substantiate true regression of disease activity and arrest of erosion. Specific training in US should be introduced for pediatric rheumatologists and should also be integrated in the educational programs for new specialists in pediatric rheumatology.

Table 6 summarizes the major future, important role of US in JIA.

Table 6. Major future role of US in JIA

- To improve evaluation and classification: number of joints involved, tenosynovitis versus arthritis, presence of enthesitis (together with MRI)
- To guide steroid injections, especially in anatomically complex areas
- To follow disease course, monitor the efficacy of treatment and assess disease remission (together with MRI)
- To identify predictors of damage (together with MRI)
- To assess the disease-modifying potential of new drugs in randomized controlled trials (together with MRI)

SVENSK SAMMANFATTNING (SUMMARY IN SWEDISH)

Tidigt insatt behandling och nya effektiva läkemedel har det senaste decenniet förbättrat prognosen för många barn med juvenil idiopatisk artrit (JIA). Som en följd av detta har behovet ökat av precisa och objektiva metoder för bedömning av sjukdomsaktivitet, och för att utvärdera effekten av insatt behandling.

Det finns inga kända biologiska sjukdomsmarkörer för JIA, och diagnoserna synovit (inflammerad ledvävnad), tenosynovit (inflammation av sena och senskida) och entesit (inflammation i fästet av sena, ligament, ledkapsel och benhinna) baseras därför huvudsakligen på kliniska fynd. Utifrån enbart klinisk undersökning är det svårt att avgöra den exakta orsaken till lednära svullnad eller smärta. Kunskap om antalet sjuka strukturer, och vilka strukturer som är drabbade, är viktigt eftersom det påverkar sjukdomsklassifikation och behandling vid JIA. Studier, på både vuxna och barn, har visat att ultraljud (UL) är bättre än klinisk undersökning för att avgöra vilka strukturer som är drabbade av sjukdom.

Steroidinjektion är en etablerad behandling inom reumatologin. Effekten av behandlingen är beroende av att kortisonpreparatet hamnar på avsedd plats. Undersökningar har visat sig att mer än hälften av alla steroidinjektioner hamnar fel, på grund av svårigheten att veta injektionsnålens läge. Genom att använda bilddiagnostiska metoder, framförallt UL, för vägledning ökar precisionen i injektionerna.

Utvärdering av behandling vid JIA baseras på klinisk undersökning och bilddiagnostik. Utvärdering med UL, en icke-invasiv och snabb teknik, är patientvänlig, väl lämpad för upprepad undersökning, och utsätter inte barnet för joniserande strålning.

Ultraljud och magnetkamera (MR), är etablerade bilddiagnostiska metoder inom vuxenreumatologin, men som inte har utvärderats på barn och ungdomar med artrit.

Denna avhandling handlar om att utvärdera UL med Doppler inom klinisk barnreumatologi, i syfte att bidra till en ökad kunskap och erfarenhet.

Specifika mål för projektet har varit att utvärdera:

- UL med Doppler för att exakt påvisa inflammerade strukturer i fotleds- och handledsområdet hos barn med symtom
- UL som vägledning vid steroidinjektioner på barn med JIA
- UL med Doppler för upprepad utvärdering av behandling med steroidinjektion
- UL med Doppler för diagnos av entesit vid infästningen av gluteus medius muskeln hos barn med JIA
- UL med Doppler, respektive MR, för diagnostik av inflammation i mjukdelar och erosion av skelett, hos barn med JIA - och att jämföra med resultat från friska barn

Baserat på resultaten i avhandlingen, är våra slutsatser att:

- UL med Doppler möjliggör exakt lokalisation av inflammerade strukturer i områden som är tillgängliga för ultraljud
- UL med Doppler förbättrar diagnostik av synovit och entesit
- UL möjliggör exakt vägledning av steroidinjektioner
- UL med Doppler är av stort värde för utvärdering av behandlingseffekt efter steroidinjektion
- UL kan användas patientnära, har god tillgänglighet och är ett användbart komplement till MR för utvärdering av sjukdomsaktivitet vid JIA

Vi tror att i en nära framtid kommer:

- UL att bli en viktig metod för patientnära bilddiagnostik hos barn och ungdomar med JIA
- Bilddiagnostik (UL och MRI), klinisk undersökning och laboratoriedata att användas tillsammans för att bekräfta, eller avfärda, närvaro av inflammation och destruktion vid JIA
- UL vägledning av steroidinjektioner, speciellt i anatomiskt komplexa områden, att genomföras rutinmässigt vid JIA

Även om mycket kunskap från UL studier på vuxna sannolikt kan tillämpas på barn, så skiljer sig de barnreumatologiska sjukdomarna från de vuxnas. Brosk och skelett hos växande barn och ungdomar ser annorlunda ut vid bilddiagnostik, och har andra egenskaper än hos vuxna. Det är därför viktigt att UL tekniken utvärderas och valideras på barn. Radiologer och barnreumatologer bör i nära samarbete slå fast normala referensvärden för leder och mjukdelar hos barn i olika utvecklingsstadier. Multicenterstudier behöver genomföras för att validera användning av Doppler UL för diagnostik, för uppföljning på kort och lång sikt, och för att fastställa kriterier för regression av inflammation och erosion.
Ultraljudsutbildning behöver introduceras för barnreumatologer, och bör bli obligatoriskt i specialistutbildningen.

ACKNOWLEDGEMENTS

I want to express my gratitude to all those who helped, encouraged, and guided me through my research and the process of completing this thesis. In particular, I thank the following people:

All the children with articular disease and all the healthy children, as well as their families, for willingly participating and for showing positive interest in my research.
Without all of you, this thesis would never have been written.

Anders Fasth, my mentor and scientific coach and Professor of Pediatric Immunology at the University of Gothenburg, Sweden. You have been the ultimate guide on my research journey! Online 24 hours a day, always ready to give general support, wise advice, and constructive criticism - and also to have friendly chats.

Michel Court-Payen, my co-mentor, US coach, and Consultant in Musculoskeletal Radiology in Copenhagen, Denmark. Your skills in clinical US and your ambition to share your knowledge with clinicians are impressive. You are a true artist in your field of work, and you have taught me everything I know about US! Being a native Frenchman and truly "European", you encouraged me to present our results in both English and French, and to train in Italy.

Marek Zak and Susan Nielsen, Consultants in Pediatric Rheumatology at Rigshospitalet, Copenhagen, devoted clinicians and scientists, and my clinical coworkers in the project. When I introduced the idea of starting a research project on US, your response was positive, yet skeptical. Today, both of you are performing bedside US examinations as an integral part of the clinical assessment of patients in your daily practice!

Carsten Thomsen, Professor of Radiology, and *Mikael Boesen*, Consultant in Radiology, Copenhagen, my coworkers in the project who taught me everything I know about MRI.

Marjatta Leirisalo-Repo, former Professor of Rheumatology in Lund, Sweden, currently working in Helsinki, Finland. By aiming to initiate research at the Pediatric Rheumatology Section in Lund, you encouraged me to develop my interest in US and gave me moral and financial support to acquire initial knowledge abroad.

Kevin Murray, former Consultant and Clinical Lead at the Paediatric and Adolescent Rheumatology Unit at Great Ormond Street Children's Hospital in London.
As my clinical mentor during my fellowship in London in 2000, you got me involved in an interesting MRI pilot project that strengthened my interest in imaging, as well as my dedication to making this my field of research.

Pat Woo, former Professor at the Centre for Paediatric and Adolescent Rheumatology, University College London, for encouragement to pursue my research in imaging.

Ellen Churchill and Michel Plantevin, for more than 35 years of close friendship and unlimited hospitality during my fellowship stay and several other visits to London.

Carlo Martinoli, Associate Professor of Radiology, and *Maura Valle*, Consultant in Radiology, Gaslini Pediatric Hospital, for being my mentors and skillful teachers in musculoskeletal US during my stay in Genova, Italy, in 2007.

