Ultrasound of hand osteoarthritis

Validity, reliability and predictive value of ultrasonography in patients with hand osteoarthritis

Thesis by
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Our knowledge of the disease is incomplete, perhaps because it is one of those dull commonplace disorders that are hard to study with enthusiasm, but new knowledge of osteoarthrosis must be gained if the later years of our lengthening lives are not to be plagued by increasing pain and disability.

– J. H. Kellgren, 1961
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<td>2D</td>
<td>Two-Dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three-Dimensional</td>
</tr>
<tr>
<td>A-mode</td>
<td>Amplitude Modulation</td>
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<tr>
<td>ACR</td>
<td>American College Of Rheumatology</td>
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<tr>
<td>AIMS-2</td>
<td>Arthritis Impact Measurement Scales-2</td>
</tr>
<tr>
<td>AUSCAN</td>
<td>Australian Canadian Hand Index</td>
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<tr>
<td>B-mode</td>
<td>Brightness Modulation</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CI</td>
<td>Confidence Intervals</td>
</tr>
<tr>
<td>CMC</td>
<td>Carpometacarpal</td>
</tr>
<tr>
<td>CPP</td>
<td>Calcium Pyrophosphate Dehydrate</td>
</tr>
<tr>
<td>CR</td>
<td>Conventional Radiography</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>DECT</td>
<td>Dual-Energy CT</td>
</tr>
<tr>
<td>dGEMRIC</td>
<td>Delayed Gadolinium-Enhanced MRI of Cartilage</td>
</tr>
<tr>
<td>DIP</td>
<td>Distal Interphalangeal</td>
</tr>
<tr>
<td>DMOADs</td>
<td>Disease-Modifying Osteoarthritis Drugs</td>
</tr>
<tr>
<td>ESCISIT</td>
<td>EULAR Standing Committee For International Clinical Studies Including Therapeutics</td>
</tr>
<tr>
<td>EULAR</td>
<td>European League Of Rheumatology</td>
</tr>
<tr>
<td>FIHOA</td>
<td>Functional Index for Hand Osteoarthritis</td>
</tr>
<tr>
<td>FOI</td>
<td>Fluorescence Optical Imaging</td>
</tr>
<tr>
<td>GEE</td>
<td>Generalized Estimating Equation</td>
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<tr>
<td>GUSS</td>
<td>Ghent University Scoring System</td>
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<tr>
<td>HOAMRIS</td>
<td>Hand Osteoarthritis MRI Scoring System</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IA</td>
<td>Intra-Articular</td>
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<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<td>IP</td>
<td>Interphalangeal</td>
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<tr>
<td>IQR</td>
<td>Interquartile Ranges</td>
</tr>
<tr>
<td>JSN</td>
<td>Joint Space Narrowing</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
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<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>KL</td>
<td>Kellgren-Lawrence</td>
</tr>
<tr>
<td>MCP</td>
<td>Metacarpophalangeal</td>
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<tr>
<td>M-mode</td>
<td>Motion Modulation</td>
</tr>
<tr>
<td>MOST</td>
<td>Multicenter Osteoarthritis Study</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MSK</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>MTP</td>
<td>Metatarsophalangeal</td>
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<tr>
<td>NSAIDs</td>
<td>Nonsteroidal Anti-Inflammatory Drugs</td>
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<tr>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>OAI</td>
<td>Osteoarthritis Initiative</td>
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<tr>
<td>OARSI</td>
<td>Osteoarthritis Research Society International</td>
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<tr>
<td>OMERACT</td>
<td>Outcome Measures In Rheumatoid Arthritis Clinical Trials (Outcome Measures In Rheumatology)</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>OST</td>
<td>Optical Spectral Transmission</td>
</tr>
<tr>
<td>PA</td>
<td>Posteroanterior</td>
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<tr>
<td>PACS</td>
<td>Picture Archiving And Communication System</td>
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<tr>
<td>PCA</td>
<td>Percentage Close Agreement</td>
</tr>
<tr>
<td>PD</td>
<td>Proton Density</td>
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<tr>
<td>PEA</td>
<td>Percentage Exact Agreement</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>PIP</td>
<td>Proximal Interphalangeal</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td>RF</td>
<td>Radio Frequency</td>
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<tr>
<td>SD</td>
<td>Standard Deviations</td>
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<td>SF-36</td>
<td>Short Form-36</td>
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<tr>
<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
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<tr>
<td>SPSS</td>
<td>Statistical Package For The Social Sciences</td>
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<tr>
<td>STT</td>
<td>Scaphotrapeziotrapezoid</td>
</tr>
<tr>
<td>STIR</td>
<td>Short Tau Inversion Recovery</td>
</tr>
<tr>
<td>TE</td>
<td>Echo Time</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition Time</td>
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List of papers


IV. Mathiessen A, Slatkowsky-Christensen B, Kvien TK, Haugen IK, Hammer HB. Ultrasound-detected osteophytes predict the development of radiographic and clinical features of hand osteoarthritis in the same finger joints 5 years later. *RMD Open* 2017; [Epub ahead of print]
1. Introduction

“The history of osteoarthrosis is long, for degenerative joint changes can be seen in fossil skeletons of prehistoric animals and in the joints of ancient Egyptian mummies. Despite this long history, our knowledge of the disease is incomplete, perhaps because it is one of those dull commonplace disorders that are hard to study with enthusiasm, but new knowledge of osteoarthrosis must be gained if the later years of our lengthening lives are not to be plagued by increasing pain and disability.”

— These are the first words of Kellgren in his epidemiological study of osteoarthritis (OA) in 1961 [1]. More than 50 years later, OA represents a massive and increasing problem in our aging society, associated with pain, stiffness and functional disabilities that have substantial effects on the quality of life of millions of people globally [2].

During the past decades, the concepts of OA have been forever changed with the application of magnetic resonance imaging (MRI) and ultrasonography. While traditionally considered a non-inflammatory “wear-and-tear” disorder of the cartilage, we now acknowledge OA as a complex and multi-tissue disorder of the whole joint, involving cartilage, subchondral bone, ligaments, menisci (if present) and (increasingly recognized) inflammation of the synovium [3]. Despite this new and detailed understanding of the pathology of OA, there are still no effective disease-modifying OA drugs (DMOADs) available, and the relevant pathological processes or phenotypes to target have not been proven. Difficulties demonstrating treatment effects in clinical trials may in part be due to limitations in the way we measure and quantify OA progression, as radiographic joint space narrowing (JSN) is the current regulatory standard for treatment response [4]. Multiple factors may explain disease progression, and it is also likely that specific phenotypes should be targeted differently. With modern imaging techniques, short-term changes of novel outcome measures may better reflect long-term changes in patient outcomes.

Also, with advances in technology and wide availability, there is a trend among physicians in various specialties to integrate ultrasonography in their clinical assessments. There is, however, a predominant focus on MRI and knee OA in the literature, and limited research has been done on the application of diagnostic ultrasound of hand OA.
With this thesis, the aim is to demonstrate the potentials (and limitations) of ultrasonography as a diagnostic tool in hand OA and how sonographic biomarkers can be used to detect early OA and predict disease progression.
2. Background

2.1 Ultrasound

Deflected echoed of inaudible high-frequency sound waves traveling through tissues generate ultrasound images. The history and physics of ultrasound is described in this section, followed by technical aspects and sources of errors (i.e., artefacts) of medical ultrasonography. The application of ultrasonography and other imaging modalities in (hand) OA is further discussed in chapter 2.3.

2.1.1 History of ultrasound: from bats and boats to bedside technology

Ultrasound technology is based on the science of sound waves, and the history of ultrasound goes back hundreds of years, beginning in the late 1700s with the studies of bat aviation. Biologist and physiologist Lazzaro Spallanzani analyzed the basic mechanisms of spatial orientation of bats, and wondered how they could fly and catch insects at night. First, he blindfolded them and they still maneuvered well. Then he sealed their ears and found that they bumped into obstacles. He concluded that hearing was their primary mode of navigation. However, he failed to recognize the possibility that insect preys might be perceived by reflected sound rather than by their own buzzing [5]. This was later proven just before World War II by Galambos and Griffen, who recorded high frequency sound waves emitted by bats with a sonic detector [6].

Several significant theoretical discoveries were then made during the 19th century. In 1801, Thomas Young described ‘phase shifting’ in relation to light waves, in which light from several sources can combine and become stronger or cancel each other out depending on the shift of the light [7]. His principles are used today in ultrasound phased array systems to control interference patterns and in the production of three-dimensional (3D) images. In Switzerland in 1826, Colladon and Sturm discovered that sound travels faster under water than in air [8]. They submerged a church bell and measured the speed of sound with an underwater rear trumpet in comparison to the light of ignited gunpowder above the surface. With 16 kilometers apart, they calculated the speed of sound underwater from a submerged church bell to be 1435 m/sec, and the under-water church bell is in principle an early ultrasound transducer. In 1842, Christian Andreas Doppler, an Austrian mathematician and physicist, suggested that the frequency of a sound wave depends on the speed of the source.
This discovery would later be known as the ‘Doppler Effect’. In 1877, lord Rayleigh (John W. Strutt) became the first to describe sound as mechanical equations in his great work ‘The Theory of Sound’, where he studies and explains fundamental principles in acoustics, including anatomization, acoustic surface waves, acoustic pressure, molecular relaxation and nonlinear effects [9].

One of the most important discoveries in ultrasound physics came in 1881, when the brothers Pierre and Jacques Curie discovered the piezoelectric effect, in which mechanical pressure on various crystals could produce an electric charge [10]. The reverse of this effect is used in modern ultrasound transducers to generate ultrasonic waves, and conversely transform sound waves into a measurable voltage (fig. 1).

**Figure 1:** Simplified sketch of piezoelectricity. Without pressure, the electrical field within the crystal is neutral. With pressure, the crystal converts mechanical energy into electrical energy. The effect may be reversed, as voltage causes the crystal to change shape. Both principles are applied in ultrasound transducers.

*The first ultrasound machine – 100 years ago*

Following the loss of the Royal Mail Ship “Titanic” in 1912, the Canadian inventor Reginald Fessenden built the very first working sonar (sound, navigation and ranging) collision avoidance system in 1914, capable of creating underwater low-frequency sounds and picking up their echoes [11]. It could detect icebergs up to 3.2 km away, but because it generated continuous oscillations rather than intermittent pulses, it tended to create its own interference. In 1917, Paul Langevin, who was a student of Pierre Curie, combined the sonar technique with piezoelectricity and developed the first ultrasound transducer, applied for submarine detection [11]. His ‘hydrophone’ emitted intense pulses of high-frequency sound from thin quartz crystals, and the amount of time for a signal to travel to an enemy submarine and echo back was used to calculate the distance under water. Langevin is often called the ‘father’ of ultrasound, and his technology was refined and used to protect North Atlantic convoys during World War II.
Ultrasound introduced in medicine

In the 1920s to 1940s, ultrasound became a ‘cure-it-all’ treatment and was used by European soccer teams as a type of physical therapy, to sterilize vaccines, to relieve arthritic pain, eczema and gastric ulcers, and even in cancer therapy in combination with radiation therapy. The strong emphasis on therapy declined in the 1950s and was replaced by the potential of ultrasound as an imaging modality.

The application of ultrasonographic imaging in medicine began during and shortly after the Second World War. The Austrian neurologist/psychiatrist Karl Dussik was the first physician to apply ultrasound for medical imaging, as he attempted to depict brain ventricle changes secondary to tumor growth in 1942 [12]. With the patient’s head partly submerged under water, he placed transducers on each side of their head and recorded changes in sound waves photographically on heat-sensitive paper, referred to as a ‘ventriculogram’. This through-transmission technique was hampered by artifacts secondary to attenuation and normal reflections of the skull, and was quickly replaced by more advanced pulse-echo transducers capable of producing sound waves and receiving the reflected echo. The pulse-echo method is used in A-, B-, and M-mode ultrasound imaging.

In 1948, George D. Ludwig developed A-mode (short for Amplitude modulation) ultrasound to detect gallstones [13]. A-mode ultrasound represents a one-dimensional examination capable of measuring the depth and dimension of an organ. Amplitude of the echo is plotted on the y-axis (tissue density) and echo travel-time on the x-axis (depth). In most areas it has been replaced by B-mode, but is still used in ophthalmology to assess orbital length and intraocular masses.

B-mode (short for Brightness modulation) ultrasound (or grey-scale ultrasound) was developed shortly after, in which a linear array of transducers simultaneously scans a plane and transmits the echo signals into a two-dimensional (2D) image of a cross-section. Douglas Howry and Joseph Holmes were two of the pioneers of B-mode equipment, including the 2D B-mode linear compound scanner. Also, John Reid and John Wild together invented a handheld B-mode device to detect breast tumors [13]. In Sweden, Inge Edler and Hellmuth Hertz performed the first successful echocardiogram in 1953, using M-mode (motion modulation) ultrasound that displays a one-dimensional image of echo amplitude over time [13]. In 1966, Don Baker, Dennis Watkins, and John Reid designed pulsed Doppler ultrasound technology to examine blood flow in the heart [13].
In the 1970s many advances including the continuous wave Doppler, spectral wave Doppler and color Doppler ultrasound instruments were found. In the late 1980s, 3D ultrasound was introduced and in the 1990s 4D ultrasound that the public could understand was introduced, as well as ultrasound-guided biopsies (endoscopic ultrasounds).

The earliest report of ultrasonography of the musculoskeletal (MSK) system was published in 1972 where the diagnostic potential of ultrasound was used to differentiate Baker’s cysts from thrombophlebitis [14]. Few years later, ultrasound was used to demonstrate synovitis and to evaluate the results of yttrium-90 injection therapy for rheumatoid arthritis (RA) of the knee [15]. The applications of ultrasound to MSK conditions have continued to expand, ranging from rheumatology to sports medicine.

### Key points

- Theoretical discoveries during the 1800s, especially the mathematical understanding of sound and the piezoelectric effect, set the stage for the first ultrasound machine in 1917, intended for submarine detection.
- The first ultrasonographic machine for medical imaging was developed in 1942 in an attempt to diagnose brain tumors.

#### 2.1.2 Physics of ultrasound

Sound is a vibration that travels through a medium such as air, water and solids as longitudinal mechanical waves of compression and decompression (fig. 2). A sound source creates pulsations in the surrounding medium and can exist only within a mass media, hence does not transmit through vacuum.

The mechanical waves are often described as sinusoidal plane waves with generic properties of amplitude, frequency, speed and direction. Amplitude is directly related to the acoustic energy, intensity or loudness of a sound and is often expressed in decibel. A wavelength corresponds to the distance between two compressions or rarefactions, expressed as lambda ($\lambda$), and the number of wavelengths oscillating during one second corresponds to a given
frequency (f), expressed in Hertz (Hz). The velocity (c) of the sound wave is thus expressed as: \( c = f \times \lambda \).

Ultrasound has to do with higher frequencies of sound (fig. 3). The human hearing ranges from 16 Hz to 20 kHz (due to limitations of the middle ear). Sound above 20 kHz is ultrasound and below 20 Hz is infrasound. Animals can emit and sense a variety of frequencies, often in the ultrasonic range. The lower ultrasonic range is applied in sonochemistry (20 to 100 kHz), ultrasonic cleaning of instruments (20 to 400 kHz), ultrasonic testing of flaws in materials (50 kHz to 10 MHz), ultrasonic welding of plastics (15 to 40 kHz), and sonar systems (10 to 50 kHz) [16].

**Figure 3:** Range of human hearing and ultrasound.

In the medical field, ultrasonography (or diagnostic sonography) applies frequencies in the higher ultrasonic range of 2 to 20 MHz, whereas frequencies up to 4 GHz are used in acoustic microscopes. In principle, ultrasound cannot detect objects that are smaller than its wavelength. Thus, higher frequencies produce better resolution. However, short wavelengths are more readily absorbed in the tissue (i.e., have a larger attenuation coefficient, see below) and are therefore not as penetrating. For these reasons, superficial structures such as finger joints can be visualized with higher frequencies (up to 18 MHz), whereas areas deeper in the body (e.g., abdominal imaging) requires lower frequencies (3.5 to 5 MHz) [17].

**Key points**
- Ultrasound is sound waves with frequencies above human audible range (>20 kHz).
- Medical ultrasound (also known as diagnostic sonography or ultrasonography) applies frequencies in the higher ultrasonic range (2 to 20 MHz).
2.1.3 From sound to image

The creation of images with a medical ultrasound scanner requires three steps: Producing a sound wave, receiving echoes, and interpreting those echoes. An ultrasound transducer achieves the first two steps. Alternating voltage applied across piezoelectric crystals makes them vibrate at a high speed that creates ultrasound. The transducer emits short pulses of ultrasound waves into the tissue. Whenever a sound wave encounters a medium with different density (acoustic impedance), a fraction of the sound is reflected as an echo, with reverse effect on the piezoelectric crystals (creates a current). The depth of a given structures is calculated from the time between pulse emission and the echo return, and the amplitude is encoded as a gray-scale value. Collection of the echoes and echo amplitudes over time provides information about the tissues along the path of travel, and with hundreds of repetitions, a grey-scale image is formed [17].

Interactions of ultrasound with matter

As the ultrasound wave travels through a medium, it will constantly be subjected to interactions with the tissue, determined by the acoustic characteristics of the specific tissue. Each tissue has its own acoustic impedance \( Z \), or resistance, for which an ultrasound wave encounters and is the product of the density \( p \) and propagation speed \( c \). When ultrasound passes an interface between two media, it will be reflected, and the difference in acoustic impedance will determine the amount of reflected echo. When adjacent tissues have similar acoustic impedance, only minor reflections occur (and most of the ultrasound will carry on through the second medium), whereas larger difference result in more reflection at the interface [17]. Strong echoes produce white pixels, whereas weak echoes produce grey pixels, and anatomic structures that do not reflect ultrasound appear as black pixels – combined they produce a complete image of the area scanned. The gain control adjusts the amplification of the returning acoustic signals and is used to optimize the ultrasound image.

Sound energy is attenuated, or weakened, as it passes through tissue. These interactions include reflection, refraction, scattering, and absorption (fig. 4) [17, 18].

Reflection – occur when sound waves passes an interphase at an angle of 90°. Specular reflection occurs when the sound wave meets a distinct surface, larger than the ultrasound wavelength. The greater the acoustic impedance between two tissue surfaces, the greater the reflection and the brighter the echo will appear on ultrasound.
**Refraction** – when ultrasound passes an interface at an angle other than 90°, it will bend from its original direction. The echo will return at an angle equal to the incoming angle, and the transmitted beam will deviate from its straight line.

**Scattering** – for objects that are large compared to the ultrasound wavelength, reflection and refraction occur, whereas smaller objects will scatter the energy in many directions. Different organs have characteristic structural compositions that give rise to defined scatter “signatures” (or echo texture) within the tissue.

**Absorption** – tissue absorption, together with scattering, contributes most to the attenuation of an ultrasound wave in tissues. Absorbed acoustic energy is converted to heat in the tissue. In soft tissue, sound intensity decreases exponentially with depth and is dependent on the frequency (higher frequency travels shorter).

