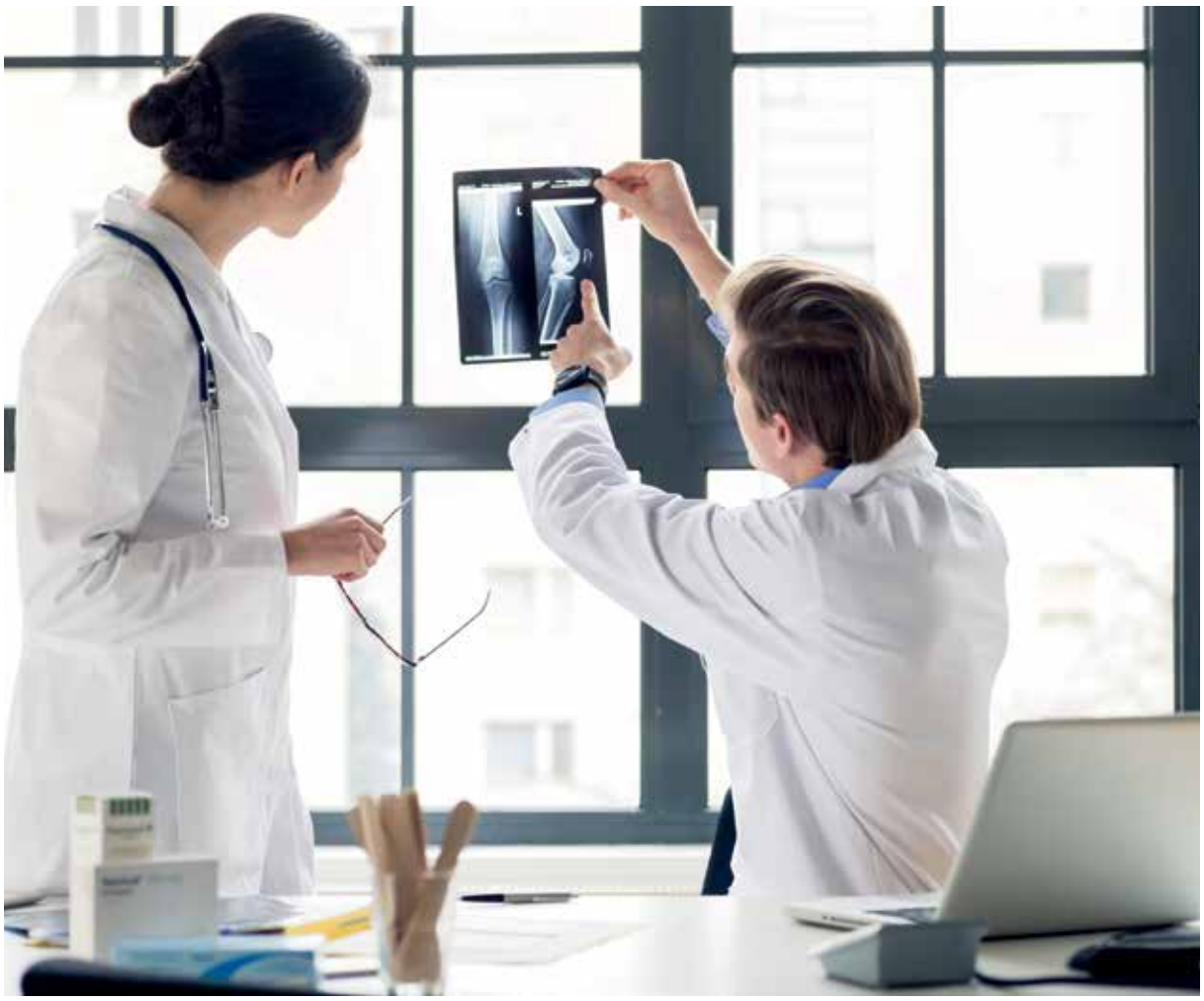
Issue-3: ORTHOPEDICS

Springer Healthcare Education

reachOut



The burden of orthopedic disorders such as osteoarthritis, rheumatoid arthritis, and osteoporosis has increased substantially, while the measures to address these problems seem inadequate. These conditions have a profound impact on the individuals' quality of life, therefore, need to be dealt with, as soon as they are diagnosed. Pharmacotherapy, a major player in the management of these conditions, aims to achieve a better quality of life through pain mitigation and prevention of further deterioration. This scientific input encompasses different orthopedic conditions commonly encountered by the clinicians in their practice. It includes numerous illustrations with detailed description to keep the readers engaged and updated of the recent developments in this field. It is sincerely hoped that this input will serve as an educational resource that will assist doctors in managing their patients.

Views and Reviews

Therapeutic Update

Case Reports

Practice Guide

Prime Time News

Visual Diagnosis

Practice Algorithm

Access the contents on the online portal:
http://collections.medengine.com/orthopedics/reachout-orthopedics/

Ankle and foot involvement can affect up to 90 % of patients with rheumatoid arthritis (RA) during the course of the disease. In RA, painful ankle can be related to joint and/or tendon inflammation which can lead to permanent anatomic damage with consequent patient walking disability.

ANKLE PAIN IN RHEUMATOID ARTHRITIS: COMPARISON OF CLINICAL AND SONOGRAPHIC FINDINGS

Cristina Hernández-Díaz[1] (✉), G. Sánchez-Bringas[2], L. Ventura-Ríos[1], M. Robles-San Román[3], E. Filippucci[4]

[1]Laboratorio de Ultrasonido Musculoesquelético y Articular, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra", Calz. Mexico Xochimilco 289, Col. Arenal de Guadalupe, Del Tlalpan, 14389 Mexico City, ZC, Mexico
cristy_hernandez@prodigy.net.mx

[2]Departamento de Embriología, Facultad de Medicina, Universidad Nacional de México, Edificio A Planta Baja, Facultad de Medicina, Circuito Interior, Ciudad Universitaria, Avenida Universidad 3000, 04510 Mexico City, ZC, Mexico

[3]Reumatólogo Práctica Privada, Centro Médico Metepec, Juan Pablo II 341, Zona Sin Asignación de Nombre de Col 1, 52140 Metepec, State of Mexico, Mexico

[4]Clínica Reumatológica, Università Politecnica delle Marche, Ospedale "Carlo Urbani", Via Aldo Moro 25, 60035 Jesi Ancona, Italy

Ankle and foot involvement can affect up to 90% of patients with rheumatoid arthritis (RA) during the course of the disease [1, 2]. In RA, painful ankle can be related to joint and/or tendon inflammation which can lead to permanent anatomic damage with consequent patient walking disability [3, 4]. Different anatomic structures can be the target of RA at ankle level including synovial tissue, tendons, bursae, ligaments, hyaline cartilage, and bony cortex [5]. Moreover, apart from inflammation, other factors may be responsible for ankle pain, including overuse, repetitive strain, minor injuries, and edema. Thus, an accurate diagnosis is essential for an adequate treatment.

In the last decade, ultrasound (US) has demonstrated to be a sensitive imaging technique that can reveal subclinical inflammatory changes at both joint and tendon levels in patients with RA [6–12].