Peter Hochbergs, Head of the Center for Medical Imaging and Physiology at Skåne University Hospital, Lund, for kind and useful advice during a situation involving MRI shortage in the region.

Anetta Bolejko, research nurse at the MRI Department of Skåne University Hospital, Malmö, for skilled assistance with the MRI examinations of healthy controls.

Diana Karpman, Professor of Pediatric Nephrology, *Vineta Fellman*, Professor of Pediatric Neonatology, and *Rolf Ljung*, Professor of Pediatrics, Department

of Pediatrics, Lund University, for general support and practical assistance that enabled me to pursue my research courses in Lund.

Irene Jakobsson, Charlotta Schaedel, and Katarina Johnsson, Heads of Children's Hospital in Lund, who kindly gave me permission to work part-time at the clinic so that I could also manage my research.

Lillemor Berntsson, Head of the Pediatric Rheumatology Section of the Swedish Pediatric Association and Consultant in Pediatric Rheumatology in Uppsala, Sweden, for friendship and for enthusiastically encouraging me to pursue my field of research.

Bo Magnusson and Stefan Hagelberg, Stockholm, *Stefan Berg*, Göteborg and *Boel Andersson Gäre*, Jönköping, Sweden, experienced pediatric rheumatologists, for general encouragement and friendly chats about JIA-related topics and more.

Göran Wettrell, Associate Professor of Pediatric Cardiology, Lund, and my former mentor in general pediatrics, for encouraging me to combine clinical work with research.

Frank Wollheim, Professor Emeritus of Rheumatology, Lund, for kindly helping me to obtain appropriate medical references.

Patricia Ödman, for skilled language revision in English, and *Holger Hövel* for translation into German.

Per-Erik Isberg, for statistical advice.

Martin, my husband, for love, support, and technical assistance. On a daily basis, you have always been ready for clinical and scientific discussions, and constantly eager to question my research activities.

Our children, *Astrid, Axel, Amanda, Alli, Alf and Anna*. I love you and appreciate your patience during the years this project has been running. All six of you have participated as healthy controls in my studies. Furthermore, Astrid

and Axel have actively helped to recruit healthy controls among friends and classmates.
You are the real experts on the practical aspects of US and MRI, and you certainly know more about medical imaging than most young people your age!

My parents, *Stephan and Siv Laurell*, for unconditional support and love.

Friends and family in Lund, in Sweden and abroad, for not neglecting me during periods of intense research activities.

REFERENCES

1. Martini A, Lovell DJ: Juvenile idiopathic arthritis: state of the art and future perspectives. *Ann Rheum Dis* 2010, 69:1260-63.

2. Ravelli A, Martini A: Juvenile idiopathic arthritis. *Lancet* 2007, 369:767-78.

3. Berntson L, Andersson Gare B, Fasth A, Herlin T, Kristinsson J, Lahdenne P, Marhaug G, Nielsen S, Pelkonen P, Rygg M: Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. *J Rheumatol* 2003, 30:2275-82.

4. Gare BA, Fasth A: Epidemiology of juvenile chronic arthritis in southwestern Sweden: a 5-year prospective population study. *Pediatrics* 1992, 90:950-58.

5. McGonagle D, Benjamin M: Towards a new clinico-immunopathological classification of juvenile inflammatory arthritis. *J Rheumatol* 2009, 36:1573-74.

6. Damasio MB, Malattia C, Martini A, Toma P: Synovial and inflammatory diseases in childhood: role of new imaging modalities in the assessment of patients with juvenile idiopathic arthritis. *Pediatr Radiol* 2010, 40:985-98.

7. Diamantberger MS: Du rhumatisme noueux (polyarthrite déformante) chez l'enfant. Thèse pour le doctorat en médecine., 1890.

8. Nistala K, Wedderburn LR: Th17 and regulatory T cells: rebalancing pro- and anti-inflammatory forces in autoimmune arthritis. *Rheumatology (Oxford)* 2009, 48:602-06.

9. Prakken BJ, Albani S: Using biology of disease to understand and guide therapy of JIA. *Best Pract Res Clin Rheumatol* 2009, 23:599-608.

10. Frosch M, Roth J: New insights in systemic juvenile idiopathic arthritis--from pathophysiology to treatment. *Rheumatology (Oxford)* 2008, 47:121-25.

11. Brewer EJ, Jr., Bass J, Baum J, Cassidy JT, Fink C, Jacobs J, Hanson V, Levinson JE, Schaller J, Stillman JS: Current proposed revision of JRA Criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Section of The Arthritis Foundation. *Arthritis Rheum* 1977, 20:195-99.

12. EULAR: Nomenclature and Classification of Arthritis in Children. *Basel, National Zeitung AG EULAR Bulletin* 1977, 4.

13. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, et al: International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004, 31:390-92.

14. Southwood TR: Classifying childhood arthritis. *Ann Rheum Dis* 1997, 56:79-81.

15. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, Maldonado-Cocco J, Suarez-Almazor M, Orozco-Alcala J, Prieur AM: Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol* 1998, 25:1991-94.

16. Fink CW: Proposal for the development of classification criteria for idiopathic arthritides of childhood. *J Rheumatol* 1995, 22:1566-69.

17. Prakken B, Albani S, Martini A: Juvenile idiopathic arthritis. *Lancet* 2011, 377:2138-49.

18. Thompson SD, Barnes MG, Griffin TA, Grom AA, Glass DN: Heterogeneity in juvenile idiopathic arthritis: impact of molecular profiling based on DNA polymorphism and gene expression patterns. *Arthritis Rheum* 2010, 62:2611-15.

19. Andersson B, Fasth A: Presentations, clinical features and special problems in children. In *Rheumatology*. 5th edition. Edited by Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH. Philadelphia, PA, USA: Mosby Elsevier; 2010: 993-1008.

20. Berntson L, Fasth A, Andersson-Gare B, Herlin T, Kristinsson J, Lahdenne P, Marhaug G, Nielsen S, Pelkonen P, Rygg M: The influence of heredity for psoriasis on the ILAR classification of juvenile idiopathic arthritis. *J Rheumatol* 2002, 29:2454-58.

21. Masters SL, Simon A, Aksentijevich I, Kastner DL: Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. *Annu Rev Immunol* 2009, 27:621-68.

22. De Benedetti F, Martini A: Is systemic juvenile rheumatoid arthritis an interleukin 6 mediated disease? *J Rheumatol* 1998, 25:203-07.

23. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, Iwata N, Umebayashi H, Murata T, Miyoshi M, et al: Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008, 371:998-1006.

24. Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J: Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med* 2005, 201:1479-86.

25. Gattorno M, Piccini A, Lasiglie D, Tassi S, Brisca G, Carta S, Delfino L, Ferlito F, Pelagatti MA, Caroli F, et al: The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum* 2008, 58:1505-15.

26. van Rossum M, van Soesbergen R, de Kort S, ten Cate R, Zwinderman AH, de Jong B, Dijkmans B, van Venrooij WJ: Anti-cyclic citrullinated peptide (anti-CCP) antibodies in children with juvenile idiopathic arthritis. *J Rheumatol* 2003, 30:825-28.

27. Colbert RA: Classification of juvenile spondyloarthritis: Enthesitis-related arthritis and beyond. *Nat Rev Rheumatol* 2010, 6:477-85.

28. Burgos-Vargas R: The juvenile-onset spondyloarthritides. In *Ankylosing spondylitis and the spondyloarthropathies*. Edited by Weisman MH, van der Heijde D, Reveille JD. Philadelphia: Mosby; 2006: 94-106.

29. Cabral DA, Oen KG, Petty RE: SEA syndrome revisited: a longterm followup of children with a syndrome of seronegative enthesopathy and arthropathy. *J Rheumatol* 1992, 19:1282-85.