![Figure 4: Ultrasound interactions with tissue, showing scattering, reflection, refraction and absorption. These processes divert energy from the main (incident) beam, resulting in attenuation, or weakening, of the signal.](image)

**Echogenicity**

The following terms describe sonographic appearances of structures (table 1 and fig. 5):

- **Echogenic** – a bright white structure against a dark background.
- **Reflective** – synonymous with an echogenic structure.
- **Isoechoic** – a shade of gray with the same echogenicity as the surrounding tissue.
- **Hyperechoic** – bright white or a shade of gray that is brighter than the surroundings.
- **Hypoechoic** – a shade of gray that is dark or less bright than the surrounding tissue.
- **Anechoic** – an absence of echoes, hence blackness.
Table 1: Typical appearance of normal musculoskeletal tissues (numbers refer to fig. 5)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Echogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Echogenic, highly reflective (3)</td>
</tr>
<tr>
<td>Fat</td>
<td>Hyperechoic with hyperechoic septae, or isoechoic (1, 4)</td>
</tr>
<tr>
<td>Bone</td>
<td>Hyperechoic due to large difference in acoustic impedance between soft tissue and bone (2); high frequency ultrasound does not penetrate bone and therefore the image is black below the bone surface (8)</td>
</tr>
<tr>
<td>Muscle</td>
<td>Hyperechoic with hyperechoic septae; fibrillar pattern in longitudinal view, patchy pattern in cross section (5)</td>
</tr>
<tr>
<td>Tendon</td>
<td>Typically hyperechoic, but may appear hypoechoic with oblique scan</td>
</tr>
<tr>
<td>Fluid</td>
<td>Blood, effusion and cysts are generally anechoic (6)</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Anechoic with hyperechoic surface when viewed perpendicular (7)</td>
</tr>
<tr>
<td>Nerve</td>
<td>Similar to that of tendons</td>
</tr>
</tbody>
</table>

Figure 5: Anterior ultrasound image of an elbow. Echogenicity explained in table 1.

Key points

- Ultrasound wave loses its energy as it propagates through the tissue (attenuation), either by reflection, refraction, scattering, or absorption.
- A reflected echo is created at the interface between two tissues, with amplitude depending on the difference in density and speed properties of the tissues.
2.1.4 Ultrasound artifacts

Image artifacts are common in clinical ultrasonography and may be a source of wrong interpretations. Artifacts may cause structures to be depicted in different sizes, shapes or localizations from reality or not be presented at all, or visualize structures that are anatomically not there. With basic knowledge of the physical properties of the ultrasound beam and how sound propagates through matter (previous chapter), one can recognize and understand how these artifacts arise. Some artifacts are also clinically useful. Important and common artifacts are listed below.

Anisotropy – or angular dependence, describes the change in echogenicity of a structure that is visualized obliquely. When the insonating sound beam hits perpendicularly on a structure, a majority of the echo is reflected back to the probe. A deviation from this angle results in reflections away from the transducer and the structure becomes more hypoechoic. Anisotropy is frequently observed in the scanning of tendons, ligaments and nerves, and may falsely lead to diagnoses of pathologies in normal tissues (such as tendinitis, tendinosis or tears; fig. 6). It is therefore important to tilt the probe from side to side or apply asymmetrical pressure on the transducer to optimize visualization of these structures [19].

Figure 6: Longitudinal view of the supraspinatus tendon. (a) Artifactual hypoechogenicity (anisotropy; curved arrow) where the distal tendon fibers curve downward to the greater tuberosity, oblique to the sound beam. With the transducer repositioned (b), the distal tendon fibers appear hyperechoic (open arrow) when they are perpendicular to the sound beam.

Acoustic shadowing – sound waves are completely reflected or absorbed by bone or calcifications and the area below will appear anechoic.
Acoustic enhancement – anechoic or hypoechoic lesions, such as effusion, cause reduced attenuation and the area below the lesion will appear brighter.

Speed-displacement artifact – the ultrasound machine calculates transmission time based on an average sound speed in soft tissue of 1540 m/sec, whereas the actual speed of sound varies between tissues. Cartilage and fat are typical outliers with reported speeds of 1696 m/sec and 1450 m/sec, respectively. Due to higher sound speed in cartilage, the pulse will reach the cartilage-bone interface earlier compared to the average sound speed, and also return too fast, and therefore depict cartilage thinner than it really is. It has been proposed to multiply the sonographic cartilage thickness with 1.1 (=1696/1540) when comparing an ultrasound measure with those obtained anatomically or by other imaging modalities [20].

Reverberation artifact – caused by the sound bouncing back and forth between highly reflective surfaces before returning back to the transducer. The first echo will be displayed in the proper location, whereas the subsequent echoes will take longer to return to the transducer and erroneously depicted at an increased distance from the transducer (“equidistantly spaced linear reflections”; fig. 7a). If the two reflective interfaces are close (e.g., cholesterol crystals), the echoes are closely spaced and later echoes will decrease in amplitude secondary to attenuation (i.e., loose its energy), causing a triangular and tapered shaped echogenic line below the interphases (“comet-tail artifact”; fig. 7b). In cases of fluid trapped between multiple gas bubbles (e.g., pneumobilia, portal venous gas, gas in abscesses), the ultrasound will cause the trapped liquid to resonate, creating a continuous sound wave that is transmitted back to the receiver. This phenomenon is shown as a line or series of bands below the gas, called “ring-down artifact” (fig. 7c) [21].

Figure 7: Reverberation artifacts. (a) Reverberation artifact from a needle. (b) Comet-tail artifact in the liver (asterix). (c) Ring-down artifact in the duodenum (arrow).
Mirror artifact – or ghosting, is created by the false assumption that an echo returns to the transducer after a single reflection. Instead, sound reflects off a highly reflective surface, e.g. bone, and the returning echoes encounter the “back side” of a structure and are then reflected back to the interface before being echoed to the transducer. This causes a duplicated structure equidistant from, but deep to, the reflective surface, and may be found both in grey scale and Doppler ultrasound (fig. 8) [21].

Refraction artifact – can occur when an incident ultrasound wave encounters an interphase at a non-perpendicular angle. Depending on the angle and difference in propagation speed between the tissues, the transmitted wave can change direction and structures below the interphase may not be positioned correctly. This artifact is commonly seen at interfaces of the abdomen, but also when depicting large vessels, nerves and tendons transversely (fig. 9). Due to this artifact, it has also been shown that an insonating angle of 30° obliquely on cartilage causes a 6% over-estimation of the cartilage thickness [20, 22].

**Figure 8**: Mirror artifacts of power Doppler ultrasound. Vessels (arrows) close to the highly reflected interface (bony cortex) are duplicated below the interface (arrow heads).

**Figure 9**: Edge shadow from the Achilles tendon. Sound waves are refracted, or bent, when encountering the tendon at an oblique angle, causing loss of energy and a hypoechoic shadow (arrows).

**Key points**

- Artifacts may arise from unavoidable errors related to intrinsic properties of the ultrasound beam, presence of multiple echoes, velocity errors or attenuation errors.
- Recognition of these artifacts is important for image quality and interpretation, and may also give clues to tissue composition and aid in diagnosis.
2.2 Hand osteoarthritis (OA)

2.2.1 Definition

The name osteoarthritis comes from Greek meaning bone (osteon), joint (arthron) and inflammation (itis). OARSI have recently defined OA as “a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness.” [23].

OA can appear as localized or generalized. Single- or multiple-joint OA has a predilection for the knees, hips, spine and hands (often bilateral), but can also affect the elbow, wrist, shoulder, ankle and feet (more often unilateral) [24]. Hand OA will target characteristic sites: thumb base, including the carpometacarpal (CMC)-1 and scaphotrapeziotrapezoid (STT) joints, as well as distal interphalangeal (DIP) joints and proximal interphalangeal (PIP) joints [25-27]. Generalized OA implies a polyarticular subset of OA, often affecting the DIP joints, thumb bases, first metatarsophalangeal (MTP) joints, lower spine, knees and hips [28]. Despite no universal definition of generalized OA, the current advice from the American College of Rheumatology (ACR) and the European League of Rheumatology (EULAR) suggests that generalized OA is present if there is OA at the spinal or hand joints, respectively, and in at least two other joint regions [26, 29].

Classification criteria

The ACR criteria for classification of hand OA is the most widely used classification system [30], in which radiography was considered of less value than clinical examination (fig. 10). They were mainly developed to differentiate OA and RA, and thus involve absence of swollen joints in the MCP joints that is common for RA but not OA. It is acknowledged that the current classification criteria for hand OA are not sensitive to classify early OA and do not differ between thumb base OA and interphalangeal (IP) OA. They also criticized for excluding patients with transient symptoms [31]. New hand OA criteria funded by EULAR are being elaborated, with separate criteria for thumb base OA and IP OA, as well as separate clinical and radiographic criteria.
Classification criteria are in general designed to select patients who are appropriate to be included in clinical trials, with emphasis on a few essential numbers of items (high specificity). Diagnostic criteria, on the other hand, are broad in order to reflect the heterogeneity of a disease (high sensitivity) [32]. The ACR hand OA classification criteria are not designed – and should not be used – to replace the clinical diagnosis of OA [33].

**Figure 10:** American College of Rheumatology criteria for hand osteoarthritis [30]; DIP, distal interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal. Reproduced with permissions from John Wiley and Sons [30] and Nature Publishing Group [34].

**Hand pain, aching or stiffness for most days of the prior month**

+ **Three of the following four criteria:**
  1. Hard tissue enlargement of 2 or more of 10 selected joints*
  2. Hard tissue enlargement of 2 or more DIP joints
  3. Fewer than 3 swollen MCP joints
  4. Deformity of at least 1 of 10 selected joints*

* The 10 selected joints are the 2nd and 3rd DIP, 2nd and 3rd PIP and the 1st carpometacarpal joints of both hands.

**Key points**
- Osteoarthritis is a degenerative joint disease caused by gradual loss of articular cartilage.
- Hand osteoarthritis will typically target the thumb base and interphalangeal joints.
2.2.2 Clinical features and diagnosis

Clinical presentation

Although the majority of the literature focuses on knee or hip OA, symptomatic hand OA may lead to significant functional impairment, mainly related to weaker grip strength and activities involving pincer grip or power grip [35, 36]. Symptoms range from mild to severe, and in hospital-based cohorts, hand OA patients demonstrate similar symptom severity with regards to pain and physical disability as patients with RA [37].

Pain is the most important symptom of hand OA that causes the patients to seek medical advice. The pain is often related to motion or activities, whereas others report a constant and dull or aching pain with unpredictable and intermittent breakthroughs [36]. The entity of pain is complex, involving nociceptive and neuropathic mechanisms in the peripheral and central nervous system [38]. Other factors influencing the subjective experience of pain includes obesity, hereditary factors, expectations to analgesics, coping strategies, pain catastrophizing, and sociocultural variances among others [39]. Pain characteristics may change over time, and the intensity may decrease whereas function loss and stiffness increases, which may reflect more inflammation at the earlier stages [40, 41].

Patients with hand OA also experience stiffness, particularly in the morning or evening or after inactivity [42]. The stiffness generally resolves within minutes (as opposed to prolonged stiffness cased by RA). Symptomatic OA is also associated with depression and sleep disturbance that further contribute to disabilities [42, 43].

Diagnosis

Hand OA is a clinical diagnosis that can be identified without the use of imaging or laboratory investigations in the presence of characteristic medical history (i.e., persistent use-related joint pain in one or multiple typical OA joints, age ≥45 years and morning stiffness ≤30 minutes) and physical examination. It may however require additional investigations to exclude differential diagnosis (especially avascular osteonecrosis, Paget’s disease, complex regional pain syndrome, systemic inflammatory joint diseases and stress fractures) and assess the degree of structural severity. Synovial fluid should be assessed if other arthropathies or septic arthritis is suspected. In patients with OA, synovial fluid is sterile, without crystals, and typically a white-cell count of less than 1500 cells/μL [42]. The EULAR Standing Committee for International Clinical Studies Including Therapeutics
(ESCISIT) has developed evidence-based recommendations for the diagnosis of hand OA (table 2) [26].

Clinical examination is mandatory to confirm and characterize joint involvement. Presentation will include tenderness upon palpation (most pronounced over the joint lines) or movement, crepitus (sensation of crunching or crackling felt on passive or active movement of a joint), joint enlargement (due to joint effusion, bony swelling, or both), malalignment and restricted passive movement [26, 42]. Heberden’s nodes at the DIP joints and Bouchard’s nodes at the PIP joints are firm swellings associated (but not synonymous) with underlying radiographic changes of OA.

**Key points**

- Joint pain and stiffness are the main symptoms of hand OA.
- Hand OA is a clinical diagnosis, but imaging and laboratory tests may aid in differential diagnostics and to assess the degree of structural severity.
Table 2: The European League Against Rheumatism recommendations for the diagnosis of hand OA according to 1) risk factors, 2–5) clinical features, 6–7) subsets, 8) differential diagnosis, and 9–10) supplementary tests [26].

<table>
<thead>
<tr>
<th>Proposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Risk factors for hand OA include female sex, increasing age over 40, menopausal status, family history, obesity, higher bone density, greater forearm muscle strength, joint laxity, prior hand injury and occupation or recreation-related usage.</td>
</tr>
<tr>
<td>2 Typical symptoms of hand OA are pain on usage and only mild morning or inactivity stiffness affecting just one or a few joints at any one time; symptoms are often intermittent and target characteristic sites (DIP, PIP, thumb base, index and middle MCP joints). With such typical features, a confident clinical diagnosis can be made in adults aged over 40.</td>
</tr>
<tr>
<td>3 Clinical hallmarks of hand OA are Heberden and Bouchard nodes and/or bony enlargement with or without deformity (e.g., lateral deviation of IP joints, subluxation and adduction of thumb base) affecting characteristic target joints (DIP, PIP, thumb base and index and middle MCP joints).</td>
</tr>
<tr>
<td>4 Functional impairment in hand OA may be as severe as in rheumatoid arthritis. Function should be carefully assessed and monitored using validated outcome measures.</td>
</tr>
<tr>
<td>5 Patients with polyarticular hand OA are at increased risk of knee OA, hip OA and OA at other common target sites (generalized OA) and should be assessed and examined accordingly.</td>
</tr>
<tr>
<td>6 Recognized subsets with different risk factors, associations and outcomes (requiring different assessment and management) include IP joint OA (with or without nodes), thumb base OA and erosive OA. Each may be symptomatic or asymptomatic.</td>
</tr>
<tr>
<td>7 Erosive hand OA targets IP joints and shows radiographic subchondral erosion, which may progress to marked bone and cartilage attrition, instability and bony ankylosis. Typically it has an abrupt onset, marked pain and functional impairment, inflammatory symptoms and signs (stiffness, soft tissue swelling, erythema, paraesthesiae), mildly elevated CRP levels, and a worse outcome than non-erosive IP joint OA.</td>
</tr>
<tr>
<td>8 The differential diagnosis for hand OA is wide. The commonest conditions to consider are psoriatic arthritis (which may target DIP joints or affect just one ray), rheumatoid arthritis (mainly targeting MCP joints, PIP joints and wrists), gout (which may superimpose on pre-existing hand OA), and hemochromatosis (mainly targeting MCP joints and wrists).</td>
</tr>
<tr>
<td>9 Plain radiographs provide the gold standard for morphological assessment of hand OA. A posteroanterior radiograph of both hands on a single film/field of view is adequate for diagnosis. Classical features are joint space narrowing, osteophyte, subchondral bone sclerosis and subchondral cyst, and subchondral erosion occurs in erosive hand OA. Further imaging modalities are seldom indicated for diagnosis.</td>
</tr>
<tr>
<td>10 Blood tests are not required for diagnosis of hand OA but may be required to exclude coexistent disease. In a patient with hand OA who has marked inflammatory symptoms and/or signs, especially involving atypical sites, blood tests should be undertaken to screen for additional inflammatory arthropitides.</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; DIP, distal interphalangeal; IP, interphalangeal; MCP, metacarpophalangeal; OA, osteoarthritis; PIP, proximal interphalangeal. Reproduced from original paper [26] with permission from BMJ Publishing Group Ltd.
2.2.3 Epidemiology

OA is the most common form of arthritis and a major cause of joint pain and disability. We live longer than our ancestors and, for the first time in history, people aged 65 years and older will outnumber children younger than 5 years [44]. Also, the number of people aged 60 years and above is expected to more than double by 2050 and more than triple by 2100 [44]. Being primarily related to aging, the prevalence of OA will steadily increase and is expected to be the single greatest cause of disability in the general population by 2030 [45]. This will not only affect individuals’ quality of life but also account for substantial burden on health care systems globally.

Risk factors include age, family history and female sex [34, 46]. Prevalence and incidence vary according to the definitions applied, e.g. symptomatic vs. radiographic criteria and the number of affected joints. Radiographic hand OA is by far more common than symptomatic hand OA. In the general population of the Framingham cohort, the age-standardized prevalence of radiographic hand OA in one or more joint(s) was similar in women and men (44% vs. 38%), whereas symptomatic hand OA in one or more joint(s) was twice as frequent in women (14% vs. 7%) [27]. In the Zoetermeer survey, more than half of men over the age of 65 and more than half of women over the age of 55 had radiographic involvement of one or more DIP joints [24], whereas hand OA was seldom in individuals below 40 years. Ultrasonographic assessment of the general population of the Newcastle thousand families birth cohort identified osteophytes in DIP joints in 70% of 63 year old persons, while it was 23%, 10% and 41% in PIP, MCP and CMC-1 joints, respectively [47].

The notion that especially women older than 50 years develop hand OA during menopause led to the hypothesis that estrogen levels were involved, but a systematic review found no clear relationship between these factors [48].

There is also evidence of the inheritance of hand OA. Heberden’s nodes are three times more common in sisters of individuals with hand OA than in the general population [49], and a twin study found 59% of hand OA to be due to genetic factors [50].

Finally, obesity has been suggested to be associated with hand OA [51, 52], but longitudinal studies have not confirmed any association with the development of hand OA [53, 54]. Similarly, possible links hand OA and metabolic syndrome, atherosclerosis and diabetes mellitus have been suggested [55], but remains controversial[53]. Strand et al. found no
associations between metabolic syndrome and hand OA using longitudinal data from the Framingham study [53, 56].

### 2.2.4 Etiology and pathogenesis

**Etiology**

While traditionally considered a non-inflammatory disease with much of the focus on hyaline cartilage degeneration, it is now recognized that all structures of the joint is commonly involved in disease initiation and progression [57, 58]. With MRI and ultrasonography studies showing us more of the whole-organ nature of OA, evidence suggests that established OA is not a homogeneous disorder, but rather a common consequence of different etiological processes. It is suggested that OA patients can be categorized into multiple phenotypic subgroups according to the main driver(s) of the disease (fig. 11), including cartilage-, metabolic-, synovitis-, subchondral bone-, traumatic injury-, and ageing-driven phenotypes [55, 59, 60]. Early in the OA process, these internal and external factors are driving the disease progression individually or in combination, with cause-specific histopathologic patterns, local gene expression and translation, and pain regulatory pathways [61]. Over time, the phenotypes become less distinct and eventually progress into a more common clinical expression [62].