The aims of this study were to describe the prevalence and distribution of clinical and US pathological findings at ankle level and to compare them, in patients with RA.

Material and Methods

Study Design

This is a descriptive, cross-sectional study assessing patients diagnosed with RA according to the 2010 ACR criteria [13], who were recruited consecutively and independently of disease status or treatment and of the presence of pain at ankle level. Age, gender, disease duration, history, and presence of ankle pain were recorded.

An experienced rheumatologist recorded the presence of spontaneous pain and carried out a physical examination of both the ankles to elicit tenderness. On the same day, another rheumatologist experienced in musculoskeletal US and blind to the clinical findings performed a bilateral US examination of the ankles.

Clinical Assessment

Clinical assessment was performed to detect the presence or absence of spontaneous pain and tenderness at four different aspects of the ankle (anterior, lateral, medial, and posterior). Ankle movements were assessed with the knee flexed. The ankle joint was palpated in slight plantar flexion for the anterior aspect; eversion and inversion movements of the ankle were assessed holding patient's calcaneus, and afterwards, abduction and adduction were done by causing the dorsiflexion movement of the ankle. Synovitis of the tibiotalar joint (TTJ) and the talonavicular joint (TNJ) was evaluated by palpation stabilizing the calcaneus with one hand while rotating the forefoot with the other, inward at 30° and outward at 20° [1, 14].

Ultrasound Equipment

We used either a MyLab 70XVG® or a portable MyLab 25® US system (Esaote SpA; Genoa, Italy) both equipped with the same transducer, a 6–18-MHz linear probe. The values assigned to the power Doppler (PD) setting parameters were the following: pulse repetition frequency is 750 Hz, 9.1 MHz frequency for tendon assessment, and 7.7 MHz for joint assessment (Fig. 1).

Ultrasound Images Acquisition

Bilateral ankle US examinations were performed using the scanning technique proposed by the latest EULAR standardized procedures for ultrasound imaging in rheumatology [15]. The patients were asked to lie on the bed with the knee flexed at 45° to scan the anterior, medial, and lateral sides of the ankle. On the anterior aspect, the following anatomic structures were scanned: tibialis anterior tendon, extensor digitorum longus tendon, extensor hallucis longus tendon, TTJ, and TNJ. In the medial and lateral aspects, the following tendons were examined: tibialis posterior tendon (TPT), flexor hallucis longus tendon, flexor digitorum longus tendon, and peroneus longus and brevis tendons (PLBT).

> *Clinical assessment was performed to detect the presence or absence of spontaneous pain and tenderness at four different aspects of the ankle (anterior, lateral, medial, and posterior).*

Finally, patients were asked to obtain a prone position with the feet hanging freely over the edge of the bed to scan Achilles tendon and retrocalcaneal bursae on the posterior aspect. All US findings were documented on at least two perpendicular planes. PD examinations were performed according to the indications provided by Torp-Pedersen S *et al.* [16].

Ultrasound Images Interpretation

The OMERACT Special Interest Group on US preliminary definitions for both joint and tendon pathology (synovial effusion, synovial hypertrophy, bone erosions, and tenosynovitis) affecting patients with RA was adopted [17]. Moreover, the presence of a partial or complete tendon rupture was recorded. Tendon damage was defined as a discontinuity of the tendon fibrillar pattern partial or complete, confirmed in two perpendicular scans [18–20]. The presence of intra-articular and intra- or peri-tendinous PD signal was recorded.

Informed Consent

Informed consent was obtained from all participants.

Statistical Analysis

Qualitative variables were described by frequencies and percentages; for quantitative variables, central tendency and dispersion measurements were used. The association between independent and dependent variables was determined by odds ratio (OR). For associations, statistic Fisher's exact test was calculated by 0.05 levels. The software employed was SSPSv 21.0 (SPSS Inc., IL, USA).

Results

A total of 112 patients (224 ankles) were evaluated; 100 (89.3 %) patients were women and 12 (10.7 %) were men, with a mean age of 51 years (ranging from 22 to 85 years). RA mean disease duration was 72 months (ranging from 2 to 456 months).

Clinical Findings

Prevalence and distribution of clinical findings are reported in Table 1. Ankle spontaneous pain was found in 63 (56.2 %) out of 112 patients: in 11 (9.8 %) patients only in the right ankle, in 15 (13.4 %) patients only in the left ankle, and in 37 (33 %) patients the ankle spontaneous pain was found in both the ankles; and no pain in 49 (43.8 %) patients. Mean duration of ankle

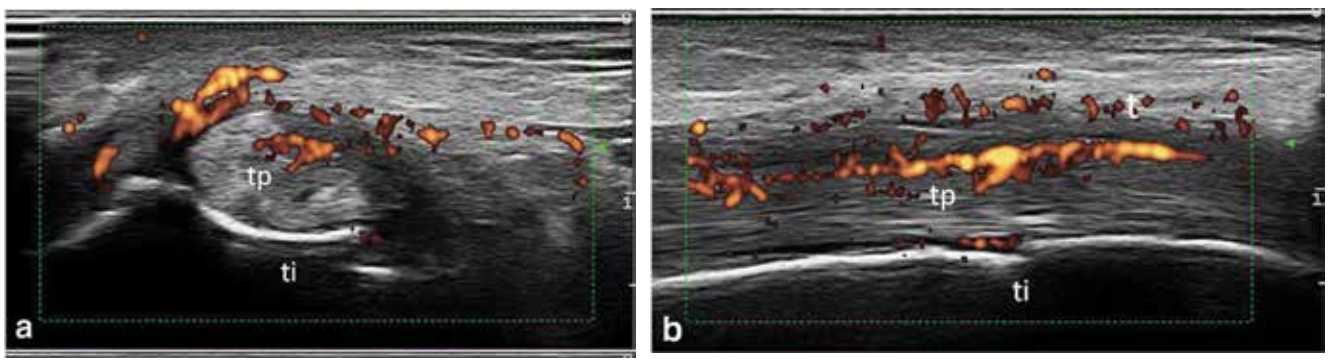


Fig. 1: Representative power Doppler ultrasound images showing an active tenosynovitis of the tibialis posterior tendon (tp). Images were acquired in transverse (**a**) and longitudinal (**b**) scans. ti = tibia

Table 1: Prevalence of clinical findings and their distribution in the four aspects of the 224 examined ankles.

	Ankle aspects				
	Anterior	Medial	Lateral	Posterior	More than one aspect
Clinical characteristics					
Spontaneous pain present at the time of the visit, *n* (%)	41 (18.3)	48 (21.4)	68 (30.4)	23 (10.3)	51 (22.8)
Tenderness, *n* (%)	18 (8)	36 (16.1)	65 (29)	7 (3.1)	35 (15.6)

pain was 13.44 months (ranging from 0 to 240 months). Both the medial and lateral aspects of the ankle were the most frequently involved aspects.

Other ankle or foot clinical findings were acquired during the physical examination including edema (19.6%), hallux valgus (4.9%), muscle hypotrophy (1.8%), venous insufficiency (1.8%), surgical deformities due to fracture and malleolar prosthesis (1.3%), and plantar fasciitis (0.9%).