30. Burgos-Vargas R, Clark P: Axial involvement in the seronegative enthesopathy and arthropathy syndrome and its progression to ankylosing spondylitis. *J Rheumatol* 1989, 16:192-97.

31. Martini A: Are the number of joints involved or the presence of psoriasis still useful tools to identify homogeneous disease entities in juvenile idiopathic arthritis? *J Rheumatol* 2003, 30:1900-03.

32. Ravelli A, Varnier GC, Oliveira S, Castell E, Arguedas O, Magnani A, Pistorio A, Ruperto N, Magni-Manzoni S, Galasso R, et al: Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. *Arthritis Rheum* 2011, 63:267-75.

33. Ravelli A, Felici E, Magni-Manzoni S, Pistorio A, Novarini C, Bozzola E, Viola S, Martini A: Patients with antinuclear antibody-positive juvenile idiopathic arthritis constitute a homogeneous subgroup irrespective of the course of joint disease. *Arthritis Rheum* 2005, 52:826-32.

34. Stoll ML, Lio P, Sundel RP, Nigrovic PA: Comparison of Vancouver and International League of Associations for rheumatology classification criteria for juvenile psoriatic arthritis. *Arthritis Rheum* 2008, 59:51-58.

35. Stoll ML, Zurakowski D, Nigrovic LE, Nichols DP, Sundel RP, Nigrovic PA: Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis Rheum* 2006, 54:3564-72.

36. Woo P, Laxer RM, Sherry DD: *Pediatric Rheumatology in Clinical Practice.* Springer-Verlag London 2007.

37. Cassidy JT, Petty RE: *Textbook of Pediatric Rheumatology.* 3 edn: W. B. Saunders Company; 2005.

38. Thastum M, Herlin T, Zachariae R: Relationship of pain-coping strategies and pain-specific beliefs to pain experience in children with juvenile idiopathic arthritis. *Arthritis Rheum* 2005, 53:178-84.

39. Kuis W, Heijnen CJ, Hogeweg JA, Sinnema G, Helders PJ: How painful is juvenile chronic arthritis? *Arch Dis Child* 1997, 77:451-53.

40. Pascoli L, Wright S, McAllister C, Rooney M: Prospective evaluation of clinical and ultrasound findings in ankle disease in juvenile idiopathic arthritis: importance of ankle ultrasound. *J Rheumatol* 2010, 37:2409-14.

41. Rooney ME, McAllister C, Burns JF: Ankle disease in juvenile idiopathic arthritis: ultrasound findings in clinically swollen ankles. *J Rheumatol* 2009, 36:1725-29.

42. Benjamin M, McGonagle D: The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites. *J Anat* 2001, 199:503-26.

43. McGonagle D, Gibbon W, Emery P: Classification of inflammatory arthritis by enthesitis. *Lancet* 1998, 352:1137-40.

44. Olivieri I, Barozzi L, Padula A: Enthesiopathy: clinical manifestations, imaging and treatment. *Baillieres Clin Rheumatol* 1998, 12:665-81.

45. Rosenberg AM, Petty RE: A syndrome of seronegative enthesopathy and arthropathy in children. *Arthritis Rheum* 1982, 25:1041-47.

46. Sherry DD, Sapp LR: Enthesalgia in childhood: site-specific tenderness in healthy subjects and in patients with seronegative enthesopathic arthropathy. *J Rheumatol* 2003, 30:1335-40.

47. Burgos-Vargas R, Pacheco-Tena C, Vazquez-Mellado J: A short-term follow-up of enthesitis and arthritis in the active phase of juvenile onset spondyloarthropathies. *Clin Exp Rheumatol* 2002, 20:727-31.

48. Mander M, Simpson JM, McLellan A, Walker D, Goodacre JA, Dick WC: Studies with an enthesis index as a method of clinical assessment in ankylosing spondylitis. *Ann Rheum Dis* 1987, 46:197-202.

49. Olivieri I, Scarano E, Ciancio G, Giasi V, Padula A: Lateral epicondylitis with marked soft tissue swelling in spondyloarthritis. *Clin Rheumatol* 2004, 23:275-76.

50. Olivieri I, Barozzi L, Padula A, De Matteis M, Pierro A, Cantini F, Salvarani C, Pavlica P: Retrocalcaneal bursitis in spondyloarthropathy: assessment by ultrasonography and magnetic resonance imaging. *J Rheumatol* 1998, 25:1352-57.

51. Olivieri I, Gemignani G, Bini C, Grassi L, Pasero G: Diffuse Achilles tendon thickening in juvenile onset seronegative HLA-B27 positive spondyloarthropathy. *J Rheumatol* 1988, 15:381-82.

52. Pagnini I, Savelli S, Matucci-Cerinic M, Fonda C, Cimaz R, Simonini G: Early predictors of juvenile sacroiliitis in enthesitis-related arthritis. *J Rheumatol* 2010, 37:2395-2401.

53. Stoll ML, Bhore R, Dempsey-Robertson M, Punaro M: Spondyloarthritis in a pediatric population: risk factors for sacroiliitis. *J Rheumatol* 2010, 37:2402-08.

54. van der Heijde D, Salonen D, Weissman BN, Landewe R, Maksymowych WP, Kupper H, Ballal S, Gibson E, Wong R: Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis Res Ther* 2009, 11:R127.

55. van der Heijde D, Landewe R, Einstein S, Ory P, Vosse D, Ni L, Lin SL, Tsuji W, Davis JC, Jr.: Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis Rheum* 2008, 58:1324-31.

56. van der Heijde D, Landewe R, Baraliakos X, Houben H, van Tubergen A, Williamson P, Xu W, Baker D, Goldstein N, Braun J: Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. *Arthritis Rheum* 2008, 58:3063-70.

57. Klassen TP, Hartling L, Hamm M, van der Lee JH, Ursum J, Offringa M: StaR Child Health: an initiative for RCTs in children. *Lancet* 2009, 374:1310-12.

58. Klassen TP, Hartling L, Craig JC, Offringa M: Children are not just small adults: the urgent need for high-quality trial evidence in children. *PLoS Med* 2008, 5:e172.

59. Ruperto N, Martini A: Use of unlabelled and off licence drugs in children. A European paediatric rule is needed to protect children. *BMJ* 2000, 320:1210-11.

60. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, Baumgartner SW, Giannini EH: Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. *Arthritis Rheum* 2008, 58:1496-1504.

61. Moorthy LN, Peterson MG, Hassett AL, Lehman TJ: Burden of childhood-onset arthritis. *Pediatr Rheumatol Online J* 2010, 8:20.

62. Lanni S, Bertamino M, Consolaro A, Pistorio A, Magni-Manzoni S, Galasso R, Lattanzi B, Calvo-Aranda E, Martini A, Ravelli A: Outcome and predicting factors of single and multiple intra-articular corticosteroid injections in children with juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2011.

63. Bloom BJ, Alario AJ, Miller LC: Intra-articular corticosteroid therapy for juvenile idiopathic arthritis: report of an experiential cohort and literature review. *Rheumatol Int* 2011, 31:749-56.

64. Ruperto N, Martini A: Pediatric rheumatology: JIA, treatment and possible risk of malignancies. *Nat Rev Rheumatol* 2011, 7:6-7.

65. Ruperto N, Murray KJ, Gerloni V, Wulffraat N, de Oliveira SK, Falcini F, Dolezalova P, Alessio M, Burgos-Vargas R, Corona F, et al: A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum* 2004, 50:2191-2201.

66. Wallace CA, Giannini EH, Huang B, Itert L, Ruperto N: American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2011, 63:929-36.

67. Magni-Manzoni S, Ruperto N, Pistorio A, Sala E, Solari N, Palmisani E, Cugno C, Bozzola E, Martini A, Ravelli A: Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. *Arthritis Rheum* 2008, 59:1120-27.