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**Figure 11:** Evidence suggests that patients with osteoarthritis (OA) fall into multiple phenotypic subgroups defined on the basis of the main driver of disease. External and internal drivers of disease, such as local inflammation, injury or biomechanical alterations, metabolic reprogramming and immunomodulation, all affect cartilage, bone and synovium. Reprint from original paper [55] with permission from Macmillan Publishers Ltd.
Pathogenesis

The pathogenesis is complex, with loss of articular cartilage, synovial hypertrophy and inflammation, meniscal damage (in knees), subchondral bone remodeling with formation of osteophytes, bone marrow lesions, as well as muscle and ligament abnormalities. There are good reviews on the pathology of OA [55, 60, 63], although most of the literature is based on studies of knee OA.

Chondrocytes, the only cellular component of articular cartilage, are very unique cells in the sense that cartilage of an 80 year-old are likely to be the same cells that were present at age 25 years. Once grown up, there is very little cell division or cell death. Chondrocytes arise from mesenchymal progenitor cells during skeletal development. In puberty, temporary cartilage is gradually replaced by bone, whereas cartilage in the joints remains unossified.

The chondrocytes are responsible for production and maintenance of extracellular matrix that gives the cartilage its load-bearing function [64]. In healthy cartilage, chondrocytes have an ability to adapt in periods of acute nutrient stress and maintain its repair and regeneration of cartilage matrix. This flexibility decreases at early stages of OA and diminish at later stages [65]. In early OA, chondrocytes are exposed to proinflammatory cytokines, prostaglandins and reactive oxidative species, as well as micro-environmental alterations including hypoxia and nutrient stress. As a result, chondrocytes undergo metabolic alterations such as mitochondrial dysfunction through loss of energy within the cells, and a shift from a resting regulatory state to a highly metabolically active state. This phenotypic shift, recently described as ‘chondrosenescence’ [66], contributes to an imbalance between anabolic activity (necessary to produce and repair damaged matrix) and catabolic activity (chondrocyte production of cytokines and proteases). Consequently, extensive matrix degradation and loss occur, and chondrocyte death can be seen.

Synovitis is increasingly recognized to have an important role in structural degradation of the OA joint and is a possible target for DMOADs [67]. Synovial inflammation is assumed to be secondary to cartilage breakdown, as molecules from degraded hyaline cartilage and subchondral bone is released into the synovial cavity. Synoviocytes react by producing pro-inflammatory mediators, which in turn attract immune cells, increase angiogenesis and induce a phenotypic shift in chondrocytes. A vicious cycle follows, as chondrocytes produce additional cytokines and proteolytic enzymes that eventually increase cartilage degradation and induce further synovial inflammation [60, 64].
A number of other pathways have been illuminated, including innate and adaptive immune system activation [68, 69]. Given that OA is age-related, immunosenescence (i.e., gradual deterioration of the immune system due to natural age advancement) may play a role in the immune response to tissue damage [66, 70]. A recent report analyzed immune cell composition of the blood of OA patients and found compromised immune function of T cells and B cells beyond what appeared directly related to ageing, and this could reflect both inflammation and autoreactivity [71]. Also, trauma can trigger release of local inflammatory mediators, and there is increasing evidence that metabolic syndrome and obesity increase systemic low-grade inflammatory mediators in OA [62].

Wojdasiewicz et al. have recently described in detail the mediating cytokines and signaling pathways that are up-regulated in OA and most often have catabolic effects, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6, IL-15, IL-17, and IL-18 [72]. IL-1β and TNF-α are the most extensively studied cytokines. Elevated in synovial fluid, synovial membrane, cartilage and subchondral bone of OA joints, they have synergistic activation on signaling pathways that increase inflammation and cartilage degradation [72]. The effects are multiple, not only by inducing aging and apoptosis of chondrocytes but also blocking chondrocyte synthesis of the key components of extracellular matrix and increasing the release of many proteolytic enzymes that damage cartilage [72]. Few studies have included hand OA, but a recent study inhibiting IL-1α and -1β with ABT-981 did not improve outcomes [73], and results on TNF-α inhibition are diverse [74, 75].

Finally, not all cytokines are pro-inflammatory and catabolic. Some cytokines (such as IL-4, IL-10, and IL-13) have anti-inflammatory and anabolic effects, and may modulate an inflammatory response and slow progression of OA [72]. Although the literature is limited, there is emerging evidence that an up-regulation of these cytokines, either individually or combined, may induce cartilage repair in OA [76].

**Key points**

- Multiple risk factors are linked to the pathogenesis of osteoarthritis, including age, joint injury, obesity, genetics, anatomical factors (joint shape and alignment) and gender.
- Proinflammatory factors appear to be driving the production of proteolytic enzymes responsible for the degradation of cartilage matrix and synovial inflammation.
2.2.5 Management

Evidence-based guidelines for the management of OA agree on several principles (fig. 12): 1) people should be involved in their own treatment strategy, including education about their disease and treatment options; 2) optimal treatment involves a combination of non-pharmacological and pharmacological approaches, starting with weight loss, exercise and paracetamol; 3) tailored therapies according to comorbidities and risk factors [77-81].

![Figure 12: General recommendations for treatments of OA in adults. Starting at the center and working outwards, the treatments are arranged in the order in which they should be considered, taking into account individuals’ different needs, risk factors, and preferences. The core treatments (center) should be considered first for every person with OA. If further treatment is required, consider the drugs in the second circle before the drugs in the outer circle. The outer circle also shows adjunctive treatments (both non-pharmacological and surgical), which have less well-proven efficacy, provide less symptom relief, or increased risk to the patient compared with those in the second circle. Adapted from original paper [79] with permission from BMJ Publishing Group Ltd.](image)

At present, with the exception of joint replacement, imaging outcomes are not included in clinical treatment algorithms, as they have not been demonstrated to direct therapeutic choices. Choosing the most appropriate strategy through a targeted and personalized approach could optimize effectiveness, in which imaging modalities may play an important role.
role. There is some evidence that patients with early disease respond better to pharmacological treatments for OA than those with late disease [82], and there may be cases where imaging could be used to identify subgroups of patients who are more or less likely to benefit from interventions. This was explored in a recent study by Knoop et al. using MRI to predict results of physical therapy on knee OA: although patients with all grades of OA severity can benefit from supervised exercise therapy, the effects were reduced in patients with advanced patellofemoral OA (large osteophytes and severe cartilage thinning) [83].

Intra-articular (IA) corticosteroid injection may be applied to patients with joint inflammation who are unresponsive to non-pharmacological treatments or oral non-steroidal anti-inflammatory drugs. Data from individual publications suggest that there are several predictors for the efficacy of IA steroid injections, including presence of effusion, withdrawal of fluid from the knee, injecting with ultrasound guidance, less structural (radiographic) severity of disease, and pain [84].

Interestingly, a recent randomized controlled trial comparing IA Triamcinolone vs. saline injections every 12 weeks for two years in patients with knee OA showed greater cartilage loss in patients who received Triamcinolone and no significant difference on knee pain severity between treatment groups [85]. Participants were included on the basis of knee pain, radiographic severity (KL=2-3) and inflammation assessed by ultrasound, of which the latter showed only mild effusion in the groups according to a previous protocol [86]. The study shows the potential harmful effect of repeated cortisone injections [85], but in clinical practice, one would not inject joints on a regular basis if inflammation decreased after the first injection(s).

**Key points**

- Treatment of (hand) OA includes education, weight loss, exercises and pain medications. In advanced cases, surgery may be an option.
- Imaging outcomes are currently not included in clinical treatment algorithms.
2.3 Imaging of osteoarthritis

In daily clinical practice, conventional radiography is still the most applied imaging technique to supplement a clinical examination of patients with suspected OA. However, more modern imaging modalities can visualize multiple aspects of the joint, and depending on diagnostic need, radiography may no longer be the modality of choice (table 3). Ultrasound can visualize bony and soft tissue pathologies and is highly feasible in a clinical setting. MRI gives a complete assessment of the joint and has a pivotal role in OA research, whereas computed tomography (CT) and nuclear medicine offer alternatives in research scenarios. This section will give an overview the recent literature on established and newer imaging modalities applied in OA, summarizing their ability to detect and quantify the range of OA pathologies in hand OA.

Table 3: Summary of the relative performance of imaging modalities in osteoarthritis.

<table>
<thead>
<tr>
<th>Performance</th>
<th>X-ray</th>
<th>MRI</th>
<th>US</th>
<th>CT</th>
<th>PET</th>
<th>Optical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage</td>
<td>–</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Joint space narrowing</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Subchondral cysts, sclerosis</td>
<td>++</td>
<td>+++</td>
<td>–</td>
<td>+++</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Bone marrow lesions</td>
<td>–</td>
<td>++++</td>
<td>–</td>
<td>+++</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>Osteophytes, erosions</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Inflammation</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Soft tissue (menisci, tendons)</td>
<td>–</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
<td>(2)</td>
<td>–</td>
</tr>
</tbody>
</table>

Clinical utility

| Early diagnosis                          | +     | +++  | +++  | +++ | ++  | –       |
| Feasibility in clinical care             | ++++  | ++   | +++  | ++  | +   | ?       |
| Favorable cost                           | ++++  | ++   | +++  | ++  | +   | ?       |
| Favorable radiation dose                 | ++    | +++  | +++  | ++  | +   | +++     |

(1) Difficult to assess in small finger joints. (2) CT arthrography with intraarticular contrast injection. (3) Dual energy CT (DECT). MRI, magnetic resonance imaging; US, ultrasound; CT, computed tomography; PET, positron emission tomography; Optical, Optical imaging. Reprint from original paper [87] with permission from Elsevier.


2.3.1 Ultrasonography

Ultrasound is a highly sensitive imaging modality, where use of high frequency probes gives a resolution up to about 0.1mm. It enables multiplanar and real-time imaging at a fairly low cost and without radiation exposure. Several aspects of the joint can be visualized in one scan, including joint capsule, synovial hypertrophy and effusion, erosive development, osteophytes, joint space narrowing, cartilage and meniscus.

Osteophytes in finger joints are easily visualized with ultrasonography and are associated with increased pain and functional impairment [88]. Ultrasonography has been shown to be more sensitive than radiography in detecting osteophytes in small and large joints [47, 88, 89], and osteophytes are independently associated with pain in hand OA [90].

Synovitis (Fig. 13) is readily detected by ultrasound in all peripheral joints. Ultrasound is more sensitive than clinical examination in detecting synovial inflammation and correlates well with MRI and arthroscopic findings [91, 92]. It has for a long time been used to assess synovitis in the small joints of patients with RA, and reliable scoring methods have been developed [93, 94]. Synovitis found in OA joints has similar appearance as in RA, and has been assessed using scoring systems developed for RA patients [95-97]. Synovitis in OA patients consists of effusion as well as synovial hypertrophy, and it is debated whether these lesions should be scored separately. Given our limited understanding of the predictive validity of these lesions, a preliminary scoring system on hand OA suggested combined scoring of the features (which was used in this thesis) [98].

Both color Doppler and power Doppler techniques (the latter used in this thesis; fig. 14) detect synovial flow, indicative of increased synovial vascularization verified by histological examination and MRI [99-101]. It offers better staging of inflammation, as elegantly demonstrated by Qvistgaard et al. in RA finger joints [102].

As for cartilage, ultrasonography have been compared with histology, showing good reproducibility and high levels of agreement in the assessment of normal to moderately damaged cartilage in knee joints [103]. In small joints of the hands, measurements of cartilage thickness by ultrasound have shown to be inversely correlated with radiological damage scores and correlated with radiographic joint space width [104, 105]. Ultrasonographic assessment of qualitative cartilage abnormalities in MCP-joints of hand OA patients have demonstrated moderate to good reliability [106].
Figure 13: A proposed scoring system for synovial grey-scale synovitis in finger joints (unpublished work from the OMERACT Ultrasonography Group).

Figure 14: A proposed scoring system for power Doppler signals in finger joints (unpublished work from the OMERACT Ultrasonography Group).
Semiquantitative evaluation of cartilage may enable the rheumatologists to identify cartilage damage in patients with OA, but few relevant studies exist. In patients with RA, moderate to good inter-observer reproducibility have been shown for a semiquantitative scoring system based on qualitative morphological cartilage damage in MCP joints [107].

Finally, calcium pyrophosphate dehydrate (CPP) crystals are frequently found in OA joints. Ultrasound is useful for the detection of CPP crystals in both cartilage and fibrocartilage [108]. The CPP crystals are detected by ultrasound as hyperechoic spots within the cartilage. With histology as reference, the sensitivity for detection of CPP crystals was similar for ultrasound and microscopic examination of joint fluid [109]. Thus, if CPP deposition is detected by ultrasound, there may be no need for joint aspiration.

Advantages and limitations of ultrasonography

Ultrasoundography is a safe, accurate and noninvasive imaging tool without any contraindications for assessing OA joints. Using sound waves, the method has no known side effects and offers opportunity for scanning of multiple musculoskeletal regions in a single sitting. It is a “bed-side” imaging modality that may be performed by the rheumatologist during the consultation. As such, it may be used as an educational tool for demonstrating relevant pathologies to patients when explaining symptoms. Such increased knowledge by patients may increase adherence to non-medical or medical treatment. In addition, if injections are necessary, ultrasound guidance will result in accurate needle placement for aspiration and injection purposes [110], and its use has been related to better pain and functional improvement than palpation-guided intra-articular injections [110, 111].

A major limitation of ultrasound in assessing hand OA is that only tissues superficial to bone may be examined, and subchondral BMLs and cysts can therefore not be detected. Also, large osteophytes may cover the joint and thus limit visualization of deeper structures such as the joint space and cartilage. The erosions are typically centrally located, which is more difficult to visualize due to the limited acoustic window, especially in joints with osteophytes. Finally, ultrasound is criticized for being operator-dependent with a very long period of training required to achieve sufficient competency. Adequate skills for careful assessments of specific targets, such as osteophytes or articular cartilage, can however be obtained in a shorter time even by a sonographer with limited training, especially with the aid of standardized atlases of relevant pathology. Important initiatives by the Outcome Measures In Rheumatology (OMERACT, previously ‘Outcome Measures In Rheumatoid
Arthritis Clinical Trials’ and EULAR groups have provided provisional definitions of relevant abnormalities [112, 113] and have subsequently examined the reliability of these measures [114, 115]. Paper I and II in this thesis is part of this ongoing work.

**Ultrasonographic scoring systems in hand OA**

The introduction of imaging atlases has improved MRI and ultrasound reliability in RA [93, 116, 117]. With an increased interest in the role of inflammation in OA, a similar reference atlas could be useful in the ultrasound assessment of hand OA. In 2008, Keen and colleagues presented a preliminary ultrasonographic scoring system for features of hand OA, including osteophytes, grey scale synovitis and power Doppler signals graded on semiquantitative 0-3 scales [98]. Grey scale synovitis was defined as a combined score of synovial hypertrophy and effusion according to earlier OMERACT definitions [113]. It was, however, decided not to include erosions and cartilage parameters or joint space narrowing due to concerns about reliable definitions, available sonographic technology at the time, and feasibility related to duration of scanning. Both intra- and inter-reader reliability was moderate to substantial and generally better on dichotomous scales, whereas semiquantitative scales were most reliable at the extremes of the scale (scores of 0 and 3) [98]. Given there was no formal or extensive standardization process prior to the exercise, these results were very encouraging, but the semiquantitative results suggested that a standardization process could improve agreement.

Recent ultrasound studies of hand OA either apply the preliminary hand OA scoring system by Keen et al., which does not include a standardized atlas, or ultrasound atlases developed for RA patients [93, 118]. The validity of applying definitions developed for RA to be used in OA patients needs further consideration.

**Key points**

- Ultrasonography is a highly sensitive imaging modality that enables clinicians to visualize both soft tissue and bony pathology in multiple joints in the same seating.
- A preliminary ultrasonographic scoring system for features of hand OA includes osteophytes, grey scale synovitis and power Doppler signals on a 0-3 scale.
2.3.2 Conventional radiography (CR)

Radiography uses *x-rays*, or electromagnetic radiation, with a wavelength in the range of 0.01 to 10 nanometers. X-rays were discovered in 1895 by Wilhelm Roentgen (who received the first Nobel Price in Physics in 1901 for this discovery) and were named so because their nature was unknown at the time. Unlike ordinary light, these waves were invisible, but still traveled in a straight line and affected photographic film in the same way as light. They were also much more penetrating than ordinary light and could easily pass through the human body, wood and even quite thick pieces of metal. Despite the lack of understanding of the radiation involved, x-rays were almost immediately put to use by physicians and engineers, and the principles and interpretations have remained nearly unchanged with the exception of digital image receptors introduced in the mid-1980s.

*Technical aspects of CR*

Radiation is created by taking energy from electrons and converting it into photons with appropriate energies [119]. This energy conversion takes place in the x-ray tube, consisting of a cathode and an anode. As electric current flows through the tube, electrons are accelerated at high voltage across the gap between the cathode and anode. When the electrons strike the anode at high speed, parts of their kinetic energy is converted into x-ray photons. The energy distribution of the photons is modified by inherent and additional filtration and then projected towards an object that will absorb a variable proportion of the x-rays (depending on density and composition). A detector (either analogous films sensitive to x-rays or digital detectors) captures the remaining x-rays and composes a 2D image.

The hands may be imaged in different angles, or projections, depending on the diagnoses in question. The posteroanterior (PA) view (i.e., x-rays in dorsal to palmar direction) is the best conventional view for demonstrating malalignment and JSN (and may also depict early soft-tissue abnormalities in RA). It is therefore applied in both research and clinical settings when imaging hand OA, and is what we used in this thesis. However, anteroposterior oblique (‘ball-catcher’ position) or lateral projections may provide additional information.

Note: Screen film radiography is sometimes termed “conventional radiography”, but in this thesis, the acronym CR (conventional radiography) is applied to the x-ray technique as described above, irrespective of detector type (computed, digital or screen film). Norwegian hospitals have mostly converted from film-based to digital radiography.
Advantages and limitations of CR

Being widely available, inexpensive and well accepted by patients, radiography remains the cornerstone in obtaining an image-based OA diagnosis. CR provides a 2D picture of bony features related to OA, including marginal osteophytes, subchondral sclerosis, and subchondral cysts, as well as joint space width as a surrogate for cartilage thickness and meniscal integrity [120].

CR exposes the patient to radiation, but standard hand radiographs corresponds to a dose of only 0.001 millisievert, or 3 hours of natural background radiation [121]. The main limitation is thus its inability to directly visualize cartilage, synovitis, BMLs and other soft tissue structures. In larger joints, reproducibility of positioning and joint alignment may be problematic, but less so for hand radiographs [122].