Ultrasound Findings

In 73 (65.2%) out of 112 patients, US found at least one pathologic sign indicative of joint and/or tendon pathology. Table 2 reports the prevalence of the US findings at ankle level. Using greyscale US, joint involvement was more frequently found than tendon pathology (37.5% and 22.3%, respectively). Conversely, the prevalence of power Doppler signal at joint and tendon levels was respectively 7.6% and 8%. No subject without pain had power Doppler signal.

Clinical Versus Ultrasound Findings

There was a significant correlation between clinical findings (i.e., spontaneous pain referred by the patient and tenderness elicited during physical examination at the lateral side of the ankle) and US findings indicative of TTJ synovitis and peroneal tenosynovitis ($p < 0.0001$); there was no significant correlation between pain and tenderness; no other associations were found.

Table 3 shows the distribution of US findings indicative of TPT and PLBT tenosynovitis and TTJ and TNJ synovitis according to the number of months of ankle pain duration. Longer ankle pain duration was not associated with a higher prevalence of US pathological findings neither at tendon nor at joint level.

> ***Ankle spontaneous pain was found in more than half of the rheumatoid arthritis patients, and abnormal US findings indicative of inflammatory pathology at ankle joint and/or tendon level were detected in 65% of the cases.***

Discussion

This is one of the largest cohort studies performed with the aim to compare clinical and US findings at ankle level in patients with RA; more than one hundred patients with or without ankle pain were consecutively enrolled. Ankle spontaneous pain was found in more than half of the RA patients, and abnormal US findings indicative of inflammatory pathology at ankle joint and/or tendon level were detected in 65% of the cases.

Ankle is a complex anatomic site and different pathologic conditions and mechanisms may concur to its final functional impairment. Thus, the US identification of the inflamed joint and/or tendon provides useful information especially in those cases in which a local steroid injection is considered a treatment option. In our cohort, the most frequently clinically involved ankle aspects were the medial and lateral ones, and US showed that tendon involvement (i.e., tenosynovitis of TPT and PLBT) represented the most prevalent pathology in those ankle aspects. Comparing the duration of the ankle pain with the US pathologic findings, we found that ankle pain lasting at least 1 year can be equally related to both joint and tendon diseases; when pain lasted less than 1 year, joint involvement was found more prevalent than the tendon one.

In the last 10 years, ankle involvement in RA has been investigated using US by a number of studies [9, 21–29]. In all the studies, US was found a sensitive imaging tool allowing for exact identification of the affected anatomic structures; moreover, not only joints but also tendons were found frequently involved and positively associated with ankle clinical involvement.

In the study by Suzuki *et al.* [21], 100 ankles in 74 RA patients were scanned, and the analysis of the US data showed that tenosynovitis is a frequent pathologic finding especially in the early stage of the disease (less than 6 months of disease duration). Elsaman

Table 2: Prevalence of US findings at ankle level. Data are presented as the number and percentage of the 224 scanned ankles.

US findings	TPT	PLBT	TTJ	TNJ
Synovitis, *n* (%)	–	–	50 (22.3)	34 (15.2)
Tenosynovitis, *n* (%)	24 (11.6)	26 (10.7)	–	–
Power Doppler signal, *n* (%)	11 (4.9)	7 (3.1)	10 (4.5)	7 (3.1)

TPT, tibialis posterior tendon; *PLBT*, peroneus longus and brevis tendons; *TTJ*, tibiotalar joint; *TNJ*, talonavicular joint

Table 3: Tenosynovitis or synovitis detected by US and time with pain in months.

Anatomic structure with tenosynovitis or synovitis detected by US	Ankle pain duration in months					
	0	6	12	24	More than 24	*p* value
TPT	3	2	5	4	3	0.02
PLBT	1	3	6	5	2	0.00
TTJ	9	5	5	4	5	0.29
TNJ	9	4	5	4	2	0.57

$n = 112$
TPT, tibialis posterior tendon; *PLBT*, peroneus longus and brevis tendons; *TTJ*, tibiotalar joint; *TNJ*, talonavicular joint

et al. obtained similar results in a cross-sectional study conducted in a cohort of 63 patients with active RA [22]. Tibialis posterior and peroneal tendons were the most frequently reported affected [23–25], and tibialis posterior tenosynovitis seems to be the more specific for RA [26]. Furthermore, Janta I *et al*. found a positive significant correlation between TPT damage assessed by US and radiographic structural damage [27]. In RA patients, the US prevalence of ankle joint involvement seems to have a tendency to increase with the increment of disease duration [26, 28].

The importance of assessing the ankle with US in patients with RA can be also estimated by the results of studies not primarily aimed at investigating ankle joint. In fact, in the study conducted by Naredo *et al*. in RA patients in clinical remission, ankle was included in the core set of the joints to scan to obtain a highly sensitive detection of residual synovitis [30].

While several studies have been carried out in RA patients, further researches are needed to investigate the prevalence of US abnormalities at ankle level in healthy subjects. In fact, some morpho-structural changes may not be due to RA.

We believe that the data obtained in the present study provide additional insights into this topic and will contribute to develop the best scanning protocol for RA patients, aiming to obtain the maximal relevant information on ankle joint and tendon pathology in the shortest possible time.

Limitations

This study has several limitations. First, it was performed at a single center. Second, despite the results acquired with the same transducer, a 6–18-MHz linear probe, two US systems were used; this could have affected mainly the Doppler findings [31]. Moreover, the disease activity score 28 was not systematically recorded in all the patients (many of the consecutively recruited patients presented without laboratory tests results), because the objective of the study was to investigate ankle pain and compare clinical and US findings at ankle level. Finally, no other imaging techniques (i.e., magnetic resonance imaging) were used to substantiate the US findings as made by Wakefield R *et al*. [9].

Conclusions

We found that US allows for a sensitive detection and exact identification of joint and/or tendon inflammatory involvement at ankle level in patients with RA, explaining the reason for ankle pain when present, and revealing subclinical disease in asymptomatic ankle.

Compliance with ethical standards

Conflict of interest: All the authors declare no conflict of interest for this manuscript.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References available on request
Healthcare.India@springer.com

Source: Hernández-Díaz, C., Sánchez-Bringas, G., Ventura-Ríos, L. *et al. Clin Rheumatol* (2019). https://doi.org/10.1007/s10067-019-04532-2.

Efficacy of Duloxetine and Gabapentin in Pain Reduction in Patients with Knee Osteoarthritis

Introduction: Knee osteoarthritis (OA) is a common form of arthritis in elders which can lead to reduced daily activity and quality of life. It is important to administer a proper treatment with high efficacy and low side effects. In this study, we evaluated the efficacy of duloxetine and gabapentin in patients with moderate to severe knee OA.

Method: In this randomized clinical trial, 150 patients with moderate to severe knee OA were randomly allocated to receive duloxetine 30 mg ($n = 50$), gabapentin 300 mg ($n = 50$), or acetaminophen 1000 mg ($n = 50$) all twice a day for 12 weeks. Pain severity using visual analogue scale (VAS) and functional status using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were measured before, 2 weeks, 1 month, and 3 months after intervention.