68. Wallace CA, Ruperto N, Giannini E: Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004, 31:2290-94.

69. Foell D, Wulffraat N, Wedderburn LR, Wittkowski H, Frosch M, Gerss J, Stanevicha V, Mihaylova D, Ferriani V, Tsakalidou FK, et al: Methotrexate withdrawal at 6 vs 12 months in juvenile idiopathic arthritis in remission: a randomized clinical trial. *JAMA* 2010, 303:1266-73.

70. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, Nemcova D, Mouy R, Sandborg C, Bohnsack J, et al: Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008, 359:810-20.

71. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, Abud-Mendoza C, Burgos-Vargas R, Gerloni V, Melo-Gomes JA, et al: Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008, 372:383-91.

72. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, Wouters C, Silverman ED, Balogh Z, Henrickson M, et al: A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2007, 56:3096-3106.

73. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, Stein LD, Gedalia A, Ilowite NT, Wallace CA, et al: Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000, 342:763-69.

74. Raine R, Sanderson C, Hutchings A, Carter S, Larkin K, Black N: An experimental study of determinants of group judgments in clinical guideline development. *Lancet* 2004, 364:429-37.

75. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ, Emery P: An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum* 2008, 58:2958-67.

76. Wakefield RJ, Green MJ, Marzo-Ortega H, Conaghan PG, Gibbon WW, McGonagle D, Proudman S, Emery P: Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. *Ann Rheum Dis* 2004, 63:382-85.

77. Rebollo-Polo M, Koujok K, Weisser C, Jurencak R, Bruns A, Roth J: Ultrasound findings on patients with juvenile idiopathic arthritis in clinical remission. *Arthritis Care Res (Hoboken)* 2011, 63:1013-19.

78. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Wakefield R, Karim Z, Quinn M, Hensor E, Conaghan PG, Emery P: Extended report: should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. *Ann Rheum Dis* 2011, 70:792-98.

79. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Karim Z, Quinn M, Wakefield R, Hensor E, Conaghan PG, Emery P: Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. *Arthritis Rheum* 2009, 60:1915-22.

80. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ, Emery P: Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis Rheum* 2006, 54:3761-73.

81. Inaba Y, Ozawa R, Imagawa T, Mori M, Hara Y, Miyamae T, Aoki C, Saito T, Yokota S: Radiographic improvement of damaged large joints in children with systemic juvenile idiopathic arthritis following tocilizumab treatment. *Ann Rheum Dis* 2011, 70:1693-95.

82. Ravelli A: The time has come to include assessment of radiographic progression in juvenile idiopathic arthritis clinical trials. *J Rheumatol* 2008, 35:553-57.

83. Rossi F, Di Dia F, Galipo O, Pistorio A, Valle M, Magni-Manzoni S, Ruperto N, Toma P, Martini A, Ravelli A: Use of the Sharp and Larsen scoring methods in the assessment of radiographic progression in juvenile idiopathic arthritis. *Arthritis Rheum* 2006, 55:717-23.

84. van Rossum MA, Boers M, Zwinderman AH, van Soesbergen RM, Wieringa H, Fiselier TJ, Franssen MJ, ten Cate R, van Suijlekom-Smit LW, Wulffraat NM, et al: Development of a standardized method of assessment of radiographs and radiographic change in juvenile idiopathic arthritis: introduction of the Dijkstra composite score. *Arthritis Rheum* 2005, 52:2865-72.

85. van Rossum MA, Zwinderman AH, Boers M, Dijkmans BA, van Soesbergen RM, Fiselier TJ, Franssen MJ, ten Cate R, van Suijlekom-Smit LW, Wulffraat NM, et al: Radiologic features in juvenile idiopathic arthritis: a first step in the development of a standardized assessment method. *Arthritis Rheum* 2003, 48:507-15.

86. Poznanski AK, Hernandez RJ, Guire KE, Bereza UL, Garn SM: Carpal length in children--a useful measurement in the diagnosis of rheumatoid arthritis and some concenital malformation syndromes. *Radiology* 1978, 129:661-68.

87. Ravelli A, Ioseliani M, Norambuena X, Sato J, Pistorio A, Rossi F, Ruperto N, Magni-Manzoni S, Ullmann N, Martini A: Adapted versions of the Sharp/van der Heijde score are reliable and valid for assessment of radiographic progression in juvenile idiopathic arthritis. *Arthritis Rheum* 2007, 56:3087-95.

88. Argyropoulou MI, Margariti PN, Karali A, Astrakas L, Alfandaki S, Kosta P, Siamopoulou A: Temporomandibular joint involvement in juvenile idiopathic arthritis: clinical predictors of magnetic resonance imaging signs. *Eur Radiol* 2009, 19:693-700.

89. Lee EY, Sundel RP, Kim S, Zurakowski D, Kleinman PK: MRI findings of juvenile psoriatic arthritis. *Skeletal Radiol* 2008, 37:987-96.

90. Pedersen TK, Kuseler A, Gelineck J, Herlin T: A prospective study of magnetic resonance and radiographic imaging in relation to symptoms and clinical findings of the temporomandibular joint in children with juvenile idiopathic arthritis. *J Rheumatol* 2008, 35:1668-75.

91. Nistala K, Babar J, Johnson K, Campbell-Stokes P, Foster K, Ryder C, McDonagh JE: Clinical assessment and core outcome variables are poor predictors of hip arthritis diagnosed by MRI in juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2007, 46:699-702.

92. Workie DW, Graham TB, Laor T, Rajagopal A, O'Brien KJ, Bommer WA, Racadio JM, Shire NJ, Dardzinski BJ: Quantitative MR characterization of disease activity in the knee in children with juvenile idiopathic arthritis: a longitudinal pilot study. *Pediatr Radiol* 2007, 37:535-43.

93. Lamer S, Sebag GH: MRI and ultrasound in children with juvenile chronic arthritis. *Eur J Radiol* 2000, 33:85-93.

94. Gylys-Morin VM: MR imaging of pediatric musculoskeletal inflammatory and infectious disorders. *Magn Reson Imaging Clin N Am* 1998, 6:537-59.

95. Brown MA, Semelka RC: MR imaging abbreviations, definitions, and descriptions: a review. *Radiology* 1999, 213:647-62.

96. Nitz WR, Reimer P: Contrast mechanisms in MR imaging. *Eur Radiol* 1999, 9:1032-46.

97. Haavardsholm EA, Boyesen P, Ostergaard M, Schildvold A, Kvien TK: Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. *Ann Rheum Dis* 2008, 67:794-800.

98. Palosaari K, Vuotila J, Takalo R, Jartti A, Niemela RK, Karjalainen A, Haapea M, Soini I, Tervonen O, Hakala M: Bone oedema predicts erosive progression on wrist MRI in early RA--a 2-yr observational MRI and NC scintigraphy study. *Rheumatology (Oxford)* 2006, 45:1542-48.

99. Benton N, Stewart N, Crabbe J, Robinson E, Yeoman S, McQueen FM: MRI of the wrist in early rheumatoid arthritis can be used to predict functional outcome at 6 years. *Ann Rheum Dis* 2004, 63:555-61.

100. McQueen FM, Benton N, Perry D, Crabbe J, Robinson E, Yeoman S, McLean L, Stewart N: Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentation predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis. *Arthritis Rheum* 2003, 48:1814-27.

101. Savnik A, Malmskov H, Thomsen HS, Graff LB, Nielsen H, Danneskiold-Samsoe B, Boesen J, Bliddal H: Magnetic resonance imaging of the wrist and finger joints in patients with inflammatory joint diseases. *J Rheumatol* 2001, 28:2193-2200.

102. Ejbjerg B, Narvestad E, Rostrup E, Szkudlarek M, Jacobsen S, Thomsen HS, Ostergaard M: Magnetic resonance imaging of wrist and finger joints in healthy subjects occasionally shows changes resembling erosions and synovitis as seen in rheumatoid arthritis. *Arthritis Rheum* 2004, 50:1097-1106.