Radiographic scoring systems in hand OA

The Kellgren-Lawrence (KL) grading scheme and atlas is the most common scoring system to assess radiographic OA severity (in hands, knees, hips, spine, shoulders), providing a global composite OA score on a 0-4 scale for each joint [123, 124]. A KL grade 2 usually defines whether OA is present and includes definite osteophytes and possible narrowing of the joint space. There are, however, discrepancies in how KL grades have been described and applied in different studies, especially the important cut-off value of KL grade 2 [125], and there are concerns about the application in longitudinal studies evaluating incidence or progression [126]. Furthermore, the KL scale has been criticized for too much emphasis on osteophytes, as these are mandatory for a joint to be classified as OA and suppresses the importance of joint space narrowing and sclerosis. Modified KL scales have been applied to overcome these limitations, but may have major consequences for our interpretation of study results [125]. Other scoring systems for global hand OA assessments have been proposed with more emphasis on JSN than KL scale [127, 128], but these have not been extensively used.

Instead of a global OA severity score, one may assess each phenotypic feature of hand OA separately and in more detail [129-131]. The semiquantitative Osteoarthritis Research Society International (OARSI) radiographic atlas is most often applied when evaluating individual radiographic features of OA and includes osteophytes, subchondral sclerosis, cysts, erosions, malalignment and JSN [130, 131]. It is, however, more time-consuming than scoring KL.
Subchondral erosions in hand OA are often centrally located, in contrast to the marginal erosions in RA. With co-occurring osteophytes, the interphalangeal joints may show a gull-wing configuration [132]. Verbruggen et al. have developed the Anatomical Phase Scoring System for radiographic evaluation of the evolution of erosions, based on the assumption that hand OA undergo predictable phases and can be scored subsequently [133]. It was recently shown that the J phase (complete joint space narrowing in part of or the whole joint and possibly subchondral cysts that do not disrupt the joint plate) could predict future erosive progression in hand OA [134]. A more complex scoring system, the Ghent University Scoring System (GUSS) shows better ability to detect progression over a shorter period of time and during the destructive phases [135]. However, radiography has a limitation in its two-dimensionality; a study compared radiography with MRI and found four times as many erosive joints with MRI [132], and there is a debate whether erosive hand OA is truly a separate inflammatory entity or just a severe form of OA [136, 137].

Key points

- Being widely available, inexpensive and well accepted by patients, radiography remains the cornerstone in obtaining an image-based OA diagnosis.
- Kellgren-Lawrence scale provides a global OA score for a joint, whereas the OARSI atlas evaluates individual radiographic features separately.

2.3.3 Magnetic resonance imaging (MRI)

MRI provides a multiplanar image of all joint components, including structural features such as osteophytes, cartilage, malalignment, erosions, cysts, and collateral ligaments, as well as inflammatory features such as synovitis and tenosynovitis (fig. 15). MRI is usually not required in clinical practice for the diagnosis of OA, as sufficient information is often obtained by the history and clinical examination. In daily clinical practice, MRI may however be helpful in individual patients, especially in large joints when the diagnosis is not clear. It is worth noting that in a large series of people over age 50 with and without knee pain but with normal, weight-bearing knee X-rays, almost 90% had MRI changes of OA [138].

MRI is the only imaging modality that is able to show BMLs, which have been associated with increased loading due to obesity, joint malalignment, and meniscal pathology, as well
as pain and structural progression in hand, knee and hip OA [139-142]. Lesions with a similar appearance are seen in systemic inflammatory joint diseases, where they are referred to as ‘bone marrow edema’ and histologically represent inflammatory osteitis. In OA, trabecular remodeling, necrosis of fatty cells, fibrosis, extracellular fluid accumulation and enhanced angiogenesis has been found histologically [143, 144].

![Figure 15: Conventional radiography (CR) and magnetic resonance imaging (MRI) (coronal/axial T1-weighted fat-suppressed images) of the right hand. Both CR (a) and MRI (b, c) show severe osteoarthritis with osteophytes (white arrowheads) and central collapse of the joint plate in the 2nd distal interphalangeal (DIP) joint. Both MRI and CR show severe joint space narrowing in the 3rd DIP joint. MRI shows the collateral ligaments (black arrowheads). CR shows a cyst-like lesion (white arrow), which on MRI was difficult to distinguish from an erosion. Reprint from original paper [145] with permission from BioMed Central.](image)

**Technical aspects of MRI**

The physical theory of MRI and pulse sequences is a vast and complicated topic and only the fundamentals can be presented here. In principle, the patient is placed in a magnet, a radio wave is sent in and then turned off, and the patient subsequently emits a signal that is used for reconstruction of a picture [146, 147]:

MRI imaging is based on the electromagnetic activity of atomic nuclei of the body; most often hydrogen (¹H) nuclei, but other nuclei, for example, fluorine (¹⁹F) nuclei, may also be assessed. The protons spin around their axis with random alignment and possess electrical charge. When the body is exposed to a strong magnetic field, such as an MRI scanner, the protons line up and create a magnetic vector oriented along the axis of the MRI scanner.
Because it is longitudinal however, it cannot be measured directly – a magnetization transverse to the external magnetic field is necessary.

The patient is then exposed to a short burst of electromagnetic wave, or a radio frequency (RF) pulse, which deflects the magnetic vector. Only when the RF pulse and the protons have the same frequency, can protons pick up some energy from the radio wave, a phenomenon called ‘resonance’. The RF pulse causes the longitudinal vector to decrease, but also establishes a new transversal magnetic vector. As the pulse is switched off, the longitudinal magnetization grows back to its original size (longitudinal recovery, by a time constant $T_1$ corresponding to 63% of the nuclei realigned), and the newly established transverse magnetization starts to disappear (transversal relaxation, or decay, by a time constant $T_2$ corresponding to 63% loss of transverse magnetization). $T_1$ is usually longer than $T_2$, about 300 to 2000 msec and 30 to 150 msec in biological tissue, respectively, depending on magnetic field strength and tissue composition. Receiver coils pick up the electromagnetic radiation produced by nuclear relaxation, and the signals are then plotted on a grey scale and cross sectional images are built up.

The image quality is mainly dependent of contrasts, resolution and noise/artefacts, in which contrast is the result of differences in signal intensity between tissues or regions as a result of $T_1$ recovery, $T_2$ decay (and $T^*$ decay, used in fast imaging sequences) and proton density (PD). Water and fat represents two extremes of MRI contrast with different $T_1$ and $T_2$ times. The intrinsic $T_1$, $T_2$ and PD mechanisms occur simultaneously, but one process can be made dominant by external contrast parameters. The most important parameters are repetition time (TR), echo time (TE) and flip angle, which all can be selected by the operator.

1. In $T_1$-weighted images, short TR intervals emphasize the $T_1$ contrast. Tissue with long $T_1$ (e.g., water) will not be able to recover longitudinal magnetization and will appear dark compared to tissues with short $T_1$ (e.g., fat, which appears bright). TE is short.
2. In $T_2$-weighted images, a prolonged TE interval is used to emphasize the inherent differences in $T_2$ between different tissues. Tissues with long $T_2$ (e.g., water) will take longer to decay and will appear brighter than signal from tissues with short $T_2$ (e.g., fat, which appear dark). TR is long.
3. In PD-weighting, the numbers of protons per unit volume determines image contrast. Long TR and short TE values diminish the effects of $T_1$ and $T_2$ contrast.
Advantages and limitations of MRI

The radiofrequency radiation used in MRI has no known biological hazards. Due to its capacity to visualize the whole joint, detect early structural disease and sensitively measure change over time, MRI plays a key role as a research tool to define the mechanisms and clinical correlations of OA. MRI should now be considered as an alternative to radiography for the demonstration of structure modification in clinical trials of knee and hip OA [148, 149], and has been implemented in large longitudinal epidemiologic studies of OA such as the Osteoarthritis Initiative (OAI) and The Multicenter Osteoarthritis Study (MOST). MRI does not yet have regulatory approval as a primary structural outcome in DMOAD trials.

Disadvantages of MRI include high costs compared to CR, motion artifacts, long acquisition time and several contraindications such as pacemaker, cochlear implants and other magnetizable materials. Also, the machine is expensive to purchase, operate and maintain [122]. Finally, some MRI examinations may require injection of a contrast agent. As such, there are several methods for detecting and quantifying synovitis in OA. Due to possible side effects and associated costs, it would be desirable not to use contrast-enhanced MRI in OA studies; however, contrast use does improve the certainty of detecting inflamed synovium [150], which has been related to pain and shown to predict progression of radiographic JSN [67, 142]. Following intra-articular corticosteroid injection, contrast-enhanced synovitis also correlated better with subjective pain improvement than conventional measurement of synovitis in 93 patients with knee OA [151].

The 1.0 T MRI machine used in our cohort cannot assess the cartilage in finger joints directly [152], and cartilage space loss was used as a marker similar to JSN on conventional radiographs. A previous study has demonstrated higher sensitivity of conventional radiography in detection of JSN [58], and may be a better modality to assess cartilage until we have better resolution and sequences.

MRI scoring systems in hand OA

There are several available semiquantitative MRI scoring systems for OA in the knee, hip, hand and shoulder that have recently been reviewed in detail by Guermazi and colleagues [153]. The knee differs from other joints by having several scoring systems available (reflecting the predominant focus on knee OA in the literature), each with strengths and limitations [153]. Most of these scoring systems employ 0-3 or 0-4 semiquantitative scores for compartment pathologies, and occasionally have within-grade scoring (e.g. 0.5
increments) in an attempt to improve responsiveness to change over time [154]. Furthermore, teaching atlases and training sets of MRI scans improve reader reliability of scoring and an electronic template that overlies MRI images has been demonstrated to improve reader reliability [155].

For hand OA, scoring systems for both the interphalangeal joints and the thumb base have been proposed [152, 156, 157]. Kortekaas et al. examined the validity of the Oslo Hand OA MRI score [158]. They found good reliability and significant associations between pain and synovitis [159]. They also compared MRI with ultrasound; favoring MRI in detecting synovitis, whereas ultrasound was more sensitive for osteophytes. However, some limitations of the Oslo Hand OA MRI scoring system resulted in a revision by the OMERACT MRI Working Group: the OMERACT Hand Osteoarthritis MRI Scoring System (HOAMRIS) [152], which included synovitis, erosive damage, cysts, osteophytes, cartilage space loss, malalignment, and BMLs on 0–3 scales. The group found good to very good inter-reader reliability for cross-sectional readings, whereas longitudinal reliability was lower due to a smaller range of change scores [152]. MRI-detected synovitis, BMLs and JSN is associated with pain and radiographic progression in hand OA [142], and further validation may lead to exclusion of less important features from the proposed scoring system.

### Key points

- MRI visualizes all joint components and plays a key role in OA research.
- Good reliability has been demonstrated for MRI hand OA atlases.

### 2.3.4 Other imaging modalities

**Computed tomography**

In rheumatology, CT is often used for the assessment of the brain and lungs in people with connective tissue diseases. With regards to bone abnormalities in the axial skeleton or other joints, CT may be obtained when radiographs are unclear and MRI is contraindicated or not available.

Some advantages exist for CT. The acquisition is so fast that motion is rarely a problem, as opposed to MRI, and thus the technique is well accepted by patients. With superior images
of the bony cortex and soft tissue calcification, CT may serve as a reasonable gold standard in OA research when validating MRI bone morphology such as cysts, erosions and osteophytes. The two main limitations are low soft-tissue contrast and radiation dose higher than that of other modalities.

Conventional multi-detector CT may be used before orthopedic surgery. By applying intra-articular contrast material (CT arthrography), it gives impressive images of cartilage thinning that correlate with (and may be an alternative to) delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) [160]. Furthermore, with dual-energy CT (DECT), in which two datasets are acquired with different x-ray spectra, one can visualize crystals (relevant for diagnosing gout and CPPD) and iron deposits (relevant for synovial hemosiderin quantification in patients with pigmented villonodular synovitis) as well as areas of increased bone marrow attenuation reported as the CT equivalent of BMLs [161]. At present, DECT appears to be a tool mainly for rheumatology clinical research.

Nuclear medicine imaging

Nuclear medicine imaging is based on radioactive isotopes, often injected intravenously or taken orally. It provides a whole body examination and identifies tissues with high metabolic activity. The most common modalities are Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) scans, and the latter has been applied to OA patients in small trials.

The potential advantages of PET depend on markers targeting specific tissues, of which bone remodeling and turnover in OA has been the primary endpoint to date. Kobayashi et al. have demonstrated that an increased uptake of $^{18}$F-Fluoride as a bone-imaging tracer in the hip represents early abnormalities in the subchondral bone prior to radiographic JSN [162]. The same group has further compared the diagnostic value of PET with MRI and radiography in early hip OA, and found that most (96%) of the MRI-positive joints were also PET positive [163], and more joints had an increased PET signal than MRI-changes in joints with mild or no OA (KL grade = 0-1) [163]. Whether these findings represent other diseases or very early OA is uncertain, but a longitudinal study demonstrated that baseline PET signals predicted incidence and progression of OA as well as worsening of pain [164].

Nuclear imaging is limited by the use of radiopharmaceuticals with radiating isotopes and potential allergic reactions. It also has a low specificity and poor anatomical resolution. Fusion with CT or MRI improves resolution significantly and provides easier anatomical
localization of radiation uptake [165-167]. The clinical application in OA is limited at present, but may increase if radiopharmaceutical markers for cartilage are developed.

**Optical imaging**

Optical spectral transmission (OST) and fluorescence optical imaging (FOI) are new imaging modalities for assessment of joint inflammation, currently limited to the hands. The principals are similar to those employed in pulse oximetry; light of specific wavelengths are measured quantitatively, and vascular enhancement (i.e., inflammation) reduces the transmission of light. OST measures the change in transmission of light before and after impeding the venous return of blood from the forearms, whereas FOI depend on intravenous fluorescence dye (Fig. 16). Both techniques are fast (90s and 6min examination time, respectively) and can be performed by trained personnel, but require special equipment.

OST and FOI have performed moderately compared to clinical examination, MRI and ultrasound in the detection of altered microcirculation as a proxy for joint inflammation in patients with RA [168-170]. Glimm *et al.* were the first to explore the use of optical imaging in hand OA patients, demonstrating similar frequencies of altered microcirculation, but differences with regards to joint distribution and the timing of enhancement [97]. These modalities are in their early stages and further studies are required, but they do have potential to be implemented in clinical and epidemiological studies as a meaningful outcome, and following treatment response when targeting inflammation. Their benefits over existing modalities will also need exploration.

*Figure 16: Fluorescence optical imaging (FOI) in finger joints with osteoarthritis, showing fluorescence enhancement in the left proximal interphalangeal joints (PIP) 2 to 5 and the right PIP 3 to 5. Picture from Diakonhjemmet Hospital.*
Key points

- CT and nuclear imaging can be used for evaluation of OA features, but are limited to smaller clinical or epidemiological studies.
- Optical imaging may offer an alternative modality for monitoring inflammation.
3. General aim and research questions

3.1 General aims

The general aim of this thesis was to improve the performance of ultrasonographic examination of hand OA by developing an ultrasonographic imaging atlas of osteophytes in hand OA and to study the validity, reliability and predictive value of structural and inflammatory ultrasound features in hand OA.

3.2 Specific research questions

• What is the agreement between ultrasound and MRI in the detection of osteophytes in hand OA (paper I)?

• What is the agreement between ultrasound and CR in the detection of osteophytes in hand OA (paper I)?

• How prevalent are ultrasound-detected osteophytes (paper I) and inflammation (paper III) in a hospital-based cohort of hand OA patients?

• What is the intra- and inter-reader reliability of semiquantitative ultrasonographic assessments of structural (osteophytes and cartilage; paper I–II) and inflammatory (paper III) features in hand OA?

• Is inflammation in a joint predictive of future radiographic OA progression (paper III)?

• Will joints with ultrasound-detected osteophytes that otherwise are assessed as normal (by CR and clinical examination) later develop features of radiographic or clinical hand OA (paper IV)?
4. Material and methods

4.1 Study design

The results presented in this thesis are based on data from a prospective cohort study of patients with established hand OA and a cross-sectional test-retest reliability exercise.

In paper I, we used cross-sectional data from the Oslo hand OA cohort to compare ultrasound-detected osteophytes in finger joints against MRI, CR and clinical examination of bony enlargement. In paper III and IV, we used longitudinal five-year data from the Oslo hand OA cohort to explore the predictive value of inflammation and osteophytes on future radiographic hand OA progression in individual finger joints.

Intra- and inter-reader reliability of osteophytes was explored on static images in paper I and in a patient-based exercise with use of an ultrasound atlas of osteophytes in hand OA patients in paper II. Paper II also included reliability of a semiquantitative cartilage assessment in MCP joints and paper III explored the reliability of ultrasonographic inflammatory features on static images.

4.2 Study population

4.2.1 The Oslo hand osteoarthritis cohort

The initiative to the Oslo hand OA cohort started in 2000 with the intention to evaluate health-related quality of life in patients with hand OA and to study the prediction of long-term outcomes. Potential study participants were identified by diagnostic codes in the hospital data system at the Department of Rheumatology (Diakonhjemmet Hospital). Men and women between 50 and 70 years, who had been examined at the outpatient rheumatology clinic within the previous 2 years, were eligible for inclusion in the cohort if they had a diagnosis of hand OA and no other rheumatic diseases. In total 275 eligible patients with hand OA were identified after a thorough review of the patient records. The patients were contacted by postal mail, and 209 of 275 (76%) consented to participate in the data collection (questionnaires/interview, clinical examination and CR of both hands).

The patients were again contacted in 2008, and 128 of 209 (61%) met for a follow-up examination in the period 2008-2009. A second follow-up was conducted in 2013, where 87
of 209 (42%) participated. Reasons for non-participation at the follow-up examinations are shown in fig. 17. The follow-up data collections included the same questionnaires and examinations (including CR) that were performed at examination 1 but also ultrasonography of both hands and contrast-enhanced MRI of the dominant hand. Results presented in this thesis (paper I, III and IV) contained data only from 2008-2009 (hereafter referred to as ‘baseline’) and 2013 (hereafter referred to as ‘follow-up’).

All patients described in this thesis had clinical and/or radiographic hand OA. The ACR classification criteria for hand OA were fulfilled by 118 of 127 patients (92%) [30], whereas 115 of 118 (97%) had radiographic hand OA defined as ≥1 joint(s) with KL grade > 2 [123].

Figure 17: Flowchart of the patients in the Oslo hand OA cohort.
4.2.2 OMERACT reliability exercise

For paper II, ten patients with hand OA were recruited from the outpatient clinic at the Diakonhjemmet Hospital (Oslo, Norway). All were women (median (range) age 74.5 (53–77) years) fulfilling the ACR classification criteria for hand OA [30]. The presence of any inflammatory joint disease was an exclusion criterion.

The study was performed on three consecutive days with consensus and training the first day followed by a reliability exercise on patients over the next 2 days. The meeting was preceded by a web-based reliability exercise on osteophyte scoring, as well as a reliability exercise on still images of cartilage lesions via a website one month after the meeting.

Of the ten sonographers from six countries participating in the reliability study, nine were rheumatologists, experts in musculoskeletal ultrasonography and members of the OMERACT ultrasonography group, whereas one (Alexander Mathiessen, AM) was an MD, PhD student, highly experienced in scoring of osteophytes and had participated in the development of the ultrasonography atlas of osteophytes (paper I). Additionally, six of the sonographers had previously performed ultrasonography reliability studies on cartilage in MCP joints [106, 107].