Results: WOMAC total and its subscale score were significantly lower in duloxetine compared to gabapentin in 2 weeks and 1 months after intervention, with no significant difference at the end of the third month. Both gabapentin and duloxetine groups had significantly more reduction in pain VAS and WOMAC and its subscales compared to acetaminophen group, with no significant difference between groups.

Conclusions: Both gabapentin and duloxetine have similar and acceptable effects in pain reduction and improvement of functional status in patients with knee OA at the end of the third month's treatment. Duloxetine effects begin from the first weeks, while gabapentin effects begin gradually with the best at the end of the third month.

Source: Enteshari-Moghaddam, A., Azami, A., Isazadehfar, K. *et al. Clin Rheumatol* (2019). https://doi.org/10.1007/s10067-019-04573-7.

Intra-articular hyaluronic acid (HA) injection is a controversial treatment for knee osteoarthritis (OA). Proponents of HA argue that efficacy has been established based on superior clinical outcomes compared to saline injections in numerous randomized trials. Critics of HA argue that the incremental efficacy benefit derived from meta-analyses is not clinically meaningful to patients when accounting for the placebo effect.

TOWARDS REACHING CONSENSUS ON HYALURONIC ACID EFFICACY IN KNEE OSTEOARTHRITIS

Larry E. Miller (✉)

Miller Scientific Consulting, 1854 Hendersonville Road, #231, Asheville, NC 28803, USA
larry@millerscientific.com

Intra-articular hyaluronic acid (HA) injection is a controversial treatment for knee osteoarthritis (OA). Proponents of HA argue that efficacy has been established based on superior clinical outcomes compared to saline injections in numerous randomized trials [1, 2]. Critics of HA argue that the incremental efficacy benefit derived from meta-analyses is not clinically meaningful to patients when accounting for the placebo effect [3, 4]. Ultimately, evidence exists to support either position, thereby fueling the debate.

The primary efficacy endpoint of many HA clinical trials involves an assessment of patient-reported knee pain or function. Patient-reported outcomes are highly susceptible to bias when patients are aware of their treatment assignment [5]. Knowledge of treatment assignment may subconsciously or consciously influence patients to alter their reporting of symptom severity and may affect rates of co-intervention and attrition [6]. Consequently, placebo controls with patient blinding are integral elements of HA studies intended for regulatory approval to minimize the risk of these biases. To date, over a dozen

Key Points

- Societal guidelines recommend nonsteroidal anti-inflammatory drugs and corticosteroid injections, but not hyaluronic acid injections, for knee osteoarthritis (OA) despite inconsistent supportive data.
- This article encourages rigorous comparative post-approval studies to clarify the role of nonsurgical treatments used in clinical practice for knee OA.

HA products have been approved by the Food and Drug Administration (FDA) and are currently marketed for sale in the U.S.A. [7].

Commercialization of drugs and medical devices involves two key milestones—FDA approval to sell the product and a positive coverage decision from healthcare payers so healthcare providers may receive reimbursement. Yet the designs of clinical trials intended to support regulatory approval of HA are often insufficient to draw conclusions about the relative efficacy of that product compared to other treatments currently available on the market. For example, trials of HA versus saline injections designed for regulatory approval are not applicable to real-world clinical practice since saline injection is not a treatment for knee OA. Therefore, it could be argued that once an HA product receives marketing approval by demonstrating superior efficacy over saline injections, the more appropriate comparison in subsequent trials would be against approved alternative treatments that are routinely used in clinical practice for the same condition.

In the clinical practice guidelines for knee OA treatment released by the American Academy of Orthopaedic Surgeons (AAOS) [4], the only recommended nonsurgical treatment appropriate for all patients was nonsteroidal anti-inflammatory drugs. In the Osteoarthritis Research Society International guidelines [8], corticosteroid injections were the only recommended nonsurgical treatment appropriate for all patients. Therefore, the efficacy of commercially available HA products would be best demonstrated by direct comparisons to nonsteroidal anti-inflammatory drugs and corticosteroid injections to further clarify their clinical utility in real-world settings.

A few direct-comparison meta-analyses have attempted to answer these questions. Bannuru and colleagues reported that the efficacy of HA was superior to corticosteroids and nonsteroidal anti-inflammatory drugs [1]. He and colleagues reported that corticosteroids were more efficacious than HA at 1 month, but HA was more efficacious at 6 months [9]. In a network meta-analysis of indirect evidence sponsored by the AAOS, improvements in knee pain were similar when HA was compared to ibuprofen, naproxen, celecoxib, diclofenac, or corticosteroid. Further, treatment effects between nonsteroidal anti-inflammatory drugs and corticosteroid injections were comparable. Lastly, despite the recommendation in favor of corticosteroid injections, pain and function outcomes with corticosteroid injections were no different than with intra-articular saline injection [10]. The number of relevant trials that informed these comparisons was limited, which lowers the confidence in these results. These findings highlight the inconsistency between study results and societal treatment recommendations for knee OA. Additionally, societal treatment recommendations should consider studies of combination HA products, several of which have reported improvements in efficacy versus HA alone [11, 12]. Based on this paucity of heterogeneous evidence, some of which is inconsistent with societal recommendations, rigorous comparative post-approval research is encouraged to further clarify the role of HA and other nonsurgical treatments in relation to knee OA therapies commonly used in real-world clinical practice.

> ***Clearly, there is no consensus on the efficacy of hyaluronic acid injections in the treatment of knee osteoarthritis. Additional high-quality randomized trials that compare HA to knee OA treatments used in clinical practice are needed.***

Certainly, the design of a randomized trial intended to compare HA to knee OA treatments such as nonsteroidal anti-inflammatory drugs or corticosteroid injections must be carefully considered in order to provide meaningful results. For example, to the author's knowledge, only 6 randomized trials of HA vs. NSAIDs have been performed [13–18]. Among these trials, 4 trials enrolled less than 100 patients per group [14–16, 18], 4 trials followed patients for 12 weeks or less [13–17], and 3 trials utilized inadequate patient blinding [13, 17, 18]. Further, no study enrolled patients with advanced disease (Kellgren-Lawrence stage IV). Ultimately, this suggests that the current evidence of the utility of HA vs. NSAIDs is of relatively low quality since sample sizes are often inadequate to detect clinically important group differences or uncommon adverse events, study duration and study quality may be inadequate, and the patients under study may not be representative of those treated in clinical practice. Sample sizes should be derived from power analyses that allow detection of the minimal clinically important difference for the primary efficacy endpoint as well as for a co-primary safety endpoint. Further, clinical trial results derived from no more than 12 weeks of follow-up offers little value since most patients are unwilling to undergo total knee arthroplasty and, therefore, must manage knee OA symptoms for many years following the initial diagnosis [19]. Patient treatment and follow-up of at least 6 to 12 months is recommended to understand the unique risks and benefits of each therapy, which should include patient-reported efficacy outcomes, health-related quality of life, treatment compliance, rates of study withdrawal with associated reasons, and adverse event rates. Finally, patient blinding remains crucial in postmarket trials in order to minimize bias and can be effectively implemented by specifying additional sham injections or oral placebo pills, depending on the comparison group.