103. Laor T, Jaramillo D: MR imaging insights into skeletal maturation: what is normal? *Radiology* 2009, 250:28-38.

104. Muller LS, Avenarius D, Damasio B, Eldevik OP, Malattia C, Lambot-Juhan K, Tanturri L, Owens CM, Rosendahl K: The paediatric wrist revisited: redefining MR findings in healthy children. *Ann Rheum Dis* 2011, 70:605-10.

105. Shabshin N, Schweitzer ME, Morrison WB, Carrino JA, Keller MS, Grissom LE: High-signal T2 changes of the bone marrow of the foot and ankle in children: red marrow or traumatic changes? *Pediatr Radiol* 2006, 36:670-76.

106. Frahm J, Haase A, Matthaei D: Rapid three-dimensional MR imaging using the FLASH technique. *J Comput Assist Tomogr* 1986, 10:363-68.

107. Ostergaard M, Hansen M, Stoltenberg M, Jensen KE, Szkudlarek M, Pedersen-Zbinden B, Lorenzen I: New radiographic bone erosions in the wrists of patients with rheumatoid arthritis are detectable with magnetic resonance imaging a median of two years earlier. *Arthritis Rheum* 2003, 48:2128-31.

108. McQueen FM, Stewart N, Crabbe J, Robinson E, Yeoman S, Tan PL, McLean L: Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. *Ann Rheum Dis* 1998, 57:350-56.

109. Malattia C, Damasio MB, Basso C, Verri A, Magnaguagno F, Viola S, Gattorno M, Ravelli A, Toma P, Martini A: Dynamic contrast-enhanced magnetic resonance imaging in the assessment of disease activity in patients with juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2010, 49:178-85.

110. Graham TB, Laor T, Dardzinski BJ: Quantitative magnetic resonance imaging of the hands and wrists of children with juvenile rheumatoid arthritis. *J Rheumatol* 2005, 32:1811-20.

111. Cakmakci H, Kovanlikaya A, Unsal E: Short-term follow-up of the juvenile rheumatoid knee with fat-saturated 3D MRI. *Pediatr Radiol* 2001, 31:189-95.

112. Ostergaard M, Peterfy C, Conaghan P, McQueen F, Bird P, Ejbjerg B, Shnier R, O'Connor P, Klarlund M, Emery P, et al: OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. *J Rheumatol* 2003, 30:1385-86.

113. Malattia C, Damasio MB, Pistorio A, Ioseliani M, Vilca I, Valle M, Ruperto N, Viola S, Buoncompagni A, Magnano GM, et al: Development and preliminary validation of a paediatric-targeted MRI scoring system for the assessment of disease activity and damage in juvenile idiopathic arthritis. *Ann Rheum Dis* 2011, 70:440-46.

114. Miller E, Roposch A, Uleryk E, Doria AS: Juvenile idiopathic arthritis of peripheral joints: quality of reporting of diagnostic accuracy of conventional MRI. *Acad Radiol* 2009, 16:739-57.

115. Miller E, Uleryk E, Doria AS: Evidence-based outcomes of studies addressing diagnostic accuracy of MRI of juvenile idiopathic arthritis. *AJR Am J Roentgenol* 2009, 192:1209-18.

116. Moore CL, Copel JA: Point-of-care ultrasonography. *N Engl J Med* 2011, 364:749-57.

117. Matsos M, Harish S, Zia P, Ho Y, Chow A, Ioannidis G, Khalidi N: Ultrasound of the hands and feet for rheumatological disorders: influence on clinical diagnostic confidence and patient management. *Skeletal Radiol* 2009, 38:1049-54.

118. Boesen M, Ellegaard K, Boesen L, Cimmino MA, Jensen PS, Terslev L, Torp-Pedersen S, Danneskiold-Samsoe B, Bliddal H: Ultrasound Doppler Score Correlates with OMERACT RAMRIS Bone Marrow Oedema and Synovitis Score in the Wrist Joint of Patients with Rheumatoid Arthritis. *Ultraschall Med* 2011.

119. Boesen M, Ostergaard M, Cimmino MA, Kubassova O, Jensen KE, Bliddal H: MRI quantification of rheumatoid arthritis: current knowledge and future perspectives. *Eur J Radiol* 2009, 71:189-96.

120. Backhaus M: Ultrasound and structural changes in inflammatory arthritis: synovitis and tenosynovitis. *Ann N Y Acad Sci* 2009, 1154:139-51.

121. Malattia C, Damasio MB, Magnaguagno F, Pistorio A, Valle M, Martinoli C, Viola S, Buoncompagni A, Loy A, Ravelli A, et al: Magnetic resonance imaging, ultrasonography, and conventional radiography in the assessment of bone erosions in juvenile idiopathic arthritis. *Arthritis Rheum* 2008, 59:1764-72.

122. Southwood T: Juvenile idiopathic arthritis: clinically relevant imaging in diagnosis and monitoring. *Pediatr Radiol* 2008, 38 Suppl 3:S395-402.

123. Doria AS, Babyn PS, Feldman B: A critical appraisal of radiographic scoring systems for assessment of juvenile idiopathic arthritis. *Pediatr Radiol* 2006, 36:759-72.

124. Johnson K: Imaging of juvenile idiopathic arthritis. *Pediatr Radiol* 2006, 36:743-58.

125. Torp-Pedersen ST, Terslev L: Settings and artefacts relevant in colour/power Doppler ultrasound in rheumatology. *Ann Rheum Dis* 2008, 67:143-49.

126. Koski JM, Saarakkala S, Helle M, Hakulinen U, Heikkinen JO, Hermunen H, Balint P, Bruyn GA, Filippucci E, Grassi W, et al: Assessing the intra- and inter-reader reliability of dynamic ultrasound images in power Doppler ultrasonography. *Ann Rheum Dis* 2006, 65:1658-60.

127. Cardinal E, Lafortune M, Burns P: Power Doppler US in synovitis: reality or artifact? *Radiology* 1996, 200:868-69.

128. Laurell L, Court-Payen M, Nielsen S, Zak M, Thomsen C, Boesen M, Fasth A: The role of Ultrasonography in Juvenile Idiopathic Arthritis (in French). In *Actualités en échographie de l'appareil locomoteur.* Edited by Brasseur J, Zeitoun-Eiss D, Renoux J, Grenier P. Paris: Sauramps médical; 2008: 73-97

129. Martinoli C, Valle M, Malattia C, Beatrice Damasio M, Tagliafico A: Paediatric musculoskeletal US beyond the hip joint. *Pediatr Radiol* 2011, 41 Suppl 1:S113-24.

130. Hogholm Pedersen M, Bachmann Nielsen M, Skjoldbye B: *Basics of Clinical Ultrasound.* Copenhagen: UltraPocketBooks ApS; 2006.

131. Chhem R, Cardinal E: *Guidelines and Gamuts in Musculoskeletal Ultrasound*. Wiley-Liss; 1999.

132. Oestreich AE: *Growth of the pediatric skeleton.* Springer; 2008.

133. Staheli LT: *Fundamentals of pediatric orthopedics.* Fourth edition edn: Lippincott Williams & Wilkins; 2008.

134. Netter F: *Musculoskeletal system: anatomy, physiology and metabolic disorders.* New Jersey: Summit; 1987.

135. MacRae VE, Farquharson C, Ahmed SF: The pathophysiology of the growth plate in juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2006, 45:11-19.

136. Peterson HA: *Epiphyseal Growth Plate Fractures.* 1st edn: Springer 2007.

137. Karmazyn B: Ultrasound of pediatric musculoskeletal disease: from head to toe. *Semin Ultrasound CT MR* 2011, 32:142-50.

138. Greulich WW, Pyle SI: *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. 2 edn: Stanford University Press; 1959.