4.3 Data collection

A broad spectrum of variables was collected in the Oslo hand OA cohort, including information about demographic and disease related variables including lifestyle, pain and general health. In addition, the patients underwent an extensive whole body clinical joint examination, CR and ultrasound of both hands, MRI of dominant hand and collection of blood and urine samples. Table 4 presents the most important variables used in the papers of this thesis.

4.3.1 Demographical and other background variables

The hand OA patients who consented to participate in the study received a booklet of questionnaires (35 pages) by postal mail approximately one week ahead of the clinical examination. The completed booklet was returned when they subsequently came to the study visit. We used the questionnaires together with clinical interviews performed by study nurses to obtain extensive information about demographic and disease-related variables.
Table 4: Variables used in the analyses in paper I-IV.

<table>
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<tr>
<th>Variables used in the analyses</th>
<th>Paper I</th>
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<td>• Osteophytes</td>
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Body mass index

All patients had their heights and weights measured wearing no shoes and light indoor clothing, and body mass index (BMI) was calculated (kg/m2).

Grip strength

Grip strength (kg) was assessed in both hands with a Jamar hand dynamometer (Therapeutic Equipment Corporation, Clifton, New Jersey, USA) with the patients sitting with the shoulder in neutral position and 90 degrees flexed elbow [171]. The best performance out of two attempts was recorded for each hand.

The Australian Canadian (AUSCAN) hand index

AUSCAN is the most widely used patient-reported outcome measure in hand OA and assesses pain (five items), stiffness (one item) and physical function (nine items) during the
last 48 hours [172]. We used the Likert scale version, which gives the patient a choice of five response options (0-4 scale, of which 4 represents worst health) for each of the 15 items. Subscale scores were obtained by calculation of the mean value of the assigned values scored on the questions within the subscale and then multiplied with the number of items in the subscale (in order to correct for missing values). At least three pain items and five physical function items had to be assigned by the patient to obtain the AUSCAN pain and physical function sum scores respectively.

The Function Index for Hand Osteoarthritis (FIHOA)

FIHOA is originally an investigator-administered hand OA-specific instrument and consists of ten questions about functional impairment on a four-point Likert scale (0-3 scale, of which 3 represents worst health) [173]. In the Oslo hand OA cohort, the patients completed the questionnaire. Total score was obtained by calculation of the mean value of the assigned values scored on the questions and then multiplied with ten (in order to correct for missing values). At least six items had to be assigned.

The Arthritis Impact Measurement Scales-2 (AIMS-2)

AIMS-2 is a multidimensional instrument that was initially developed for RA, but it can also be used in other rheumatic joint diseases like OA [174]. It consists of 57 items covering 12 dimensions of health status, of which one captures hand and finger function. This subscale consists of five questions on a five-point Likert scale (0-4, of which 4 represents worst health). The subscale score was obtained by calculation of the mean value of the assigned values scored on the questions within the subscale and then multiplied five (in order to correct for missing values). At least three items had to be assigned.

4.3.2 Physical examination

One rheumatologist (Barbara Slatkowsky-Christensen, BSC) with more than 20 years of experience in rheumatology performed the clinical joint assessment at all patient visits (paper I, III and IV). Absence or presence of soft tissue swelling and/or bony enlargement was assessed in the CMC-1, MCP, PIP (including the thumb) and DIP joints as described in the EULAR hand book [175]. The joint examination also included assessment of tenderness upon palpation and limited motion, but these joint abnormalities were not used as outcome measures in the current thesis.
4.3.3 Ultrasonography

The Oslo Hand OA cohort

One trainee (AM) and one expert in musculoskeletal ultrasonography and rheumatologist (Hilde Berner Hammer, HBH) performed the ultrasound assessments together and reached consensus on each scoring at baseline (paper I, III and IV). Two medical students performed the ultrasound examinations at follow-up, but these data were not included in papers in this thesis.

A linear array transducer was used (5-13 MHz, Siemens Antares, Sonoline; Siemens Medical Solutions, Mountain View, CA, USA) with fixed settings of the machine (including grey scale of 11.4 MHz and optimization for power Doppler with PRF of 391). To ensure standardization, the same machine without software upgrades was used throughout the study. The sonographers were blinded for other clinical and imaging assessments.

The bilateral CMC-1, MCP, PIP (including the IP-1) and DIP joints were scanned on the dorsal aspect longitudinally from the radial to the ulnar side, with the patient sitting opposite to the investigator with his/her hands resting on a small table. In addition, a transverse scanning was performed if there was uncertainty about the presence of pathology. Osteophytes, grey scale synovitis and power Doppler signals were assessed semiquantitatively [98]. The largest osteophyte in a joint was scored on a 0-3 scale (paper I and IV): 0 = absent, 1 = minor, 2 = moderate, and 3 = major. Grey scale synovitis (i.e., combined synovial hypertrophy and effusion) was scored on a 0-3 scale (paper III): 0 = neither effusion nor synovial thickening, 1 = minimal amount of joint effusion and/or synovial thickening, 2 = moderate amount of joint effusion and/or synovial, and 3 = extensive amount of joint effusion and/or synovial thickening. Power Doppler signals were scored on a 0-3 scale (paper III): 0 = no flow in the synovium, 1 = minor, or single vessel signals (one or more), 2 = moderate, or confluent vessel signals in less than half of the area of the synovium, and 3 = major, or vessel signals in more than half of the area of the synovium [93].

The sonographers collected static images from ultrasound examinations and AM developed a novel ultrasonographic atlas of osteophytes including representative example images of each grading from the different groups of finger joints (paper I).
Reliability was tested on static ultrasonographic images selected from a database. Ida Kristin Haugen (IKH) randomly selected images showing varying severity of osteophytes (n=150; paper I), grey scale synovitis (n=103; paper III) and power Doppler signals (n=20; paper III), and rearranged the images for a second scoring. AM and HBH separately performed two scorings (one week apart) with use of the osteophyte atlas (paper I) or an ultrasonographic atlas of synovitis in RA patients [93] as reference. They were blinded for previous scoring results, and the calculations were performed by IKH.

*The OMERACT reliability exercise*

Ten sonographers participated in a real-life reliability exercise (paper II). Five identical General Electric Logic E9 machines (GE, Medical Systems, Milwaukee, Wisconsin, USA), equipped with two multi-frequency linear probes (hockey stick 8–18 MHz used for scoring of cartilage and regular probe 6–15MHz used for scoring of osteophytes) both operating at a frequency of 15 MHz were used (the ultrasonography machines were supplied free of charge by GE Norway). The same grey scale setting with 50% gain and positioning of focus at the level of interest was pre-fixed in all machines and not modified during the study.

Osteophytes were scored as described above. By keeping the joints in maximal flexion, cartilage in the 2\textsuperscript{nd}-5\textsuperscript{th} MCP joints was assessed with the joints maximum flexed in a longitudinal dorsal scan at the level of the mid-portion of the metacarpal head and scored semiquantitatively on a 0-3 scale as previously described [106]: 0 = normal cartilage, 1 = loss of anechoic structure and/or focal thinning of cartilage layer OR irregularities and/or loss of sharpness of at least one cartilage margin, 2 = loss of anechoic structure and/or focal thinning of cartilage layer AND irregularities and/or loss of sharpness of at least one cartilage margin, and 3 = focal absence or complete loss of the cartilage layer.

**4.3.4 Conventional radiography**

Digital bilateral hand radiographs with PA view were obtained in 117 of 128 patients at baseline (of which five patients only imaged the right hand, paper I), and in all 87 patients at follow-up (paper III and IV).

Blinded to clinical and other imaging findings, IKH scored the baseline images according to the KL scale and the OARSI atlas (used in paper I) [123, 131]. The paired images from baseline (2008-09) and follow-up (2013) were re-read by IKH with known time-sequence (used in paper III and IV). This evaluation also included the first examination in 2001-03
but was not included in the present papers. Intra-reader reliability for radiographic status and change scores were ‘good’ to ‘very good’ [176].

The KL scale gives a global score of the DIP, PIP, MCP and CMC-1 joints on a 0-4 scale based on the presence and size of osteophytes, JSN, sclerosis, cysts and altered shape of bony ends: 0 = no OA, 1 = doubtful OA, 2 = definite minimal OA, 3 = moderate OA, 4 = severe OA [123]. Epidemiological studies often use KL grade ≥ 2 as the definition of OA.

The OARSI atlas shows example images of different grades of individual radiographic OA features such as osteophytes (grade 0-3), JSN (grade 0-3), erosions (grade 0-1), pseudo-widening (grade 0-1), cysts (grade 0-1), sclerosis (grade 0-1) and malalignment (grade 0-1) [131]. Adaptation was made from the original OARSI atlas: all features were scored in the DIP, PIP (including the IP-1), MCP and CMC-1, as done for the KL scale.

### 4.3.5 Magnetic resonance imaging

A 1.0 T extremity MRI scanner (ONI, General Electric Healthcare, Waukesha, Wisconsin, USA) was used for all examinations. The patients rested in a comfortable chair during the examination with their hand resting in a cylindrical coil (diameter 10 cm). The hand was fixed to a plate and the space around the plate and hand was filled with rubber sponge to ensure extended fingers and reduce motion artefacts.

The image sequences were tested in a pilot study in collaboration with a musculoskeletal radiologist and MRI technicians. Coronal, sagittal and axial T1- weighted fat-saturated pre- and post-Gd (0.1 mmol Gd/kg body weight; Magnevist, Bayer Schering Pharma AG, Leverkusen, Germany) images were acquired from a 3D dual-echo Dixon technique [177] in addition to coronal and axial Short Tau Inversion Recovery (STIR) images. Both T1 and T2 differences may contribute to the contrasts on the STIR sequence, but in this protocol the T1 contrast was made dominant due to short TE time.

One physician (IKH) later read all MRI scans according to the Oslo Hand Osteoarthritis MRI score [158], unaware of clinical and other imaging data. Osteophytes were graded 0-3 in the distal and proximal part of the joint separately, and the largest score in each joint was used in this thesis. In a reliability exercise with two other colleagues, IKH has demonstrated high intra- and inter-reader reliability for scoring of osteophytes with use of this scoring system and its corresponding atlas (intraclass correlation coefficient, ICC>0.88), and MRI-defined osteophytes have also shown good validity against CR [58, 158]. JSN, cysts,
malalignment, synovitis, flexor tenosynovitis, BMLs, collateral ligament discontinuity, BMLs at collateral ligament insertions, erosions and bone attrition were also scored but not included as outcome measures in this thesis. All MRI scans were read on large screens (24 inches) with use of Picture Archiving and Communication System (PACS) Sectra software (IDS5, SECTRA, Linköping, Sweden).

4.4 Statistical methods

AM in collaboration with a statistician performed all statistical analyses in papers from the Oslo Hand OA cohort presented in this thesis. Software included the Statistical Package for the Social Sciences (SPSS) Statistics for Mac, Version 17.0 (SPSS Inc., Chicago, IL, USA) in paper I, and IBM SPSS Statistics for Mac, Version 21.0 (IBM Corp., Armonk, NY, USA) in paper III and Version 24.0 (IBM Corp., Armonk, NY, USA) in paper IV. Philippe Aegerter (MD, PhD) performed the statistical analyses in paper II using SPSS Statistics for Windows, Version 21.1 (IBM Corp., Armonk, NY, USA). P-values below a cut-off of 0.05 were considered statistically significant. Only information regarding the main analyses is presented in this section whereas details in the statistical approaches are presented in the respective papers.

4.4.1 Descriptive analyses and group comparison

In all papers, we presented means with standard deviations (SD) and/or medians with interquartile ranges (IQR) depending on the distribution of the variables. Categorical variables were presented as numbers with percentages of totals. We examined group differences (e.g., of participants completing versus missing, or joints with or without erosions) using parametric and non-parametric test for continuous variables as well as Pearson's chi-squared test or Fisher’s exact test for categorical data.

4.4.2 Reliability

The observed agreement was calculated as the percentage exact agreement (PEA) of which the scoring value was identical between all readers (i.e., inter-reader) or between the first and second reading (i.e., intra-reader). PEA = 100% is perfect agreement. Percentage Close Agreement (PCA) was similarly calculated as the percentage of occasions of which the difference was ≤1, and should ideally approach 100%.
Kappa statistics are statistical measures of agreement, or concordance, between raters or among repeated measures by a single rater. It is generally thought to be a more robust measure than simple percent agreement, as kappa takes into account the possibility of the agreement occurring by chance [178]. In the current thesis, intra- and inter-reader reliability was assessed by using standard Cohen’s kappa (κ) for binary assessment (paper II) and weighted kappa (κw) with absolutes weights for semiquantitative assessments (paper I, II and III) [179, 180]. Weighted κ is useful when there are ordered response categories and takes into account the seriousness of disagreement [180]. Global inter-observer reliability between more than two raters (paper II) was obtained by calculating the mean of the n(n-1)/2 kappas obtained from each pair of raters, n being the number of sonographers (i.e., Light’s Kappa) [181, 182]. Kappa coefficients were interpreted according to Landis and Koch (poor = 0, slight = 0.01–0.20, fair = 0.21–0.40, moderate = 0.41–0.60, substantial = 0.61–0.80, excellent = 0.81–1.00) [183].

4.4.3 Test performance

Sensitivity and specificity are statistical measures of the performance of a binary classification test (here: ultrasound). Sensitivity measures the proportion of true positives, which are correctly identified as such, while specificity measures the proportion of negatives correctly identified. In paper I, we calculated the sensitivity and specificity of ultrasound in detection of osteophytes at the joint level (dichotomized as absent/present) using dichotomized osteophyte assessments by MRI and CR or clinical examination of bony enlargement as reference. Identical calculation was performed for ultrasound with MRI as reference in paper IV.

As a measure of accuracy, we also calculated PEA between ultrasound, MRI, CR and clinical examination at the joint level in paper I, defined as the proportion of identical agreement on semiquantitative (0-3) assessments of osteophytes or bony enlargement upon palpation. PCA was similarly calculated for ultrasound, MRI and CR as the percentage of occasions of which the osteophyte score difference was ≤1.

Comparison of modalities at the patient level (sum score) in paper I was conducted by use of the Friedman’s Test. Post-hoc analyses compared two and two modalities with Wilcoxon Signed-Rank Tests and Bonferroni correction (comparing three modalities gave an adjusted significance level at p<0.017).
4.4.4 Univariate and multivariate regression analyses

In longitudinal analyses at the joint level, we applied logistic regression with Generalized Estimating Equations (GEE; exchangeable correlation matrix) in order to account for several joints within one patient (i.e., within-subject dependency), presented as odds ratios (OR) with 95% confidence intervals (CI) [184].

In paper III, we calculated whether ultrasound-detected grey scale synovitis or power Doppler signals at baseline (independent variable) could predict radiographic progression (dependent variable) in the same joint at follow-up. We used four definitions of radiographic change: (1) increasing global OA severity according to the KL scale, (2) progression of osteophytes, (3) progression of JSN and (4) incident radiographic erosions in joints without erosions at baseline. Joints with no potential for progression from baseline (i.e., KL = 4, osteophyte = 3, JSN = 3 and presence of erosions) were excluded from the respective analyses, and joints without progression served as reference. In multivariate analyses, age, sex, BMI at baseline and follow-up time were included as covariate. Adjusted analyses were repeated with additional adjustment for baseline KL grade. Analyses on erosive development were also adjusted for absence/presence of other erosive joints at baseline.

In paper IV, we selected joints with KL grade = 0 or no clinical bony enlargements at baseline and examined whether ultrasound-detected osteophytes (independent variable) could predict incident radiographic OA features (KL grade ≥ 1, radiographic osteophytes or JSN) or clinical bony enlargement (dependent variables) in the same joint at follow-up. Joints without sonographic osteophytes served as reference. In multivariate analyses, age, sex, BMI at baseline and follow-up time were included.

4.5 Legal and ethical aspects

The studies reported in paper I-IV were conducted according to the ethical principles of the Declaration of Helsinki. All participants provided a written informed consent prior to entering the studies. The regional ethical committee approved the studies, and the Data Inspectorate approved storage of data. External funding sources did not influence or comment on planned methods, protocol, data analysis or drafted reports.
5. Summary of results

5.1 Paper I

Ultrasonographic assessment of osteophytes in 127 patients with hand osteoarthritis: exploring reliability and associations to MRI, radiographs and clinical joint findings

The main objectives in this cross-sectional study were to examine the prevalence of sonographic osteophytes in 127 patients with hand OA recruited from a rheumatology outpatient clinic, to develop a standardized ultrasonographic imaging atlas with example images of semiquantitative scoring of osteophytes in hand OA, to test the reliability of this scoring system, and to explore the construct validity of ultrasound-detected osteophytes in hand OA with MRI, CR and clinical examination as reference.

The participants underwent ultrasonographic examination of both hands, in which the CMC-1, MCP, PIP (including the IP-1) and DIP-joints were scored for osteophytes on a 0-3 scale. In total 117 participants also had bilateral hand radiographs assessed according to the KL scale and the OARSI atlas for individual radiographic features, as well as a clinical examination of bony enlargement upon palpation in the same finger joints. Finally, 107 participants had MRI examinations of their dominant hand with assessment of osteophytes in the 2nd to 5th PIP and DIP joints.

All participants had sonographic osteophytes in at least four finger joints, and the prevalence of osteophytes was similar in the dominant and non-dominant hand. Ultrasound detected osteophytes in more than half of the joints (53%) and statistically significantly more than CR and clinical examination. Of all modalities, CR detected the lowest number of joints with pathology, especially in the PIP and DIP joints, whereas clinical examination was less sensitive for bony enlargements in the thumb base.

Ultrasound had high sensitivity (0.83) and specificity (0.75) to detect osteophytes with MRI as reference, and the percentage of close agreement was excellent (96%) between the two modalities. Severe pathology (grade 2-3) was detected more often by ultrasound than by MRI (p<0.001). MRI-detected osteophytes in joints where ultrasound could not detect pathology were grade 1 on MRI in 98% of the joints.
A novel ultrasonographic imaging atlas of osteophytes in hand OA was developed, with examples of osteophytes grade 0 to 3 in CMC-1, MCP, PIP and DIP joints. Two sonographers used the novel ultrasound atlas as reference for a reliability exercise, with excellent inter- and intra-reader reliability (PEA>88%, PCA=100% and weighted kappa >0.91).

We concluded that osteophytes are very common in hand OA patients with established disease, and that ultrasound and MRI show good agreement in the detection of osteophytes in hand OA. With the application of a novel ultrasonographic imaging atlas of osteophytes, excellent agreement on static images was made between two sonographers. These results support the use of ultrasound for detection of osteophytes in patients with hand OA and suggests the ultrasonographic atlas to be a helpful tool in future hand OA studies.
5.2 Paper II

Global ultrasound assessment of structural lesions in osteoarthritis: a reliability study by the OMERACT ultrasonography group on scoring cartilage and osteophytes in finger joints

The main objective of this cross-sectional reliability study was to assess the real life reliability of ultrasonographic assessments of osteophytes and cartilage in ten patients with hand OA.