Clearly, there is no consensus on the efficacy of HA injections in the treatment of knee OA. Additional high-quality randomized trials that compare HA to knee OA treatments used in clinical practice are needed. Manufacturers of HA are therefore encouraged to plan their clinical trial programs to not only conduct randomized trials to support regulatory approval, but to also plan equally rigorous postmarket trials with active controls used in clinical practice. Until such data become available, the impasse towards reaching consensus regarding HA efficacy for knee OA will likely remain.

Acknowledgments: No funds were received for this work.

Compliance with ethical standards

Conflict of interest: The author has previously received personal fees from DePuy Synthes, OrthogenRx, and OsteoArthritis Centers of America and has previously published manuscripts related to hyaluronic acid efficacy in knee osteoarthritis.

Ethical standards: The manuscript does not contain clinical studies or patient data.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References available on request
Healthcare.India@springer.com

Source: Miller, L.E. *Clin Rheumatol* (2019). https://doi.org/10.1007/s10067-019-04597-z.

Thoracolumbar kyphosis (TLK) is very common in achondroplastic infants. This deformity appears to defy the Heuter-Volkmann principle in that progression is not invariable and in certain instances may resolve. Generally, the treatment options for treating the TLK deformity depend on the flexibility as well as the time of presentation.

THE NATURAL HISTORY OF THORACOLUMBAR KYPHOSIS IN ACHONDROPLASIA

Malik Ahmed[1] (✉), Mahmoud El-Makhy[1], Michael Grevitt[1]

Malik Ahmed
mspinesurgeon@yahoo.com

Michael Grevitt
michael.grevitt@nuh.nhs.uk

[1]Centre for Spinal Studies and Surgery, Queen's Medical Centre Campus, Nottingham University Hospitals NHS Trust, Derby Road, Nottingham NG7 2UH, UK

Case Presentations

Case 1

The first case is a 12-year-old female who has been under follow-up for 6 years since she was initially seen in the outpatient clinic.

This infant female at first presentation aged 6 years, had a TLK angle of 57°. She was asymptomatic, and walking independently without aids. She had a normal neurological examination.

Diagnostic Imaging

On her regular annual follow-up, she had whole spine X-rays that shows increased TLK progressively rising to 70°, 97°, 98° and 104° at age of 10, respectively (Figs. 1, 2).

Whole spine MRI (Fig. 3) showed stretching and compression of the cauda equina over a 114° gibbus.

Outcome

Although at age 11 years, she had normal activities of daily living. After that she developed increasing bilateral sciatic pain and neurogenic claudication symptoms.

At the time of writing, the parents preferred a watchful wait policy.

Case 2

An infant with known achondroplasia was noted at the age of 2 years with a thoracolumbar kyphosis. With increased walking, this deformity increased over the next 4 years. At 5 years of age, he presented with increasing lower back pain and stiffness in the legs. Physical examination showed a large thoracolumbar kyphosis and an exaggerated lumbar lordosis beneath it. There was bilateral clonus with extensor plantar responses.

Imaging

Magnetic resonance imaging (MRI) scan showed conus terminating at T12/L1 with severe L2 vertebral wedging and stenosis at that level.

Procedure

In 2003, he underwent first-stage L1 and L2 vertebrectomies. One week later, he underwent posterior instrumented correction of the deformity and insertion of fibular allograft strut graft.

Procedure Rationale

In surgical planning the approach should be carefully considered. Posterior alone, standalone and combined are the available approaches for surgical interventions. Spinal surgeons should respect the stability and the biomechanics of the spine when operating on this pathology. Not only the neurological decompression is the target but also the deformity correction and prevention of subsequent deformity and adjacent levels affection to be considered.

In rare cases of low (<30°) symptomatic thoracolumbar kyphosis, a posterior decompression (laminectomies or multiple foraminotomies) with instrumented fusion is an option. The classic presentation in this group of patients is due to foraminal canal narrowing.

In kyphotic angles more than 30° or compromise of the spinal cord, anterior vertebrectomy and instrumented posterior fusion is mandatory [14–16].

Spinal cord and cauda equina compression are considered surgical emergencies, which need urgent surgical intervention. These usually occur with fixed angular deformity. In these situations more complex, staged operations will be necessary, depending on the particular deformity characteristics and patient's features.

In 2010, Auregan *et al.* reported a case of 180° achondroplastic kyphotic deformity which illustrates some of these principles. Their case was first seen at the age of 16 years old because of cosmetic concerns and was neurologically normal. At the age of 18, he developed severe neurogenic claudication with abnormal central spinal cord signal in front of the apex of the kyphosis associated with the narrow spinal canal. The authors performed

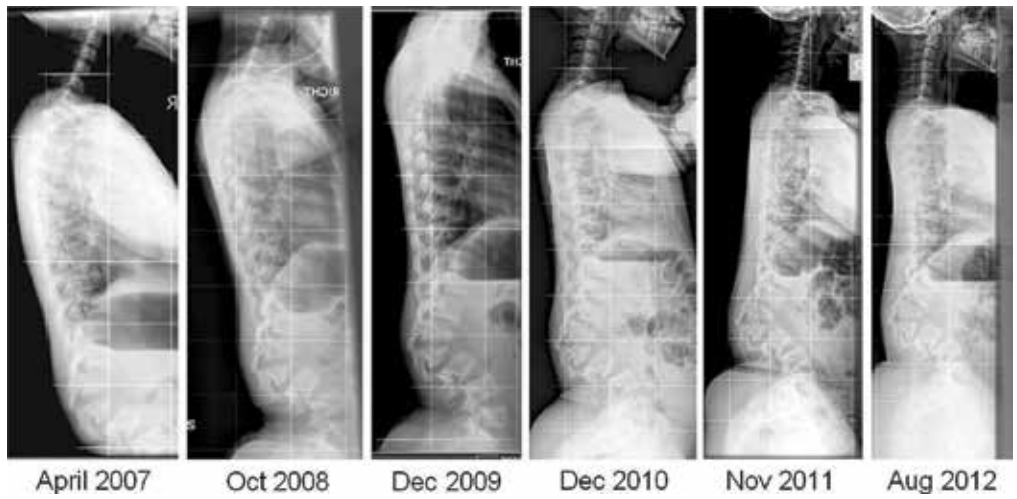


Fig. 1: Case 1: whole spine lateral X-rays showing progression of TLK and sagittal profile.