139. Laurell L, Hochbergs P, Rydholm U, Wingstrand H: Capsular distance in the hip of the healthy child - normal values with sonography and MR imaging. *Acta Radiol* 2002, 43:213-16.

140. Fedrizzi MS, Ronchezel MV, Hilario MO, Lederman HM, Sawaya S, Goldenberg J, Sole D: Ultrasonography in the early diagnosis of hip joint involvement in juvenile rheumatoid arthritis. *J Rheumatol* 1997, 24:1820-25.

141. Gaucher H, Hoeffel JC: Anterior synovial recess of the hip: how to assess a pathological condition? *Pediatr Radiol* 1997, 27:835-36.

142. Eich GF, Halle F, Hodler J, Seger R, Willi UV: Juvenile chronic arthritis: imaging of the knees and hips before and after intraarticular steroid injection. *Pediatr Radiol* 1994, 24:558-63.

143. Terjesen T, Osthus P: Ultrasound in the diagnosis and follow-up of transient synovitis of the hip. *J Pediatr Orthop* 1991, 11:608-13.

144. Kallio P, Ryoppy S, Jappinen S, Siponmaa AK, Jaaskelainen J, Kunnamo I: Ultrasonography in hip disease in children. *Acta Orthop Scand* 1985, 56:367-71.

145. Harcke H, Clarke N, Lee M: Examination of the infant hip with real-time ultrasonography. *J Ultrasound Med* 1984, 3:131-37.

146. Graf R: The diagnosis of congenital hip-joint dislocation by the ultrasonic compund treatment. *arch Orthop Trauma Surg* 1980, 97:117-33.

147. Spannow AH, Stenboeg E, Pfeiffer-Jensen M, Fiirgaard B, Haislund M, Ostergaard M, Andersen NT, Herlin T: Ultrasound and MRI Measurements of Joint Cartilage in Healthy Children: a Validation Study. *Ultraschall Med* 2010.

148. Spannow AH, Pfeiffer-Jensen M, Andersen NT, Stenbog E, Herlin T: Inter- and intraobserver variation of ultrasonographic cartilage thickness assessments in small and large joints in healthy children. *Pediatr Rheumatol Online J* 2009, 7:12.

149. Spannow AH, Pfeiffer-Jensen M, Andersen NT, Herlin T, Stenbog E: Ultrasonographic Measurements of Joint Cartilage Thickness in Healthy Children: Age- and Sex-Related Standard Reference Values. *J Rheumatol* 2010.

150. Breton S, Jousse-Joulin S, Cangemi C, de Parscau L, Colin D, Bressolette L, Saraux A, Devauchelle-Pensec V: Comparison of Clinical and Ultrasonographic Evaluations for Peripheral Synovitis in Juvenile Idiopathic Arthritis. *Semin Arthritis Rheum* 2011.

151. Jousse-Joulin S, Breton S, Cangemi C, Fenoll B, Bressolette L, Parscau LD, Saraux A, Devauchelle-Pensec V: Ultrasonography for detecting enthesitis in juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2011.

152. Sparchez M, Fodor D, Miu N: The role of Power Doppler ultrasonography in comparison with biological markers in the evaluation of disease activity in Juvenile Idiopathic Arthritis. *Med Ultrason* 2010, 12:97-103.

153. Magni-Manzoni S, Epis O, Ravelli A, Klersy C, Veisconti C, Lanni S, Muratore V, Scire CA, Rossi S, Montecucco C: Comparison of clinical versus ultrasound-determined synovitis in juvenile idiopathic arthritis. *Arthritis Rheum* 2009, 61:1497-1504.

154. Haslam KE, McCann LJ, Wyatt S, Wakefield RJ: The detection of subclinical synovitis by ultrasound in oligoarticular juvenile idiopathic arthritis: a pilot study. *Rheumatology (Oxford)* 2010, 49:123-27.

155. Guzman J, Burgos-Vargas R, Duarte-Salazar C, Gomez-Mora P: Reliability of the articular examination in children with juvenile rheumatoid arthritis: interobserver agreement and sources of disagreement. *J Rheumatol* 1995, 22:2331-36.

156. Filippou G, Cantarini L, Bertoldi I, Picerno V, Frediani B, Galeazzi M: Ultrasonography vs. clinical examination in children with suspected arthritis. Does it make sense to use poliarticular ultrasonographic screening? *Clin Exp Rheumatol* 2011, 29:345-50.

157. Collado P, Naredo E, Calvo C, Crespo M: Assessment of the joint recesses and tendon sheaths in healthy children by high-resolution B-mode and power Doppler sonography. *Clin Exp Rheumatol* 2007, 25:915-21.

158. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, Fink CW, Newman AJ, Cassidy JT, Zemel LS: Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. *N Engl J Med* 1992, 326:1043-49.

159. Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, Sanchez EN, Iagnocco A, Schmidt WA, Bruyn GA, et al: Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005, 32:2485-87.

160. FitzGerald O, Soden M, Yanni G, Robinson R, Bresnihan B: Morphometric analysis of blood vessels in synovial membranes obtained from clinically affected and unaffected knee joints of patients with rheumatoid arthritis. *Ann Rheum Dis* 1991, 50:792-96.

161. El-Miedany YM, Housny IH, Mansour HM, Mourad HG, Mehanna AM, Megeed MA: Ultrasound versus MRI in the evaluation of juvenile idiopathic arthritis of the knee. *Joint Bone Spine* 2001, 68:222-30.

162. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, Wakefield RJ, Manger B: Guidelines for musculoskeletal ultrasound in rheumatology. *Ann Rheum Dis* 2001, 60:641-49.

163. Ostergaard M, Court-Payen M, Gideon P, Wieslander S, Cortsen M, Lorenzen I, Henriksen O: Ultrasonography in arthritis of the knee. A comparison with MR imaging. *Acta Radiol* 1995, 36:19-26.

164. Mandl P, Naredo E, Wakefield RJ, Conaghan PG, D'Agostino MA: A Systematic Literature Review Analysis of Ultrasound Joint Count and Scoring Systems to Assess Synovitis in Rheumatoid Arthritis According to the OMERACT Filter. *J Rheumatol* 2011, 38:2055-62.

165. Ejbjerg B, McQueen F, Lassere M, Haavardsholm E, Conaghan P, O'Connor P, Bird P, Peterfy C, Edmonds J, Szkudlarek M, et al: The EULAR-OMERACT rheumatoid arthritis MRI reference image atlas: the wrist joint. *Ann Rheum Dis* 2005, 64 Suppl 1:i23-47.

166. Kane D, Balint PV, Sturrock RD: Ultrasonography is superior to clinical examination in the detection and localization of knee joint effusion in rheumatoid arthritis. *J Rheumatol* 2003, 30:966-71.

167. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Ostergaard M: Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. *Arthritis Rheum* 2003, 48:955-62.

168. Frosch M, Foell D, Ganser G, Roth J: Arthrosonography of hip and knee joints in the follow up of juvenile rheumatoid arthritis. *Ann Rheum Dis* 2003, 62:242-44.

169. Murphy KJ, Rubin JM: Power Doppler: it's a good thing. *Semin Ultrasound CT MR* 1997, 18:13-21.

170. Albrecht K, Muller-Ladner U, Strunk J: Quantification of the synovial perfusion in rheumatoid arthritis using Doppler ultrasonography. *Clin Exp Rheumatol* 2007, 25:630-38.

171. Terslev L, Torp-Pedersen S, Savnik A, von der Recke P, Qvistgaard E, Danneskiold-Samsoe B, Bliddal H: Doppler ultrasound and magnetic resonance imaging of synovial inflammation of the hand in rheumatoid arthritis: a comparative study. *Arthritis Rheum* 2003, 48:2434-41.

172. Walther M, Harms H, Krenn V, Radke S, Kirschner S, Gohlke F: Synovial tissue of the hip at power Doppler US: correlation between vascularity and power Doppler US signal. *Radiology* 2002, 225:225-31.