Osteophytes were assessed according to the ultrasound atlas in paper I. Since only two of the sonographers were familiar with this scoring system, the same reliability exercise as in paper I on static images was conducted for the remaining sonographers with excellent reliability ($\kappa_w$ values $>0.9$). Therefore, no practical training was performed before the exercise on patients.

Cartilage was assessed according to a novel semiquantitative 0-3 scoring system in a longitudinal scan of MCP joints. On the first day of the study, the sonographers reached consensus on the scanning technique and on how to use the new scoring system by grading formerly collected static images of different cartilage lesions as well as performing practical ultrasonography training.

Each patient-based ultrasonography examination included bilateral scoring of cartilage in the 2nd-5th MCP joints by use of a hockey stick (i.e., 8 joints) and osteophytes in the CMC-1, MCP, PIP (including IP-1) and DIP joints by use of a linear probe (i.e., 30 joints).

Osteophyte scores were evenly distributed, and the intra- and inter-reader reliabilities were substantial to excellent ($\kappa$ range 0.68–0.89 and mean $\kappa$ 0.65 (day 1) and 0.67 (day 2), respectively). Cartilage scores were unevenly distributed, and the intra- and inter-reader reliability was fair to moderate ($\kappa$ range 0.46–0.66 and mean $\kappa$ 0.39 (day 1) and 0.33 (day 2), respectively). Due to unsatisfactory results on the scoring of cartilage in patients with hand OA, a web-based exercise on 125 static images of cartilage was subsequently performed 1 month after the reliability exercise on patients. The web-based exercise showed acceptable agreement for cartilage being normal ($\kappa$ 0.47) or with complete loss ($\kappa$ 0.68), but poor for the intermediate scores ($\kappa$ 0.22–0.30).
We concluded that the use of the examined 0-3 semiquantitative ultrasonography scoring system for cartilage pathology in hand OA is not recommended (while normal or total loss of cartilage may be assessed). However, the OMERACT ultrasonography group would endorse the use of semiquantitative scoring of osteophytes with the ultrasonography atlas as reference. The finding of high reliability for scoring of osteophytes suggest that ultrasonography is a promising tool for diagnosing and follow-up of finger joints in patients with hand OA.
5.3 Paper III

Ultrasound-detected inflammation predicts radiographic progression in hand osteoarthritis after 5 years

The main objectives in this longitudinal study were to examine how prevalent ultrasound-detected synovial inflammation were in 78 patients with hand OA recruited from a rheumatology outpatient clinic, to test the reliability of ultrasonographic assessments of joint inflammation, and to explore the predictive value of synovial inflammation on radiographic OA progression in the same finger joint.

The participants underwent ultrasonographic examination of both hands at baseline, in which the CMC-1, MCP, PIP (including IP-1) and DIP-joints were scored for grey scale synovitis (combined score of synovial hypertrophy and effusion) and power Doppler signals on a semiquantitative 0-3 scale. The participants also had bilateral hand radiographs at baseline and follow-up that were scored pairwise with known time sequence according to the KL scale and the OARSI atlas for individual radiographic features, as well as clinical examinations of soft tissue swelling upon palpation in the same finger joints.

At baseline, 94% and 42% of the patients had grey scale synovitis and power Doppler signals in at least one finger joint. In joints with definite radiographic OA (i.e., KL grade ≥2), grey scale synovitis was present in 309 of 1078 joints (29%), of which 50 joints (16%) presented power Doppler signals. Synovitis was most commonly mild or moderate.

Ultrasound-detected inflammation predicted KL progression, and dose–response associations were observed for grey scale synovitis grade 1 (OR=2.8, 95% CI 1.8 to 4.2), grade 2 (OR=3.6, 95% CI 2.2 to 5.8) and grade 3 (OR=15.2, 95% CI 6.9 to 33.6), and for power Doppler signal grade 1 (OR=2.9, 95% CI 1.2 to 6.8) and grades 2–3 (OR=12.0, 95% CI 3.5 to 41.0). Statistically significant associations were also observed between ultrasound inflammation and progression of all individual radiographic features (osteophytes, JSN, and erosions), and between clinical soft tissue swelling at baseline and radiographic progression.

A reliability exercise of 103 static images with different grades of grey scale synovitis and 20 images of power Doppler signals demonstrated ‘good’ to ‘very good’ inter-reader reliability (κw=0.74 and κw>0.93, respectively), and ‘very good’ intrareader reliability for both features (κw>0.86).
Our results confirmed that both grey scale synovitis and power Doppler activity predict radiographic progression in hand OA. The association was strong and coherent for all radiographic features. Thus, by detecting inflammation, ultrasound could prove beneficial in predicting future radiographic progression and be used in prospective medical trials of hand OA.
5.4 Paper IV

Ultrasound-detected osteophytes predict the development of radiographic and clinical features of hand osteoarthritis in the same finger joints 5 years later

The main objective in this longitudinal study was to examine whether joints with ultrasound-detected osteophytes that otherwise were assessed as normal (by CR and clinical examination) later develop features of radiographic or clinical hand OA.

The 78 participants underwent ultrasonographic examination of both hands at baseline, in which the CMC-1, PIP (including the IP-1) and DIP-joints were scored for osteophytes on a 0-3 scale. The participants also had bilateral hand radiographs at baseline and follow-up that were assessed according to the KL scale and the OARSI atlas for individual radiographic features, as well as clinical examinations of bony enlargement upon palpation in the same finger joints. In this study, we also included a limited number of joints (second to fifth PIP and DIP joints of the dominant hand in 73 participants) with MRI at baseline.

In radiographically normal joints, ultrasound demonstrated osteophytes in 29% joints, and the highest discordance was found in DIP joints with sonographic osteophytes present in 53% joints. Most of these osteophytes (79%) were small (grade=1) and could be confirmed in 87% of joints where MRI-assessment was available.

Significant associations were found between ultrasound-detected osteophytes and development of both radiographic OA (OR=4.1, 95% CI 2.0-8.1) and clinical bony enlargement (OR=3.5, 95% CI 2.4-5.1), and also incident radiographic osteophytes (OR=4.2, 95% CI 2.1–8.5) and JSN (OR=5.3, 95% CI 2.1–13.4).

Our longitudinal study demonstrated that ultrasound-detected osteophytes (in joints assessed as normal on radiographs and clinical examination) predicted future development of radiographic and clinical osteoarthritic features in the same finger joints five years later. Taken together with a series of other studies, our data suggest that sensitive imaging modalities such as ultrasound (or MRI) should be applied when an early (pre-radiographic) hand OA diagnosis is warranted.
6. Discussion

6.1 Methodological aspects

Methodological limitations may contribute to bias and limit the strength of our study. Bias occurs when systematic errors are introduced into sampling (i.e., how the patients are recruited) or testing (i.e., how the data are collected or by using incorrect statistical analysis). The following section will discuss possible limitations in our studies.

6.1.1 Study design

The Oslo hand OA cohort is a hospital-based, single-center and observational prospective cohort study. A prospective cohort study is the strongest observational study design and suitable for studying predictors and prognostic factors [185-187]. With longitudinal observation (paper III and IV) of a group of similar individuals whose joints differ with respect to OA features assessed with ultrasound, one can determine how these features affect certain outcomes, and has the advantage of being tailored to collect specific exposure data. The disadvantage of a prospective cohort study may be the long follow-up time that is required for disease features to occur, and also potential high loss to follow-up. In the Oslo hand OA cohort, 61% and 42% of those initially enrolled met at the first and second follow-up. Whether non-responders did not meet due to improvement or worsening is unknown. However, at inclusion in 2001-03, there were no differences between participants with complete follow-up data and participants without, except for non-completers having statistically significantly lower educational level and more often being smokers [188].

Paper I and II was cross-sectional in design, and therefore limited abilities to investigate cause and effect. Therefore, the focus in these papers was on reliability and validity of ultrasound. Test-retest readings of static, restructured and anonymized images were performed with one week apart, and it is highly unlikely that the readers recalled the first scores. In the patient-based exercise in paper II, ten patients were scored with four hours apart. Test-retest reliability is sensitive to the time interval between testing, and although many joints were scored in each patient, an observer error may arise if readers recall certain joints with such short time frame.
Strengths of our study design include an extensive data collection involving several imaging modalities and clinical examinations that require trained personnel and equipment, of which especially MRI is associated with high costs, and extensive patient-reported outcomes.

### 6.1.2 Study population

For scientific results to be generalizable to a larger population, the study population must represent the general population it aims to investigate (i.e., external validity). A possible limitation of a cohort study is selection bias due to a non-random sample of a population, causing higher likelihood for some members of the population to be included and reduced external validity. Traditionally, data from hand OA cohorts have been based on large, population-based surveys with substantial numbers of participants and often self-reported data [27, 51, 136, 189-194], whereas few studies have recruited patients from a clinic or outpatient-clinic [195-198]. In the Oslo hand OA cohort, participants were recruited from the outpatient clinic at Diakonhjemmet Hospital and had mostly been referred from their general practitioner with questions about hand OA or other differential diagnoses such as inflammatory rheumatic diseases. Therefore, the participants represent a preselected group with a more distinct disease, and it is possible that findings in our cohort might not represent the general hand OA population and limits the external validity.

In addition to the selection process, generalizability of our cohort may be biased by the overrepresentation of women and elderly patients. The female/male ratio in our cohort was higher than what is common in population-based hand OA studies [27, 51, 194], whereas similar ratios have been reported in other hospital-based cohorts [196-198]. Hand OA may affect both women and men, and a study from the Framingham cohort found radiographic hand OA in almost as many men (38%) as women (44%) with age between 40 and 84 years [27]. OA in certain age groups (below 60 years) and joints (wrist and MCP joints) was even slightly higher in men. However, symptomatic hand OA seems to be more prevalent in women (14) than in men (7%) [27]. Severe hand-related disability that affects daily function is shown to be more common in females than males and increases with age [193]. Women have lower grip strength and may earlier reach a level of strength that disturbs everyday activities. These factors may explain why more women than men seek medical care and were more likely to be recruited to our cohort.

Similar cohorts examining the validity of ultrasound have been performed in Leeds (United Kingdom), Ghent (Belgium) and Leiden (the Netherlands). Keen et al. compared ultrasound
with CR in 37 patients (31 female, median age 57) with hand OA (34 subjects met the ACR criteria) [89]. Wittoek et al. performed ultrasound, CR and MRI on nine patients (with EOA and five with non-erosive hand OA (median age 60.9 and 63.2 years, respectively) who all fulfilled the ACR-criteria for hand OA and were recruited from the outpatient clinic [95]. Kortekaas et al. compared ultrasound with CR and MRI in 16 patients with hand OA (10 women, 13 with erosive OA, median age 57 years) [159]. Hence, all these studies have similar characteristics of patients to the Oslo hand OA cohort, but the Oslo cohort is (at publication date) by far the largest longitudinal observational hand OA cohort with both ultrasound, MRI and CR.

In paper IV, we investigated if ultrasound-detected osteophytes in joints otherwise assessed as normal could predict later radiographic or clinical OA. The high age and large number of joints with radiographic OA at baseline limits the external validity of the results to patients with established OA only. A similar approach in early OA patients, or even patients yet not fulfilling the ACR criteria, would be of interest.

Finally, misclassification of patients is an important source of bias and can occur if the inclusion- and exclusion criteria are poorly defined or utilized. In the Oslo hand OA cohort, other chronic inflammatory rheumatic diseases (e.g., RA, spondyloarthritis, psoriatic arthritis, hemochromatosis or gout) were excluded at baseline. However, early signs and symptoms of hand OA may be difficult to distinguish from other inflammatory joint diseases, and 13 of the initial 209 participants were later reclassified as inflammatory arthritis and excluded in the papers included in the current thesis.

6.1.3 Study duration

Studies of predictors must have sufficient observational time to detect changes, especially in (usually) slowly developing and progressing conditions such as OA [199]. However, recommended duration of studies also depends on responsiveness of individual imaging biomarkers [200]. Recent large observational cohorts with focus on risk factors for incidence and progression of knee OA, such as the MOST and the OAI study, have applied 48 to 84 months of follow-up [201-203]. Two studies have examined rates of cartilage loss in the OAI and found only a modest cartilage loss of 2-3% over the first year of follow-up, although the rate of loss differed considerable between subjects and locations in the knee [204, 205]. The participants in the Oslo hand OA cohort were followed for more than 11 years, but the longitudinal papers (III and IV) in this thesis have applied data from the
second and third visits with a mean follow-up time of 56 months. A cross-section of persons with existing disease was enrolled and the sample is thus heterogeneous in terms of disease duration and previous rates of progression. The 78 patients with longitudinal observations in paper III and IV had mean disease duration of 18.5 years (range 9 to 41 years). It is possible that disease of longer duration is more stable than recent onset disease with more rapid progression, as shown for knee OA [206], which may bias analyses of progression. To accommodate this issue, analyses were performed on joint level and joints with no potential for progression (i.e., highest radiographic KL, JSN and osteophyte score) were excluded.

### 6.1.4 Outcome measures

An ideal cohort study uses objective and unbiased outcome criteria. Validation of ultrasonography compared to MRI, CR and clinical examination was the main objective in our study. We observed ‘very good’ intra- and inter-reader reliability for the MRI (ICC>0.88) and radiographic (ICC>0.87) assessments. Intra- and inter-reader reliability for ultrasonographic assessment of osteophytes was ‘excellent’ in both static images and the patient based exercise (κw values >0.9), and ‘good’ to ‘very good’ for grey scale synovitis and power Doppler signals (κw values >0.74). Unfortunately, a reliability exercise was not performed for the clinical examination of bony enlargements and soft tissue swelling. However, the same rheumatologist (BSC) with more than 20 years of experience within the field of rheumatology performed these examinations, which limit inter-rater bias.

In this thesis, radiographs with PA view were used to assess radiographic severity of hand OA according to the KL scale and OARSI atlas. In the longitudinal analyses (paper III and IV), radiographs were scored in known time sequence, which may lead to overestimation of progression. However, blinding may increase the error rate and un-blinding is the recommended approach to serial images [207]. Furthermore, we excluded joints that could not progress further on the scale of 0-3 (JSN and osteophytes) or 0-4 (KL). However, there are concerns about the end stage of radiographic scoring systems, as Guermazi and colleagues recently highlighted in a paper where they looked at MRI changes over 30 months in knee OA joints with radiographic KL grade 4 at baseline (i.e., ‘end stage’) [208]. MRI frequently detected further cartilage loss and fluctuation of BMLs, effusion, synovitis, and Hoffa-synovitis at follow up. Thus, KL grade 4 knees could still progress and the term ‘end stage’ seems not to be appropriate.
Hand OA has a predilection for DIP, PIP and thumb base joints [25-27], whereas MCP joints are less frequently involved [27]. The participants in the Oslo hand OA cohort underwent bilateral hand radiographs, ultrasonographic examination and clinical examination of CMC-1, MCP, PIP and DIP joints, but only the 2nd to 5th DIP and PIP joints were imaged with MRI. In most cases, the exclusion of MCP joints with MRI was due to limited field of view, whereas MRI of the thumb base would have required a separate acquisition. As such, feasibility and costs balanced the number of joints with available MRI.

6.1.5 Statistical considerations

Analyses exploring risk factors for OA progression are prone to null results, as elegantly described by Zhang et al. [209]. However, based on the fact that statistically significant associations between synovitis and radiographic progression were demonstrated in paper III, and between osteophytes and incident radiographic hand OA features in paper IV, this issue is not relevant. Our results were also in line with previous studies [142, 198], which strengthen the validity of the current results.

Internal validity refers to the strength of the inferences from the study; whether the exposure (inflammation or osteophytes) actually caused a difference in the outcome (incidence or progression of radiographic OA) [210]. The internal validity may be compromised by not having a control group, but our analyses were performed by GEE on joint level not at patient-level, which account for intra-person dependency [184]. The large number of joints included in the analyses may further have enhanced the internal validity.

The degree of radiographic progression, which was our outcome in the analyses, depends on the follow-up time, age, gender and (possibly) BMI, which we wanted to adjust for in our analyses (paper III and IV). Few studies have explored whether anti-inflammatory treatment affect future radiographic progression. Verbruggen et al. demonstrated less erosive development in swollen joints in persons on anti-TNF therapy as compared to placebo [74]. However, future studies are needed to confirm these findings. In the Oslo hand OA cohort, patients were not treated with synthetic or biological disease-modifying antirheumatic drugs. Some patients reported use of nonsteroidal anti-inflammatory drugs (NSAIDs) (39.7%) and prednisolone (5.1%), but multivariate analyses including these medications did not change our results, as expected, as they most likely do not affect the risk of radiographic progression.
6.2 Main results

6.2.1 Prevalence of inflammation in hand OA

Essential structural features of hand OA, such as osteophytes, JSN and erosions, were frequently present in our cohort (paper I). Perhaps more interesting was the high amount of inflammation in our cohort (paper III).

OA synovial tissue typically displays a mild to moderate degree of inflammation on standard histological staining [211]. In smaller histological studies, the prevalence of inflamed synovium ranges greatly from approximately half to nearly all tissue samples depending on patient pre-selection and OA severity [212]. When comparing microscopic synovial changes in early and late OA, the literature has shown conflicting results [212], probably due to different definitions of ‘early’ and ‘late’ OA.

At the ‘macroscopic’ level, synovial inflammation is commonly found in cohorts of persons with moderate pain and concurrent radiographic OA. In our study, we found grey scale synovitis present in 94% and power Doppler signal in 42% of 78 patients (paper III). At the joint-level, 29% of 1078 joints with KL grade ≥2 had grey scale synovitis. MRI-data from the same cohort demonstrated synovitis in median (IQR) 6 (4–7) of potentially eight interphalangeal joints of the dominant hand, with moderate to severe synovitis (grade 2–3) being infrequent [67]. Similar prevalence was demonstrated in a study from Leiden (Netherlands) where nearly all (96%) of the patients had sonographic grey scale synovitis in at least one finger joint, and median (IQR) number of affected joints was 6 (0-13) of potentially 30 finger joints [213].

6.2.2 Reliability of ultrasonography in hand OA

For all imaging modalities, the skill of the assessor may be a limitation for the examinations. This is especially the case for US, where evaluations are based on acquisition and interpretation. Thus, the quality of ultrasonographic examinations is related to the operator skill, training and experience. Although quantitative assessment of ultrasound findings in clinical practice is often neglected, accurate reports of ultrasonographic data are useful when evaluating a patient during follow-up or after medical interventions. To overcome the operator dependency, consensus on joints to be evaluated, domains to be scored, definitions of domains and atlases of scaling systems have been made for knee, hip and hand OA [98,
The following sections will discuss the reliability of osteophyte, cartilage and inflammatory assessments with ultrasonography.