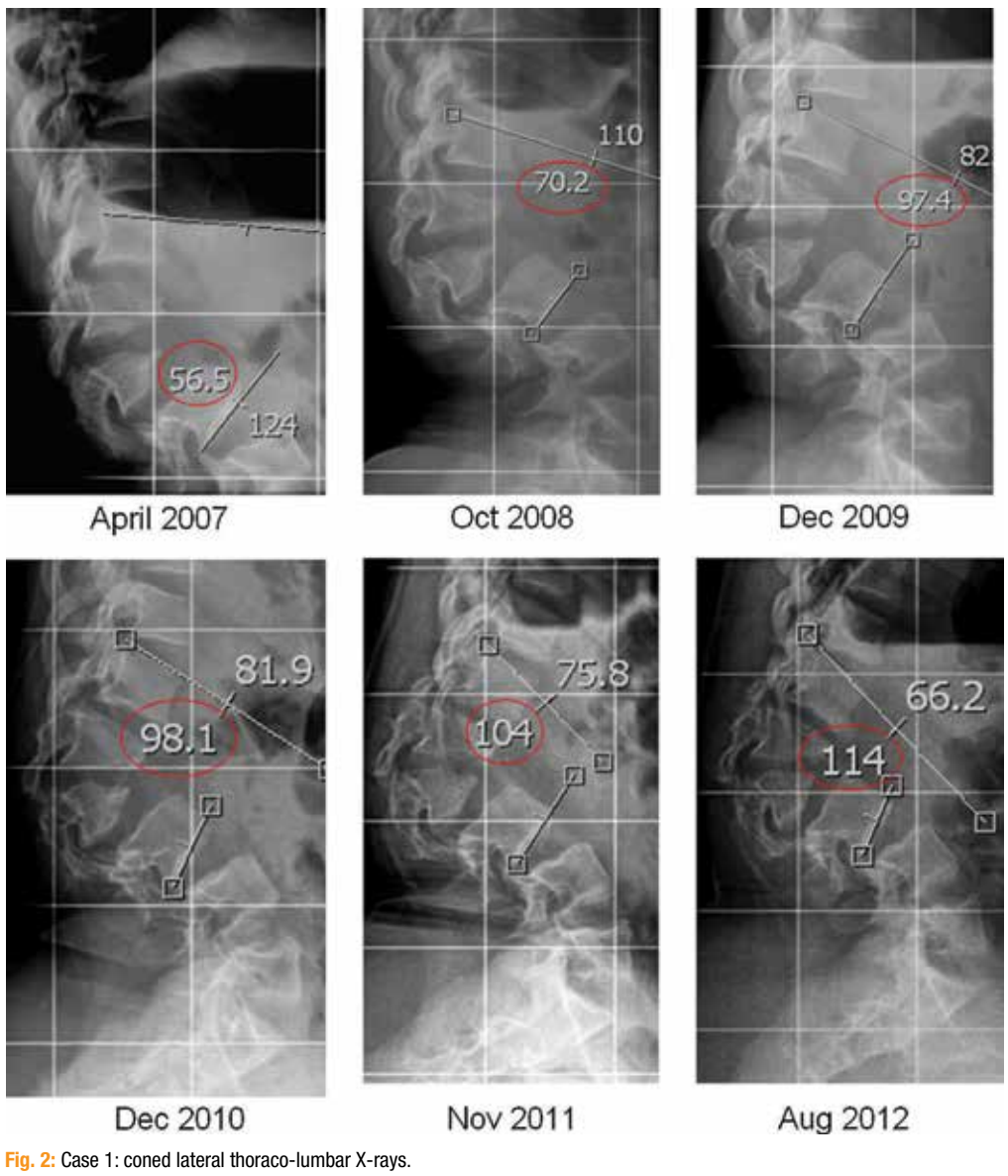


Fig. 2: Case 1: coned lateral thoraco-lumbar X-rays.

decompression of the spinal cord with five-level hemilaminectomies, decancellation osteotomy of three apical vertebrae with disc excision and translation of the spinal cord anteriorly and posterolateral fusion. A peroneal strut graft was inlayed anterolaterally. Patient was immobilized in a cast for 3 months, then, 6 months in a moulded orthosis. There was improved clinical status after 3 years [17].

Pedicle screws have been recently considered as the implant of choice in management of the achondroplastic deformities because of the abnormally narrowed spinal canal, which is likely to be compromised if, hooks or wires are used.

The conservative treatment has been offered to our cases as long as there is no incapacitating spinal deformity nor any

neurological deficit was encountered. They are also kept under yearly basis follow-up for clinical and radiological evaluation. Whole spine standing PA and lateral X-rays are routinely performed for assessment of the whole spine sagittal balance as well as thoracolumbar kyphosis. Surgical treatment was offered to the case which neurologically deteriorated.

Postoperative Imaging

Outcome

His symptoms resolved and his walking ability improved. Four years later, he was walking normally without symptoms.

Case 3

This male child was noted at birth to have a TLK gibbus and initial X-rays showed an angulation of 25°.

Diagnostic Imaging

Outcome

One year later, additional wedging of L2 occurred and increased to 34° till the age of three at which point progression ceased (Fig. 4). Thereafter, there was regression of TLK and correction of the gibbus; the TLK had reduced to 2.5° at the last follow-up 5 years after initial presentation. This has remained stable in the intervening years (Fig. 5).

Historical Review

Achondroplasia ("without cartilage formation") was first described in 1878. It is an autosomal dominant inherited mutation in the fibroblast growth factor receptor-3 (FGFR3) gene on the short arm of chromosome 4. This affects the maturation of chondrocytes in the growth plate [1]. However, 80–90 % of the patients have new mutations [2]. It is the most common form of human skeletal dysplasia, with frequency of between 1 in 15,000 and 1 in 40,000 live births [3].

Intracartilaginous ossification commences in the developing fetus in the thoracolumbar region and progresses in a cranial and caudal direction from the thoracolumbar junction. The primary ossification centers are located in the vertebral centrum and one on each side in the posterior elements, located anterior to the pedicle. The junction of these is the neurocentral synchondrosis. During maturation, there is increasing vertebral size and progressive expansion of the spinal canal. Fusion of these synchondroses at 6–8 years of age signals the cessation of spinal canal widening. This is also the period in which longitudinal growth of the posterior elements of the vertebrae ceases.

Anterior longitudinal growth, which occurs at the epiphyseal plates, continues in individuals to the age of 18–20 years. Factors interfering with the anterior longitudinal growth during the intervening period will, therefore, be accompanied by kyphosis [9].