173. Szkudlarek M, Court-Payen M, Strandberg C, Klarlund M, Klausen T, Ostergaard M: Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging. *Arthritis Rheum* 2001, 44:2018-23.

174. Schmidt WA, Volker L, Zacher J, Schlafke M, Ruhnke M, Gromnica-Ihle E: Colour Doppler ultrasonography to detect pannus in knee joint synovitis. *Clin Exp Rheumatol* 2000, 18:439-44.

175. Walther M, Harms H, Krenn V, Radke S, Faehndrich TP, Gohlke F: Correlation of power Doppler sonography with vascularity of the synovial tissue of the knee joint in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum* 2001, 44:331-38.

176. Naredo E, Bonilla G, Gamero F, Uson J, Carmona L, Laffon A: Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. *Ann Rheum Dis* 2005, 64:375-81.

177. Karmazyn B, Bowyer SL, Schmidt KM, Ballinger SH, Buckwalter K, Beam TT, Ying J: US findings of metacarpophalangeal joints in children with idiopathic juvenile arthritis. *Pediatr Radiol* 2007, 37:475-82.

178. Shahin AA, el-Mofty SA, el-Sheikh EA, Hafez HA, Ragab OM: Power Doppler sonography in the evaluation and follow-up of knee involvement in patients with juvenile idiopathic arthritis. *Z Rheumatol* 2001, 60:148-55.

179. Shahin AA, Shaker OG, Kamal N, Hafez HA, Gaber W, Shahin HA: Circulating interleukin-6, soluble interleukin-2 receptors, tumor necrosis factor alpha, and interleukin-10 levels in juvenile chronic arthritis: correlations with soft tissue vascularity assessed by power Doppler sonography. *Rheumatol Int* 2002, 22:84-88.

180. Terslev L, Torp-Pedersen S, Bang N, Koenig MJ, Nielsen MB, Bliddal H: Doppler ultrasound findings in healthy wrists and finger joints before and after use of two different contrast agents. *Ann Rheum Dis* 2005, 64:824-27.

181. Esposito F, Di Serafino M, Sgambati P, Mercogliano F, Tarantino L, Vallone G, Oresta P: Ultrasound contrast media in paediatric patients: is it an off-label use? Regulatory requirements and radiologist's liability. *Radiol Med* 2011.

182. Doria AS, Kiss MH, Lotito AP, Molnar LJ, de Castro CC, Medeiros CC, Cerri GG: Juvenile rheumatoid arthritis of the knee: evaluation with contrast-enhanced color Doppler ultrasound. *Pediatr Radiol* 2001, 31:524-31.

183. Resnick D, Niwayama G: Entheses and enthesopathy. Anatomical, pathological, and radiological correlation. *Radiology* 1983, 146:1-9.

184. Gutierrez M, Filippucci E, De Angelis R, Salaffi F, Filosa G, Ruta S, Bertolazzi C, Grassi W: Subclinical entheseal involvement in patients with psoriasis: an ultrasound study. *Semin Arthritis Rheum* 2011, 40:407-12.

185. Wiell C, Szkudlarek M, Hasselquist M, Moller JM, Vestergaard A, Norregaard J, Terslev L, Ostergaard M: Ultrasonography, magnetic resonance imaging, radiography, and clinical assessment of inflammatory and destructive changes in fingers and toes of patients with psoriatic arthritis. *Arthritis Res Ther* 2007, 9:R119.

186. Kamel M, Eid H, Mansour R: Ultrasound detection of knee patellar enthesitis: a comparison with magnetic resonance imaging. *Ann Rheum Dis* 2004, 63:213-14.

187. Kamel M, Eid H, Mansour R: Ultrasound detection of heel enthesitis: a comparison with magnetic resonance imaging. *J Rheumatol* 2003, 30:774-78.

188. D' Agostino M, Palazzi C, Olivieri I: Entheseal involvement. *Clin Exp Rheumatol* 2009, 27:S50-55.

189. Balint PV, Kane D, Wilson H, McInnes IB, Sturrock RD: Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis* 2002, 61:905-10.

190. Alcalde M, Acebes JC, Cruz M, Gonzalez-Hombrado L, Herrero-Beaumont G, Sanchez-Pernaute O: A sonographic enthesitic index of lower limbs is a valuable tool in the assessment of ankylosing spondylitis. *Ann Rheum Dis* 2007, 66:1015-19.

191. Borman P, Koparal S, Babaoglu S, Bodur H: Ultrasound detection of entheseal insertions in the foot of patients with spondyloarthropathy. *Clin Rheumatol* 2006, 25:373-77.

192. Genc H, Cakit BD, Tuncbilek I, Erdem HR: Ultrasonographic evaluation of tendons and enthesal sites in rheumatoid arthritis: comparison with ankylosing spondylitis and healthy subjects. *Clin Rheumatol* 2005, 24:272-77.

193. Naredo E, Batlle-Gualda E, Garcia-Vivar ML, Garcia-Aparicio AM, Fernandez-Sueiro JL, Fernandez-Prada M, Giner E, Rodriguez-Gomez M, Pina MF, Medina-Luezas JA, et al: Power Doppler Ultrasonography Assessment of Entheses in Spondyloarthropathies: Response to Therapy of Entheseal Abnormalities. *J Rheumatol* 2010.

194. de Miguel E, Cobo T, Munoz-Fernandez S, Naredo E, Uson J, Acebes JC, Andreu JL, Martin-Mola E: Validity of enthesis ultrasound assessment in spondyloarthropathy. *Ann Rheum Dis* 2009, 68:169-74.

195. Kiris A, Kaya A, Ozgocmen S, Kocakoc E: Assessment of enthesitis in ankylosing spondylitis by power Doppler ultrasonography. *Skeletal Radiol* 2006, 35:522-28.

196. D'Agostino MA, Said-Nahal R, Hacquard-Bouder C, Brasseur JL, Dougados M, Breban M: Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. *Arthritis Rheum* 2003, 48:523-33.

197. Cellerini M, Salti S, Trapani S, D'Elia G, Falcini F, Villari N: Correlation between clinical and ultrasound assessment of the knee in children with mono-articular or pauci-articular juvenile rheumatoid arthritis. *Pediatr Radiol* 1999, 29:117-23.

198. Sureda D, Quiroga S, Arnal C, Boronat M, Andreu J, Casas L: Juvenile rheumatoid arthritis of the knee: evaluation with US. *Radiology* 1994, 190:403-06.

199. Magni-Manzoni S, Rossi F, Pistorio A, Temporini F, Viola S, Beluffi G, Martini A, Ravelli A: Prognostic factors for radiographic progression, radiographic damage, and disability in juvenile idiopathic arthritis. *Arthritis Rheum* 2003, 48:3509-17.

200. Ravelli A, Martini A: Early predictors of outcome in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2003, 21:S89-93.

201. Szkudlarek M, Klarlund M, Narvestad E, Court-Payen M, Strandberg C, Jensen KE, Thomsen HS, Ostergaard M: Ultrasonography of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis: a comparison with magnetic resonance imaging, conventional radiography and clinical examination. *Arthritis Res Ther* 2006, 8:R52.

202. Wakefield RJ, Gibbon WW, Conaghan PG, O'Connor P, McGonagle D, Pease C, Green MJ, Veale DJ, Isaacs JD, Emery P: The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum* 2000, 43:2762-70.

203. Hoving JL, Buchbinder R, Hall S, Lawler G, Coombs P, McNealy S, Bird P, Connell D: A comparison of magnetic resonance imaging, sonography, and radiography of the hand in patients with early rheumatoid arthritis. *J Rheumatol* 2004, 31:663-75.

204. Backhaus M, Kamradt T, Sandrock D, Loreck D, Fritz J, Wolf KJ, Raber H, Hamm B, Burmester GR, Bollow M: Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. *Arthritis Rheum* 1999, 42:1232-45.