**Osteophytes**

Accumulative evidence in the literature supports the use of ultrasound in the assessment of osteophytes. With the application of a novel ultrasonographic imaging atlas of osteophytes in hand OA (paper I), we demonstrated excellent intra- and inter-reader reliability in the assessment of static images (paper I). However, reliability based on stored images limits the variability related to the performance and technique of the ultrasound examination. Therefore, a patient based exercise was performed (paper II), and we found high reliability for the scoring of osteophytes. The sonographers participated in a web-based reliability exercise in advance accompanied by the osteophyte ultrasonography atlas, and did not elsewhere train on the semiquantitative scoring before the patient based exercise. As such, the use of a reference atlas may have contributed to the good results. An atlas can be helpful by permitting the sonographer to have a direct comparison between the scanned ultrasonography findings and examples of defined scoring level images in the atlas. It is thus plausible that the use of a reference atlas can facilitate good reliability of ultrasound examination in multicenter clinical trials [93].

There are limited number of studies examining the reliability of ultrasonographic assessment of osteophytes in hand OA, and the number of patients and joints included are inferior to our study, but the results are in concordance with those presented in the current thesis. Wittoek et al. examined the inter-observer agreement between two sonographers who evaluated the presence of osteophytes on a dichotomous score (i.e., yes/no) in 90 joints from five patients, and found excellent agreement (PEA 92%, $\kappa=0.833$), whereas MRI of osteophytes did not reproduce similar good agreement (PEA 61%; $\kappa=0.152$) [95]. Kortekaas et al. examined intra-reader reliability for one sonographer in five patients, and found acceptable reliability for of osteophytes (each joint graded on a semiquantitative 0-3 scale) (ICC=0.71) [90].

Similar studies have been performed in knee and hip OA patients, which support the proof of concept of ultrasound application in OA patients. Abraham et al. found substantial to excellent inter-reader agreement between two sonographers on the presence of osteophytes in 18 participants with knee OA ($\kappa=0.65$ to 0.88) [217]. Semiquantitative assessment of osteophytes (on a 0-3 scale) in 13 patients with knee OA have shown substantial intra- and
inter-observer agreement between 11 sonographers (mean $\kappa=0.73$ and 0.60, respectively) [94]. Finally, ultrasound assessment of osteophytes on a 0-3 scale in 100 hips (femoral neck) was reported by Qvistgaard et al. to be moderate to excellent for intra- and inter-reader agreement (ICC=0.80 and 0.65, respectively, and $\kappa=0.75$ and 0.49, respectively) [214], although the reliability was performed on stored still images.

With the application of a tibiofemoral osteophyte atlas similar to the atlas for osteophyte scoring in finger joints (paper I), Koski et al. found substantial agreement between 14 sonographers in the semiquantitative scoring of osteophytes in knee OA (mean intra- and inter-reader $\kappa=0.64$ to 0.75 and 0.48 to 0.70, respectively) [216]. The agreement was lower than reported in our cohort, which is explained by the high number of sonographers that induce more variation in average agreement but also increase the strength of their study, as the average agreement was still substantial.

**Cartilage**

Several studies on cartilage in OA patients have been performed. They have shown ultrasound to be reliable and valid for qualitative evaluation of cartilage pathology (i.e., altered echogenicity and thinning) in cross-sectional studies, primarily of large joints such as the knee [103, 217-221], whereas semiquantitative scoring systems of femoral cartilage have shown fair to substantial agreement [94, 222, 223].

In the small joints of the hands, few studies have been performed, but an important finding is that ultrasound may reliably differentiate between normal and pathological cartilage in MCP and PIP joints of both RA and hand OA patients [104, 106]. A semiquantitative evaluation of different degrees of cartilage pathology in MCP joints in patients with RA demonstrated good reliability [107]. In the present study, however, even if highly experienced sonographers agreed on the scoring system, the inter-observer reliability was not satisfactory (paper II). Ultrasound assessment of cartilage has several limitations. First, due to acoustic window only a limited area of the cartilage is available for scanning. In addition, as pathology in the cartilage develops, the physics of sound waves in this tissue changes. Moreover, the scanning angle is of major importance, as linear measurements may be distorted if not performed perpendicular to the cartilage lining [20]. Additionally, since the cartilage may not be uniformly damaged, obtaining high reliability would require the sonographers to evaluate exactly the same part of the cartilage, which is difficult to control for. For these reasons, evaluation of cartilage pathology may be difficult in OA patients.
Even if our study did not support the use of the present semiquantitative scoring system of cartilage pathology in hand OA, there was good agreement for scoring cartilage with normal cartilage as well as complete loss of the layer. This supports the previous results of the OMERACT ultrasonography group [106]. However, MCP joints are less affected by OA than the interphalangeal joints and have limited value. With sufficient resolution of the ultrasound probes, cartilage of the interphalangeal joints may be reliably visualized.

**Inflammatory features**

The additional application of an ultrasound atlas enables short learning time for the assessment of specific lesions, and good agreement have been demonstrated between experienced and less experienced sonographers in the assessment of inflammatory features in RA patients [93]. Although intended for RA patients, we used the same atlas and found ‘good’ to ‘very good’ intra- and inter-reader agreement for sonographic assessments of grey scale synovitis and power Doppler signals on still images of hand OA joints (paper III). To examine reliability across varying degree of ultrasound experience, we also included a medical student with limited ultrasonographic experience (Pernille Stendal Robinson). With the application of the reference atlas [93], the medical student achieved as good intra- and inter-reader reliability for scoring of grey scale synovitis and power Doppler signals as the sonographers with moderate (AM) and long (HBH) experience [224]. We acknowledge that evaluation of patients will also depend on the performance of the actual examination and not only interpretation of images, which may require additional training and experience. Because ultrasound is an operator dependent modality, our results support the inclusion of reference atlases in ultrasound studies of hand OA patients.

Other groups have performed similar studies on the reliability of ultrasonographic assessments of inflammation in hand OA, with comparable results. Wittoek *et al.* found excellent inter-observer agreement between two sonographers in the detection of grey scale synovitis (PEA 98%; $\kappa=0.931$) and effusion (PEA 92.4%, $\kappa=0.841$) in patients with hand OA, whereas the reproducibility of MRI was good for the detection of synovitis (PEA 85%, $\kappa=0.581$), but only moderate for effusion (PEA 75%; $\kappa=0.500$) [95]. Kortekaas *et al.* examined intra-reader reliability for one sonographer in five patients, and found moderate to good variability for effusion (ICC=0.73), synovial thickening (ICC=0.73) and power Doppler signals (ICC=0.57) [90].
Several studies have examined the agreement of ultrasonographic assessment of inflammation in finger joints of RA patients, and a systematic literature review of 35 studies from 2010 concluded that highly trained observers demonstrate good intra- and inter-observer reliability of still-image interpretation, especially for power Doppler [225]. Reliability in semiquantitative and binary scoring appeared similar, but when the observer is responsible for acquiring and interpreting the image, agreement was more variable [225].

Several studies on knee and hip OA support the use of ultrasonography of inflammatory features. Riecke et al. demonstrated substantial inter-rater agreement between two sonographers for knee effusion and inflammation in different compartments of the knees (ICC=0.79 to 0.89) [226]. Bevers et al. found good inter-reader reliability of synovitis scored dichotomously by two sonographers (κ=0.74) [220], whereas Bruyn et al. showed moderate to good intra- and inter-observer reliability (between 11 sonographers) of a semiquantitative assessment of synovitis in 13 patients with knee OA (mean κ=0.67 and 0.52, respectively) [94]. Abraham et al. found substantial agreement between two trained sonographers in the assessment of effusion size in 18 knee OA patients (ICC=0.70 for right and 0.85 for left knee). Finally, ultrasound assessment of the synovial profile (i.e., the course of the capsule, either concave, flat or convex, and thus including effusion, synovium and the capsule) on a 0-2 scale in 100 hips was reported by Qvistgaard et al. to be good to excellent for intra- and inter-reader agreement (ICC=0.69 and 0.60, respectively, and κ=0.55 and 0.43, respectively) [214], which was comparable to a global ultrasound evaluation of synovitis [214].

In summary, ultrasound shows moderate to good reliable in assessments of grey scale synovitis and power Doppler signals in hand OA, but more patient based studies are warranted.

### 6.2.3 Validity of ultrasonography against MRI and CR in hand OA

Validity of ultrasound includes aspects concerning whether ultrasound is measuring what it intends to measure, i.e., if it is covers relevant OA features and anatomical coverage, if it makes biological sense, and if the outcome measure truly reflects a gold standard [227]. A comprehensive evidence-based expert consensus found ultrasonography examination relevant for most joints in a clinical setting, especially for detecting joint synovitis, effusion and fluid collections [228].
Evidence on ultrasonography validity compared to histology, arthroscopy and imaging modalities in knee OA is increasing [86, 103, 216, 217, 219, 222, 226, 229, 230], which overall shows significant agreement between ultrasonographic assessments of cartilage, osteophytes, synovial inflammation and meniscal pathology with other modalities.

We found significantly more osteophytes with ultrasonography than CR in the small joints of the hands in our cohort (paper I). This is in agreement with several previous studies [89, 90, 231], and it is speculated that the main reason for this is the multiplanar nature of ultrasound, especially its ability to image a joint in the dorsal longitudinal plane, in contrast to the PA projection of CR that limits the view to the lateral and medial aspects of the joint [95]. We also found high sensitivity (0.96) and moderate specificity (0.65) for sonographic osteophytes with CR as reference. As compared to MRI, the specificity of ultrasonography was higher (0.75) and the sensitivity remained good (0.83). CT, although not better validated than MRI, may serve as a reasonable gold standard for the presence of osteophytes. In support of our results, Wittoek et al. demonstrated high agreement between ultrasound and MRI in the assessment of bone erosions, osteophytes and grey scale synovitis of synovial hyper-proliferation in 14 patients with erosive and non-erosive hand OA, but ultrasound seemed less sensitive for DIP joints than MRI in detection of synovitis [95].

6.2.4 The role of inflammation in hand OA

More than 40 years ago in his groundbreaking contribution to OA-related public health, George Ehrlich emphasized the importance of inflammation as an element of OA [232]. The importance of his work was not recognized until recent years, as OA researchers have now proposed a connection between synovitis and the continuation of structural changes in OA [142, 202, 203, 233-238].

Synovitis and structural progression

We found the presence of power Doppler activity and grey scale synovitis in finger joints at baseline to strongly predict subsequent increased joint damage (paper III). Kortekaas et al. showed similar results in a smaller cohort, and the predictive value was even stronger when inflammation persisted [198]. Contrast-enhanced MRI was also applied on the patients in the Oslo hand OA cohort, as well as in a Dutch hand OA cohort, and both studies demonstrated an association between synovitis and both onset and progression of
radiographic hand OA, including development of erosions [142, 238]. A dose response relationship between synovitis and radiographic progression was demonstrated [238].

There is mounting evidence from studies on knee OA to support the important role of synovitis on structural degradation of the OA joint. With arthroscopy, Ayral et al. observed more joint damage after 1 year when the medial perimeniscal synovium had ‘inflammatory’ appearance at baseline (OR=3.11, 95% CI 1.07–5.69) [239]. An MRI study of 347 knees with minimal baseline cartilage damage demonstrated that the presence of synovitis or effusion was associated with an increased risk of fast cartilage loss (OR=3.36, 95% CI 0.91–12.4) [240]. Higher synovial volumes are shown to correlate with other measures of worsening OA, such as KL score, joint space narrowing and subchondral bone marrow lesions [241]. In a large, multicenter EULAR prospective study on more than 500 subjects with knee OA, presence of baseline joint effusion by ultrasound was a statistically significant predictor of joint replacement within 3 years [233]. Keen and colleagues recently used ultrasound to demonstrate short-term synovial responses (synovial thickening, effusion and power Doppler signals) to intra-articular corticosteroid therapy of the knee [242]. Finally, Wang et al. indicate that knee effusion-synovitis on MRI, i.e., a combined measure of joint fluid and thickening, which cannot be distinguished on non-contrast-enhanced MRI, is predictive of, but not predicted by, other structural abnormalities, suggesting a potential role of inflammation in early knee OA changes [243].

The effect of synovitis on structural OA progression is confounded by concurrent pathologies, raising an important question: does synovitis have an independent effect on OA progression? Felson and colleagues recently examined the risk for incident radiographic knee OA after adjusting for structural pathology known to cause synovitis [203]. The authors compared 239 cases and 731 control knees in the MOST cohort and found that cartilage lesions, meniscal damage, synovitis, and BMLs were all risk factors for incident radiographic knee OA. Furthermore, when adjusting for confounding pathologies, synovitis remained associated with incident radiographic OA when total synovitis score was 3 or higher on a 0-9 scale (OR 1.6, 95% CI 1.2–2.1). Another paper from the same cohort showed that knees without OA (i.e., having neither MRI-defined cartilage damage nor tibiofemoral radiographic OA) had a significant increased risk of future cartilage loss whenever effusion-synovitis was present (OR 2.7, 95% CI 1.4–5.1), independent of confounders for inflammation and cartilage loss [234]. These results suggest that synovitis-
effusion assessed on non-contrast-enhanced MRI is an independent predictor of incident radiographic OA.

Taken together, these results support the importance of synovitis as a potential target to treat, as well as demonstrating that ultrasound may be a useful outcome measure for studies treating inflammation. However, we have very limited information that targeting inflammation with medical therapy leads to less structural progression. In a randomized controlled trial of repeated steroid injections in the knee, no beneficial effect on cartilage loss was observed as compared to placebo [72]. Furthermore, trials on hydroxychloroquine, anti-TNF and IL-1\(\alpha\) and \(\beta\) therapy have shown conflicting results regarding the effect on synovitis in hand OA [73-75]. It should be noted that a potential beneficial effect has been demonstrated on structural progression in patients with erosive hand OA treated with anti-TNF [74], but more trials are needed. We need more data to know if targeting synovitis translates into beneficial outcomes for the patients.

### 6.2.5 Pre-radiographic hand OA

Cross-sectional studies in both knee and hand OA have demonstrated that ultrasound is more sensitive than conventional radiography in detecting osteophytes, but little is known about the implication of osteophytes detected by ultrasound before OA becomes apparent on radiographs or clinical examination. In paper IV, we found that finger joints with ultrasound-detected osteophytes (usually small) that otherwise were assessed as normal (by CR and clinical examination) later developed features of radiographic or clinical hand OA. In the field of inflammatory rheumatic disorders, growing evidence has made it clear that early and targeted treatment significantly improves prognosis [244]. Similar strategies may be applied to OA patients if DMOADs become available [82, 245]. Our cohort was indeed of older age and all participants had established OA, and the concept should therefore be examined in a younger cohort without hand OA or early disease.

MRI has been used to examine pre-radiographic changes in early knee OA. A recent case-control study by Roemer et al. looked at repeated MRI-images up to 4 years prior to the diagnosis of radiographic knee OA [202]. They found that presence of Hoffa synovitis, effusion synovitis, medial BMLs and medial meniscal damage increased the risk of OA two years prior to incident radiographic OA, and that the number of present features increased the risk more than the presence of any single feature [202]. Interestingly, cartilage damage only became significantly predictive of OA development one year prior to incident
radiographic OA [202]. On the other hand, very early MRI features that were found 3 or 4 years prior to onset of radiographic OA fluctuated more over time (and could potentially regress) and were less strongly associated with incident OA [202].

Taken together with a series of other studies, MRI can detect early OA. Our result suggests that ultrasonography may have a similar function, but further studies are needed to confirm this.
7. Conclusions

7.1 Answer to research questions

The following answers conclude the research questions stated in section 3.2:

• We developed an ultrasonographic atlas of osteophytes in hand OA with representative images of different grades in CMC-1, MCP, PIP (including IP-1) and DIP joints (paper I).

• Agreement between ultrasound and MRI was substantial. Ultrasound had high sensitivity (0.83) and specificity (0.75) for osteophytes with MRI as reference, and close agreement was excellent (96%) between the two modalities. Large osteophytes (grade 2–3) were detected more often by ultrasound than by MRI (paper I).

• Ultrasound had high sensitivity (0.96) and moderate specificity (0.65) for osteophytes with CR as reference. On the individual joint level, osteophytes were detected more often by ultrasound (53%) than by CR (30%) (paper I).

• All participants had at least four joints with osteophytes, which were most common in CMC-1, PIP and DIP joints, whereas 94% of the participants had grey scale synovitis and 42% had power Doppler signals present in one or more joints. Synovitis was most often mild to moderate. In joints with definite radiographic OA (i.e., KL grade ≥2), grey scale synovitis was present in 29% of joints, of which only 16% presented power Doppler signals (paper I and III).

• We demonstrated excellent intra- and inter-reader reliability in the assessment of osteophytes on static images, and substantial to excellent reliability of osteophyte assessment in a patient based exercise. We also found substantial to excellent agreement in the assessment of grey scale synovitis and power Doppler signals on static images. Agreement on cartilage pathology was only fair to moderate (paper I-III).

• Grey scale synovitis and power Doppler signals strongly and dose-dependently predicted future radiographic OA progression 5 years later (paper III).

• Joints with ultrasound-detected osteophytes that otherwise were assessed as normal (by CR and clinical examination) demonstrated higher odds of developing features of radiographic and clinical hand OA 5 years later (paper IV).
7.2 Clinical implications

Imaging offers a potential supplement to the clinical evaluation of patients with suspected OA, but the choice of correct modality is becoming more complex with major advancement of newer modalities. Radiography will probably continue to be the cornerstone in an image-based OA diagnosis, whereas MRI and ultrasonography gives a more complete assessment of the joint. Ultrasonography offers evaluation of both soft tissue and structural abnormalities, and is proven to be reliable, valid and highly sensitive in the assessment of key OA features. As such, ultrasonography may be used in OA research and clinical trials to evaluate disease activity and treatment response, and in a clinical setting to facilitate an image-based diagnosis of OA.

The combination of sensitive imaging modalities and tissue examination has confirmed a high prevalence of synovial inflammation in all stages of OA, with a number of studies demonstrating that synovitis is related to greater levels of pain and poorer function. Recent work suggests synovitis may even be an independent driver of radiographic OA onset and progression. The ability to identify and quantify synovial inflammation before irreversible joint failure occurs holds great promise for not only early symptomatic benefits but also structure-modification, despite the contrasting results in previous trials on anti-inflammatory treatment in OA. Difficulties demonstrating treatment effects in clinical trials may in part be due to limitations in the way we measure and quantify OA progression with conventional radiographs, and inadequate selection of patients or phenotypes.

Imaging may in the future be used to identify patients who are more or less likely to benefit from interventions in order to increase the likelihood of good treatment response, and future treatment may be guided by selection for particular pathologies, such as those involving synovium and bone. In the field of inflammatory rheumatic disorders, growing evidence has made it clear that early and targeted treatment significantly improves prognosis. Similar strategies may be applied to OA patients if DMOADs become available. More work is required on the molecular pathways initiating and perpetuating cartilage breakdown, bone remodeling and synovial inflammation, because dissection of these pathways may provide novel therapeutic opportunities. In this regard, ultrasonography is a promising tool for detecting OA patients at an early stage, and thus increases the possibility for response to treatment.
8. References


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9. Papers I-IV
ORIGINAL ARTICLE

Ultrasound-detected osteophytes predict the development of radiographic and clinical features of hand osteoarthritis in the same finger joints 5 years later

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ABSTRACT

Background Structural pathology may be present in joints without radiographic evidence of osteoarthritis (OA). Ultrasound is a sensitive tool for early detection of osteophytes. Our aim was to explore whether ultrasound-detected osteophytes (in radiographically and clinically normal finger joints) predicted the development of radiographic and clinical hand OA 5 years later.