Radiologically, the achondroplastic spine has short pedicles, particularly in the

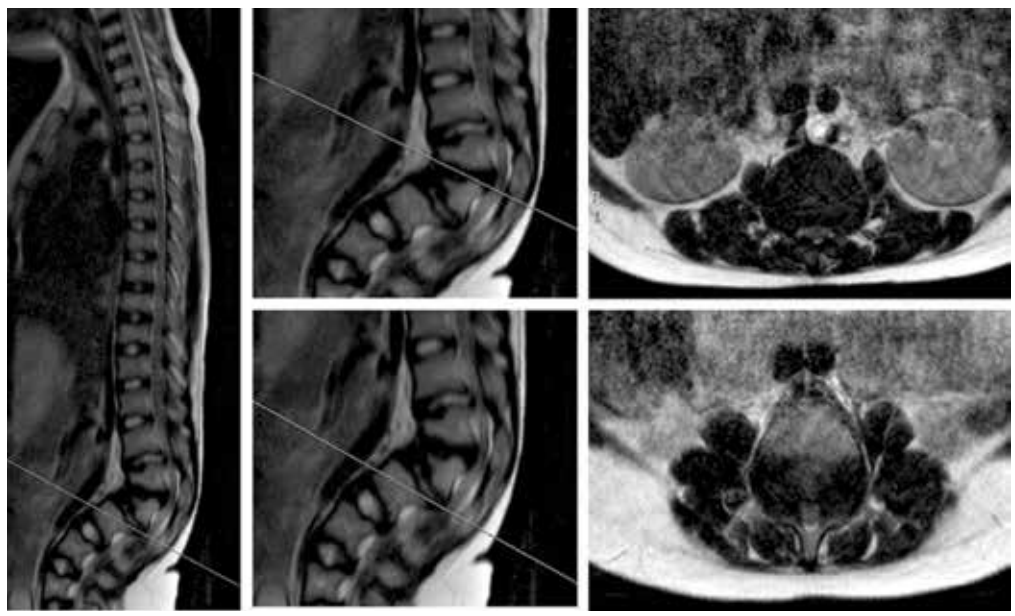


Fig. 3: Case 1: sagittal and axial MRI sections demonstrating spinal canal stenosis and thoracolumbar gibbus.

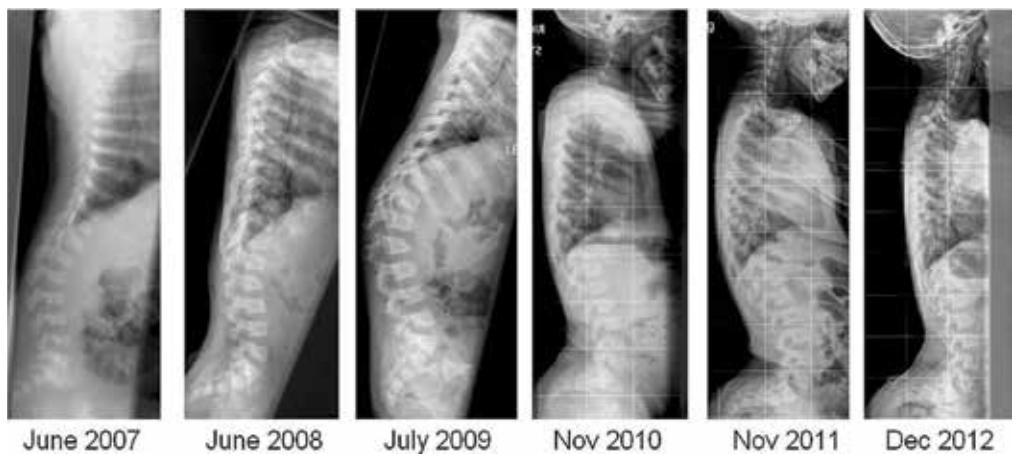


Fig. 4: Case 3: whole spine lateral follow-up X-rays showing spontaneous correction of TLK.

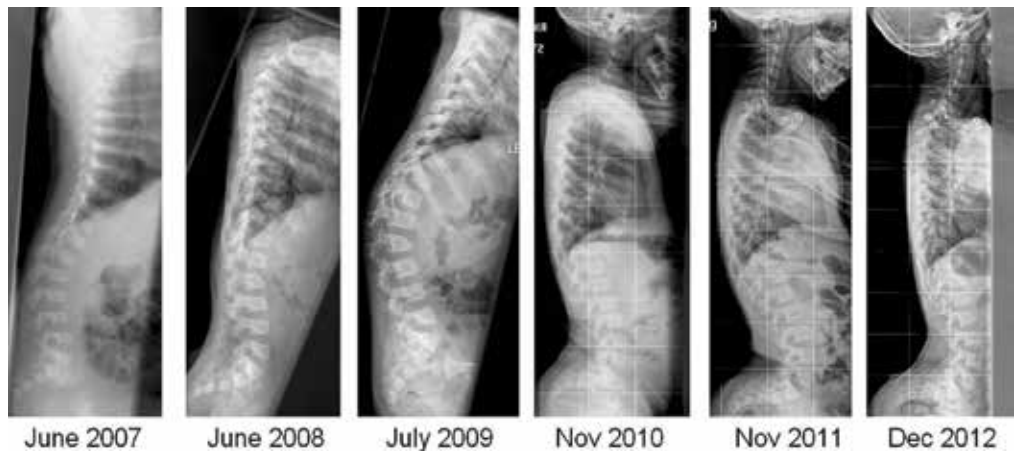


Fig. 5: Case 3: coned thoraco-lumbar lateral X-rays.

thoracolumbar region and progressive decrease in interpedicular distance in lumbar spine, which is progressively smaller in the caudal direction [6]. In some cases, there is narrowing of the foramen magnum and a short clivus. Most of the cases are characteristically accompanied by kyphosis at the thoracolumbar junction. When the kyphosis progresses there is wedging of the vertebral bodies at the apex of the deformity (bullet-shaped/hypoplastic vertebra) [7].

Other radiological features include posterior vertebral scalloping, laminar thickening, widening of intervertebral discs and increased angle between sacrum and lumbar spine [8] (Fig. 6).

Disrupted intracartilaginous ossification at the neurocentral synchondroses is thought to be the basis for the abnormal growth of the axial skeleton in achondroplasia. As the synchondroses have an oblique orientation, their normal growth results in an increase of the spinal canal in all dimensions, as well as growth of the pedicles. Abnormal maturation of these synchondroses results in short pedicles with a narrow spinal canal. A simultaneous occurrence is the underdeveloped and narrow sacrum, because this too forms from intracartilaginous ossification. The iliac wings undergo unimpeded growth and hence are located relatively higher in achondroplastic individuals. Consequently, the sacroiliac articulations are well below the iliac wings [10].

At birth, there is normal prominence of the mid-to-lower back with a small TLK, which usually resolves by the time of independent walking. Lumbar lordosis then evolves and increases till skeletal maturity.

In achondroplasia the exact factors associated with progression of TLK and the subsequent development of fixed kyphosis in adolescence or adulthood have not been fully elucidated but are thought to be connected to generalized hypotonia, a large head, hydrocephalus, and delayed walking [5, 13, 14].

Siebens *et al*. presented a hypothesis explaining the persistent curvature and resultant TLK in achondroplasia. The postulate was that occurrence of the deformity was related to the disproportionately enlarged head, lax ligaments with unusual vertical load on the anterior column of the spine. This is most apparent at the thoracolumbar junction where the transition from the relative rigidity of the thoracic cage to the upper lumbar spine creates an additional stress riser. Inhibited anterior vertebral growth reflects the Hueter-Volkmann principle on the vertebral apophyses and the subsequent development of vertebral wedging.