205. Stitik TP, Kumar A, Kim JH, Tran JJ, Lee C: Pharmacotherapy of Joint and Soft Tissue Injections. In *Injection Procedures: Osteoarthritis and Related Conditions.* Edited by Stitik TP: Springer Science 2011: 33-53

206. Cunnington J, Marshall N, Hide G, Bracewell C, Isaacs J, Platt P, Kane D: A randomized, double-blind, controlled study of ultrasound-guided corticosteroid injection into the joint of patients with inflammatory arthritis. *Arthritis Rheum* 2010, 62:1862-69.

207. Jones A, Regan M, Ledingham J, Pattrick M, Manhire A, Doherty M: Importance of placement of intra-articular steroid injections. *Bmj* 1993, 307:1329-30.

208. Balint PV, Kane D, Sturrock RD: Modern patient management in rheumatology: interventional musculoskeletal ultrasonography. *Osteoarthritis Cartilage* 2001, 9:509-11.

209. Qvistgaard E, Kristoffersen H, Terslev L, Danneskiold-Samsoe B, Torp-Pedersen S, Bliddal H: Guidance by ultrasound of intra-articular injections in the knee and hip joints. *Osteoarthritis Cartilage* 2001, 9:512-17.

210. Grassi W, Lamanna G, Farina A, Cervini C: Synovitis of small joints: sonographic guided diagnostic and therapeutic approach. *Ann Rheum Dis* 1999, 58:595-97.

211. Holm HH, Skjoldbye B: Interventional ultrasound. *Ultrasound Med Biol* 1996, 22:773-89.

212. Christensen RA, Van Sonnenberg E, Casola G, Wittich GR: Interventional ultrasound in the musculoskeletal system. *Radiol Clin North Am* 1988, 26:145-56.

213. Sibbitt WL, Jr., Peisajovich A, Michael AA, Park KS, Sibbitt RR, Band PA, Bankhurst AD: Does sonographic needle guidance affect the clinical outcome of intraarticular injections? *J Rheumatol* 2009, 36:1892-1902.

214. d'Agostino MA, Ayral X, Baron G, Ravaud P, Breban M, Dougados M: Impact of ultrasound imaging on local corticosteroid injections of symptomatic ankle, hind-, and mid-foot in chronic inflammatory diseases. *Arthritis Rheum* 2005, 53:284-92.

215. Remedios D, Martin K, Kaplan G, Mitchell R, Woo P, Rooney M: Juvenile chronic arthritis: diagnosis and management of tibio-talar and sub-talar disease. *Br J Rheumatol* 1997, 36:1214-17.

216. Marti P, Molinari L, Bolt IB, Seger R, Saurenmann RK: Factors influencing the efficacy of intra-articular steroid injections in patients with juvenile idiopathic arthritis. *Eur J Pediatr* 2008, 167:425-30.

217. Job-Deslandre C, Menkes CJ: Complications of intra-articular injections of triamcinolone hexacetonide in chronic arthritis in children. *Clin Exp Rheumatol* 1990, 8:413-16.

218. Beukelman T, Arabshahi B, Cahill AM, Kaye RD, Cron RQ: Benefit of intraarticular corticosteroid injection under fluoroscopic guidance for subtalar arthritis in juvenile idiopathic arthritis. *J Rheumatol* 2006, 33:2330-36.

219. Kakati P, Sodhi KS, Sandhu MS, Singh S, Katariya S, Khandelwal N: Clinical and ultrasound assessment of the knee in children with juvenile rheumatoid arthritis. *Indian J Pediatr* 2007, 74:831-36.

220. Shanmugavel C, Sodhi KS, Sandhu MS, Sidhu R, Singh S, Katariya S, Khandelwal N: Role of Power Doppler sonography in evaluation of therapeutic response of the knee in juvenile rheumatoid arthritis. *Rheumatol Int* 2008, 28:573-78.

221. Scire CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R: Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. *Rheumatology (Oxford)* 2009, 48:1092-97.

222. Habib GS, Saliba W, Nashashibi M: Local effects of intra-articular corticosteroids. *Clin Rheumatol* 2010, 29:347-56.

223. De Zordo T, Mur E, Bellmann-Weiler R, Sailer-Hock M, Chhem R, Feuchtner GM, Jaschke W, Klauser AS: US guided injections in arthritis. *Eur J Radiol* 2009, 71:197-203.

224. Epis O, Iagnocco A, Meenagh G, Riente L, Delle Sedie A, Filippucci E, Scire CA, Valesini G, Grassi W, Bombardieri S, Montecucco C: Ultrasound imaging for the rheumatologist. XVI. Ultrasound-guided procedures. *Clin Exp Rheumatol* 2008, 26:515-18.

225. Koski JM: Ultrasound guided injections in rheumatology. *J Rheumatol* 2000, 27:2131-38.

226. Maillefert JF, Dardel P, Cherasse A, Mistrih R, Krause D, Tavernier C: Magnetic resonance imaging in the assessment of synovial inflammation of the hindfoot in patients with rheumatoid arthritis and other polyarthritis. *Eur J Radiol* 2003, 47:1-5.

227. Cahill AM, Cho SS, Baskin KM, Beukelman T, Cron RQ, Kaye RD, Towbin RB: Benefit of fluoroscopically guided intraarticular, long-acting corticosteroid injection for subtalar arthritis in juvenile idiopathic arthritis. *Pediatr Radiol* 2007, 37:544-48.

228. Boesen M, Jensen KE, Torp-Pedersen S, Cimmino MA, Danneskiold-Samsoe B, Bliddal H: Intra-articular distribution pattern after ultrasound-guided injections in wrist joints of patients with rheumatoid arthritis. *Eur J Radiol* 2009, 69:331-38.

229. Hammer H, Kvien T: Ultrasonography shows significant improvement in wrist and ankle tenosynovitis in rheumatoid arthritis patients treated with adalimumab. *Scand J Rheumatol* 2011, 40:178-82.

230. Ziswiler HR, Aeberli D, Villiger PM, Moller B: High-resolution ultrasound confirms reduced synovial hyperplasia following rituximab treatment in rheumatoid arthritis. *Rheumatology (Oxford)* 2009, 48:939-43.

231. Terslev L, Torp-Pedersen S, Qvistgaard E, Danneskiold-Samsoe B, Bliddal H: Estimation of inflammation by Doppler ultrasound: quantitative changes after intra-articular treatment in rheumatoid arthritis. *Ann Rheum Dis* 2003, 62:1049-53.

232. Filippucci E, Farina A, Carotti M, Salaffi F, Grassi W: Grey scale and power Doppler sonographic changes induced by intra-articular steroid injection treatment. *Ann Rheum Dis* 2004, 63:740-43.

233. McQueen F, Ostergaard M, Peterfy C, Lassere M, Ejbjerg B, Bird P, O'Connor P, Genant H, Shnier R, Emery P, et al: Pitfalls in scoring MR images of rheumatoid arthritis wrist and metacarpophalangeal joints. *Ann Rheum Dis* 2005, 64 Suppl 1:i48-55.

234. Brown AK, O'Connor P J, Roberts TE, Wakefield RJ, Karim Z, Emery P: Recommendations for musculoskeletal ultrasonography by rheumatologists: setting global standards for best practice by expert consensus. *Arthritis Rheum* 2005, 53:83-92.

235. Schirmer M, Duftner C, Schmidt WA, Dejaco C: Ultrasonography in inflammatory rheumatic disease: an overview. *Nat Rev Rheumatol* 2011, 7:479-88.

236. Gare BA, Fasth A: The natural history of juvenile chronic arthritis: a population based cohort study. I. Onset and disease process. *J Rheumatol* 1995, 22:295-307.

ISBN 978-91-628-8367-6
Printed by Media-Tryck, Lund