Methods We included finger joints without radiographic OA (Kellgren-Lawrence grade (KLG)=0; n=301) or no clinical bony enlargements (n=717) at baseline and examined whether ultrasound-detected osteophytes predicted incident radiographic OA (KLG ≥1, osteophytes or joint space narrowing (JSN)) or incident clinical bony enlargement (dependent variables) in the same joints 5 years later. We applied logistic regression with generalised estimating equations adjusted for age, sex, body mass index and follow-up time.

Results Ultrasound demonstrated osteophytes in 86/301 (28.6%) joints without radiographic OA and 392/717 (54.7%) joints without clinical bony enlargement. These osteophytes were confirmed in the majority of joints where MRI assessment was available. Significant associations were found between ultrasound-detected osteophytes and development of both radiographic OA (OR=4.1, 95% CI 2.0 to 8.1) and clinical bony enlargement (OR=3.5, 95% CI 2.4 to 5.1) and also incident radiographic osteophytes (OR=4.2, 95% CI 2.1 to 8.5) and JSN (OR=5.3, 95% CI 2.1 to 13.4).

Conclusion Ultrasound-detected osteophytes predicted incident radiographic and clinical hand OA 5 years later. These results support the use of ultrasound for early detection of OA.

INTRODUCTION

In the field of inflammatory rheumatic disorders, growing evidence has made it clear that early and targeted treatment significantly improves prognosis.1 Similar strategies may be applied to patients with osteoarthritis (OA) if disease-modifying OA drugs (DMOADs) become available.2 3 Conventional radiography remains the cornerstone in obtaining an image-based OA diagnosis.4 However, previous studies on knee OA have shown that cartilage degradation is well established and often substantial by the time radiographic changes are identified.5 6 Hence, we need instruments to identify OA at an earlier stage.

Osteophyte formation is considered a key feature of OA leading to pain and loss of function.7 Knee OA studies suggest that osteophytes represent a more reliable indicator of early disease than joint space narrowing (JSN).7 Cross-sectional studies in both knee and hand OA have demonstrated that ultrasound is more sensitive than conventional radiography in detecting osteophytes, but little is known about the implication of osteophytes detected by ultrasound before OA becomes apparent on radiographs or clinical examination.

Prepublication history and additional material for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2017-000505).

Key messages

What is already known about this subject?

► Osteophyte formation is considered a key feature of osteoarthritis (OA) leading to pain and loss of function.

► Cross-sectional studies in both knee and hand OA have demonstrated that ultrasound is more sensitive than conventional radiography in detecting osteophytes, but little is known about the implication of osteophytes detected by ultrasound before OA becomes apparent on radiographs or clinical examination.

What does this study add?

► Our longitudinal study demonstrated that ultrasound-detected osteophytes (in joints assessed as normal on radiographs and clinical examination) predicted future development of radiographic and clinical osteoarthritic features in the same finger joints.

How might this impact on clinical practice?

► Taken together with a series of other studies, our data suggest that sensitive imaging modalities such as ultrasound (or MRI) should be applied when an early hand OA diagnosis is warranted.
whereas few studies have explored the predictive value of osteophytes on hand OA progression. In 74 patients with hand OA, MRI-defined osteophytes predicted the development of erosions 5 years later, but no statistically significant associations were found for radiographic progression according to Kellgren-Lawrence grade (KLG) or JSN.11

To our knowledge, no previous study has explored whether ultrasound-detected osteophytes predict future development of radiographic OA. The present objective was to determine whether ultrasound-detected osteophytes in finger joints without radiographic or clinical OA at baseline could predict the development of radiographic or clinical hand OA 5 years later.

METHODS

Patients

Participants in the Oslo Hand OA cohort were recruited from the rheumatology outpatient clinic at Diakonhjemmet Hospital (Oslo, Norway) in 2001–2003 (n=209) with follow-up examinations in 2008–2009 (n=128) and 2013 (n=87).12 13 We included men/women (50–70 years) with hand OA and no diagnosis of systemic inflammatory rheumatic disease.

In the current analyses, we used data from 2008 to 2009 (hereafter referred to as ‘baseline’) and 2013 (hereafter referred to as ‘follow-up’) due to no ultrasound examination in 2001–2003. Of the 87 patients who were examined in 2013, 78 participants had available ultrasound examination at baseline and conventional radiography as well as clinical examination at baseline and follow-up. The 78 participants who were included in analyses and the nine patients who were excluded due to missing data had similar gender distribution (p=0.35), mean age (p=0.59) or KLG sum score at follow-up (p=0.76).

The regional ethics committee approved the study, and all participants gave their written informed consent.

Ultrasound

Sonographic examination of hands was performed at baseline using the same ultrasound machine (Siemens Medical Solutions, Excellence version, Mountain View, California, USA) with fixed settings and a 5–13 MHz linear array transducer. Blinded to clinical and other imaging results, two sonographers (AM and HBH) performed the assessments together and reached consensus on each scoring. The scanning protocol and ‘very good’ reliability have previously been described.8 In the current analyses, we included the n=20 joints most likely to develop OA: the bilateral first carpometacarpal (CMC-1) (longitudinal palmolateral scan), the thumb interphalangeal (IP-1) and the second to fifth proximal interphalangeal and distal interphalangeal (PIP and DIP, respectively) joints (longitudinal dorsal scan from the radial to the ulnar side).

Conventional radiography

Bilateral hand radiographs (posteroanterior view) were obtained at baseline and follow-up. Blinded to clinical and ultrasound findings, one reader (IKH) scored the paired images (20 joints, same as ultrasound) with known time sequence for OA according to KLG (grade 0–4), as well as osteophytes (grade 0–3) and JSN (grade 0–3) according to the Osteoarthritis Research Society International atlas.14 15 Intrareader reliability for radiographic status and change scores were ‘good’ to ‘very good’.16

Incident radiographic OA at follow-up was defined as an increase in KLG from 0 to 1–4, and incident radiographic osteophytes and incident JSN both corresponded with an increase from grade 0 to grades 1–3.

Magnetic resonance imaging

With a 1.0 T extremity MRI unit (ONI; GE Healthcare, Waukesha, Wisconsin, USA), presence of osteophytes was examined in second to fifth DIP and PIP joints of the dominant hand in 73 participants. The acquisition, scoring and good reliability have previously been described.5

Clinical examination

Blinded to imaging results, one experienced rheumatologist (BSC) examined the above-mentioned 20 joints for bony enlargements on palpation (‘absent’ or ‘present’) at baseline and follow-up.

Incident clinical OA at follow-up was defined as development of bony enlargement (from absent to present).

Statistics

Data are presented as mean (SD) values. Independent samples t-test, Mann-Whitney U test and Fisher’s exact test were applied as appropriate to compare variables.

In longitudinal analyses at the joint level, we applied logistic regression with generalised estimating equations (exchangeable correlation matrix), presented as OR with 95% CI. We selected joints with KLG=0 or no clinical bony enlargements at baseline and examined whether ultrasound-detected osteophytes (independent variable) could predict incident radiographic OA (KLG ≥1, osteophytes or JSN) or clinical bony enlargement (dependent variables) in the same joint at follow-up. Joints without sonographic osteophytes served as reference. Analyses were adjusted for age, sex, body mass index at baseline and follow-up time. Missing joints were due to unilateral radiographs (n=3 participants), trapezeectomy (12 joints), fixation (6 joints) and unrecorded ultrasound findings (4 joints).

Statistical analyses were performed using IBM SPSS Statistics V.24.0 (IBM, Armonk, New York, USA).

RESULTS

Mean (SD) age at baseline was 67.8 (5.2) years and 91% were women. Mean (SD) follow-up time was 4.7 (0.4) years.
At baseline, 1508 joints had available radiographic and ultrasound examinations, of which 301 (20.0%) joints were assessed normal on conventional radiographs (KLG=0). In these radiographically normal joints, ultrasound demonstrated osteophytes in 28.6% joints (table 1a), and highest discordance was found in DIP joints with sonographic osteophytes present in 53.2% joints. The majority of these osteophytes (79.1%) were small (grade=1). In joints with radiographic ‘doubtful OA’ (KLG=1, n=186) and ‘definite OA’ (KLG=2–4, n=1021), sonographic osteophytes were found in 62.9% and 90.7% joints, respectively (table 1b and c). Similarly, in 717/1508 joints without clinical bony enlargement at baseline, sonographic osteophytes were demonstrated in 54.7% joints (table 1d).

In a limited number of joints with available MRI, we were able to confirm the presence of these baseline sonographic osteophytes (ie, positive predictive value) in 86.5% (n=32/37), 90.2% (n=37/41) and 97.0% (n=356/367) of the joints assessed as KL=0, KL=1 and KL=2–4 by radiographs, respectively, and similarly in 91.6% (n=120/131) and 97.1% (n=305/314) joints without or with clinical bony enlargement, respectively.

In longitudinal analyses, incident radiographic and clinical OA occurred during follow-up in 46.5% and 60.5% of joints with baseline sonographic osteophytes. Analyses on joint level demonstrated that ultrasound-detected osteophytes (in radiographically and clinically normal finger joints at baseline) significantly predicted development of radiographic OA according to KLG and clinical bony enlargement during follow-up (table 2a and c and figure 1) and also a development of radiographic osteophytes and JSN (table 2a). Sonographic osteophytes predicted radiographic OA even stronger when incident

### Table 1 Baseline data: ultrasound-detected osteophytes in joints assessed as (A) normal, (B) doubtful OA or (C) definite OA on radiographs, as well as in (D) clinical normal joints

<table>
<thead>
<tr>
<th></th>
<th>(A) n (%)</th>
<th>(B) n (%)</th>
<th>(C) n (%)</th>
<th>(D) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ultrasound-detected osteophytes in joints without radiographic OA (KLG=0)</td>
<td>Ultrasound-detected osteophytes in joints with doubtful radiographic OA (KLG=1)</td>
<td>Ultrasound-detected osteophytes in joints with radiographic OA (KLG=2–4)</td>
<td>Ultrasound-detected osteophytes in clinical normal joints (bony enlargement=0)</td>
</tr>
<tr>
<td>All joints</td>
<td>86/301 (28.6)</td>
<td>117/186 (62.9)</td>
<td>926/1021 (90.7)</td>
<td>392/717 (54.7)</td>
</tr>
<tr>
<td>DIP 2–5</td>
<td>25/47 (53.2)</td>
<td>34/52 (65.4)</td>
<td>475/511 (93.0)</td>
<td>135/192 (70.3)</td>
</tr>
<tr>
<td>PIP 2–5</td>
<td>40/184 (21.7)</td>
<td>43/79 (54.4)</td>
<td>295/349 (84.5)</td>
<td>147/350 (42.0)</td>
</tr>
<tr>
<td>IP-1</td>
<td>18/48 (37.5)</td>
<td>30/36 (83.3)</td>
<td>66/67 (98.5)</td>
<td>60/95 (63.2)</td>
</tr>
<tr>
<td>CMC-1</td>
<td>3/22 (13.6)</td>
<td>10/19 (52.6)</td>
<td>90/94 (95.7)</td>
<td>50/80 (62.5)</td>
</tr>
</tbody>
</table>

CMC, carpometacarpal joints; DIP, distal interphalangeal joints; IP, interphalangeal joints; KLG, Kellgren-Lawrence grade; PIP, proximal interphalangeal joints.

### Table 2 Associations between ultrasound-detected osteophytes at baseline (independent variables) and incident radiographic or clinical OA at follow-up (independent variables in separate models)

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Incidence (percentage) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Joints with ultrasound-detected OP at BL</td>
</tr>
<tr>
<td>a) Joints without radiographic OA (KLG=0) at BL (n=301)</td>
<td></td>
</tr>
<tr>
<td>Incident radiographic OA (KLG ≥1) at FU</td>
<td>40/86 (46.5)</td>
</tr>
<tr>
<td>Incident radiographic JSN ≥1 at FU</td>
<td>15/86 (17.4)</td>
</tr>
<tr>
<td>Incident radiographic OP ≥1 at FU</td>
<td>31/86 (36.0)</td>
</tr>
<tr>
<td>b) Joints without or doubtful radiographic OA (KLG=0–1) at BL (n=487)</td>
<td></td>
</tr>
<tr>
<td>Incident radiographic OA (KLG ≥2) at FU</td>
<td>67/203 (33.0)</td>
</tr>
<tr>
<td>Incident bony enlargement at FU</td>
<td>237/392 (60.5)</td>
</tr>
</tbody>
</table>

Generalised estimating equations presented as ORs for development of OA features at follow-up with separate models for each feature.

*Adjusted for age, sex, body mass index and FU time.

BL, baseline; FU, follow-up; JSN, joint space narrowing; KLG, Kellgren-Lawrence grade; OA, osteoarthritis; OP, osteophytes; ref, reference in regression analyses.
radiographic OA was defined as KLG ≥2 at follow-up (table 2b). Analyses including non-steroidal anti-inflammatory drugs or oral glucocorticoids did not change our results. Statistically significant associations between baseline ultrasound-detected osteophytes and incident radiographic OA was found in PIP and DIP joints but not CMC-1 and IP-1, in which the association was statistically non-significant due to few joints with incident radiographic OA (online supplementary table). Significant associations were demonstrated for sonographic osteophytes and incident clinical bony enlargement in all joint groups (online supplementary table).

In a separate analysis, we compared progression in joints with baseline radiographic KL grade=0 and KL grade=1. Interestingly, 35% (n=65/186) of joints categorised as ‘doubtful OA’ (ie, KL grade=1) at baseline went on to develop true hand OA (KL grades 2–4) after 5 years compared with only 9% (27/301) of joints with no

Figure 1  Ultrasound examination and conventional radiography of the second proximal interphalangeal joint at baseline (2009) and follow-up (2013). Ultrasound (A) showed small osteophytes at the proximal and distal joint surface (arrows), while concurrent radiographs (B) was assessed as normal (Kellgren-Lawrence grade=0). At followup (C), the same joint had progressed to radiographic OA (arrowhead), with development of joint space narrowing and subchondral sclerosis (arrowhead) as well as malalignment.
radiographic sign of disease at baseline (p=0.001). When further stratifying for presence of baseline sonographic osteophytes, 41.0% versus 24.6% of the joints developed true OA (p=0.006).

**DISCUSSION**

In this longitudinal observational hand OA study, ultrasound-detected osteophytes were frequently found in finger joints with no radiographic OA and no clinical bony enlargements. Furthermore, the presence of ultrasound-detected osteophytes strongly predicted incident radiographic and clinical OA 5 years later at joint level, supporting that ultrasound is more sensitive than radiography and clinical examination to detect early hand OA.

Osteophytes, mostly small, were found by ultrasound in 29% and 55% of joints assessed as normal on radiographs and clinical examination (table 1), respectively. Our findings are in line with those of Keen and colleagues, who reported sonographic osteophytes in 24% finger joints that were normal on radiographs. In knee OA, Guermazi et al found osteophytes by MRI in as much as 74% of knee joints with no radiographic features of OA, but prevalence was only 14% when stringent definitions of MRI osteophytes were applied. With the radiographic posteroanterior view of the hands, small osteophytes may go unnoticed on radiographs, especially when present on the dorsal or palmar aspects of the joints. Our findings highlight the limitation of conventional radiography to diagnose a large number of finger joints with small osteophytes. This was especially true in DIP joints, where sonographic osteophytes were found in half of the joints assessed as normal on radiographs, although MRI assessment was available in a limited number of joints and patients, the high positive predictive values indicate that (even small) osteophytes detected by ultrasound in our cohort were in fact true osteophytes.

Furthermore, with longitudinal data, we had the opportunity to explore the importance of these early-detected sonographic osteophytes, which were shown to strongly predict development of radiographic and clinical OA at follow-up (table 2). Most predictive studies have been performed on patients with knee OA. Saunders et al found that both JSN and osteophytes act as independent predictors of cartilage volume loss over a 2-year period in a large cohort of randomly selected older adults. With data from the Osteoarthritis Initiative study, Roemer and colleagues recently evaluated MRI of knee OA patients at multiple time points prior to radiographic disease onset and found that the number of features (or involved structures) were more important than any single feature. Ultrasonography enables examination of several aspects of the joint, both bony changes such as osteophytes and erosions, and soft tissue changes such as synovial effusion, hypertrophy and vascularisation. MRI has a limited role in everyday clinical practice due to costs and availability, whereas our results support recent years appreciation of ultrasound as a complementary imaging tool along with radiography for more accurate diagnostics of hand OA.

The relation between osteophytes and radiographic progression is complex and multifactorial. Several structures of the joint may at some point individually or together drive the disease. In animal models, osteophytes develop at sites adjacent to cartilage loss. While OA knees with large osteophytes are more likely to progress than knees without osteophytes, it is assumed that the strong relation between osteophytes and malalignment, in part, explains the progression. It is further suggested that osteophytes do not have any direct role on disease progression but serve as markers of the location and severity of other pathologic processes. Thus, the importance of the present results is that ultrasound-detected osteophytes may be markers of early joint changes (and not having a causal effect on OA progression).

Still, conventional radiography will remain the cornerstone in obtaining an image-based OA diagnosis in our daily clinical practice. However, the most accepted scoring system, the KL scale, is criticised over its inconsistencies of grade 1. Do these ‘doubtful changes’ of osteophytes or JSN represent normal joints or early OA? In our cohort, we found progression to ‘true OA’ in significantly more joints with baseline KL grade=1 than KL grade=0. Similarly, a 10-year study found 62% of women having small radiographic tibiofemoral osteophytes at baseline to develop true osteophytic knee OA during follow-up compared with only 22% of controls with no signs of disease at baseline. We support the conclusion by Hart et al so-called ‘doubtful’ osteophytes appear to be ‘real’ and cannot be ignored or classified as normal.

Our study is limited by the high age of patients with mostly extensive OA at baseline. However, although patients already have established disease, they still had joints with no OA. A similar study on patients not fulfilling the criteria for hand OA at baseline is of interest. It is also uncertain whether our results can be generalised to other OA joints. Third, radiographs were scored in known time sequence, which may lead to overestimation of progression. However, blinding may increase the error rate, and unblinding is the recommended approach to serial images. Finally, we do not have reliability for the bony enlargement examination.

**CONCLUSION**

Our study provides evidence confirming that ultrasound may identify finger osteophytes at an earlier stage than conventional radiographs and clinical examinations. Early identification of preradiographic OA may be especially important in the event of a future DMOAD.

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**Contributors** Data collection: AM, BS-C, HBH and IKH. Study design: AM and IKH. Analyses, interpretation of data and drafting of the paper: AM. Critical revision and final approval: AM, BS-C, HBH, IKH and TKK.

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