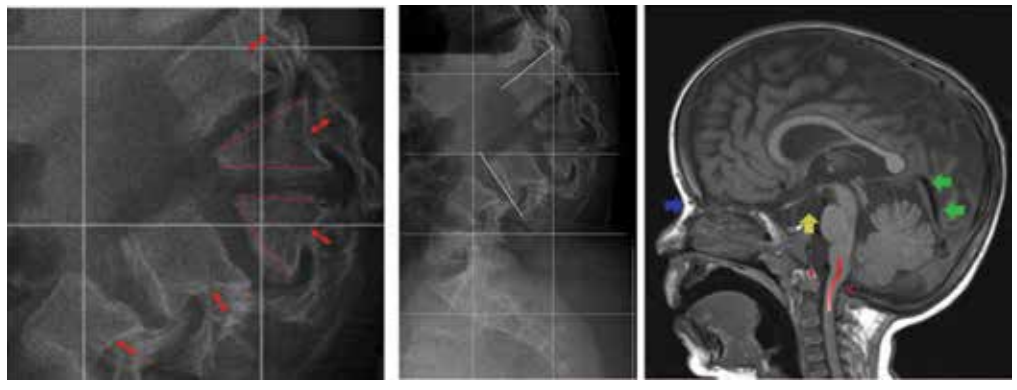


Fig. 6: (*Left*) Wedging of the vertebrae at the apex with short pedicles. (*Centre*) Thoraco-lumbar kyphotic deformity. (*Right*) Relatively large cranial vault with small skull base, prominent forehead with depressed nasal bridge (*blue arrow*), narrow foramen magnum is narrowed (*red arrowheads*), cervico-medullary kink (*red line*). Elevation of the brainstem gives rise to a large suprasellar cistern (*yellow arrow*) and a vertically oriented straight sinus (*green arrows*). Cranio-cervical junction constriction.

Neurologically they are liable to spinal compression because their spinal canal is abnormally narrowed by the short pedicles as well as by the compensatory hyperlordosis [11].

> ***Early life diagnosis should be treated conservatively then bracing with a serial follow-up and curve assessment. If this line of treatment fails, then surgery will be an option.***

With walking and maturation, there is exacerbation of thoracolumbar kyphosis with compensatory lumbar hyperlordosis, pelvic tilt and subsequent fixed flexion deformity of the hip joints [12].

The above hypotheses would accord with a reported prevalence of thoracolumbar kyphosis in achondroplastic children under 1 year of age of 94 % [4].

However, the biomechanical postulate would predict that with the initiation of wedging of the vertebral body and subsequent adoption of walking stance, there would be increasing differential growth between the anterior and posterior halves of the vertebrae. Thus, invariable progression of TLK should be the rule. This is illustrated in cases 1 and 2.

In contrast, the reported risk of progressive deformity and resultant spinal cord or cauda equina compression is only approximately 11 % [5]. In addition, the above theory cannot explain the regression of TLK seen in case 3. This anomaly cannot be explained by differential muscle tone as these reported cases were walking normally throughout the later follow-up period.

In summary, TLK is very common in achondroplastic infants. This deformity appears to defy the Hueter-Volkmann principle in that progression is not invariable and in certain instances may resolve. Generally, the treatment options for treating the TLK deformity depend on the flexibility as well as the time of presentation. Early life diagnosis should be treated conservatively then bracing with a serial follow-up and curve assessment. If this line of treatment fails, then surgery will be an option. In adults or undiagnosed cases with a fixed deformity, there is no role for the conservative treatment. The progression of the deformity and the neurological impairments are the factors, which should be considered for decision-making.

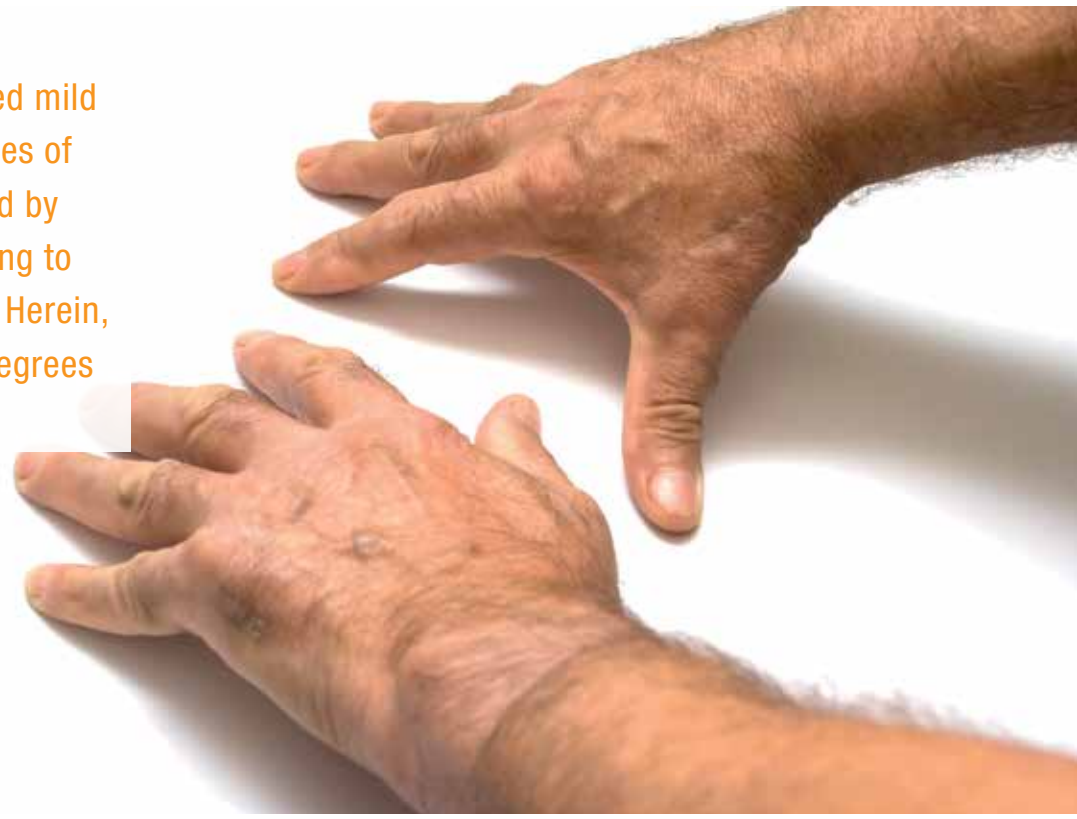
Compliance with ethical standards

Conflict of interest: None.

References available on request
Healthcare.India@springer.com

Source: Ahmed, M., El-Makhy, M. & Grevitt, M. *Eur Spine J* (2016). https://doi.org/10.1007/s00586-016-4861-1.

Patients with ulnar hemimelia may be asymptomatic in the presence of isolated mild ulnar deficiency. On the other hand, cases of prominent ulnar deficiency accompanied by complex upper limb abnormalities leading to severe disability may also be observed. Herein, we present four patients with varying degrees of ulnar hemimelia.



ULNAR HEMIMELIA: A REPORT OF FOUR CASES

Meltem Özdemir[1,2], Aynur Turan[1], Rasime Pelin Kavak[1]

Meltem Özdemir (✉)
meltemkaan99@gmail.com

[1] Department of Radiology, University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

[2] Radyoloji Kliniği, Sağlık Bilimleri Üniversitesi Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Ziraat mah. Şehit Ömer Halisdemir cad. No:20, Altındağ, Ankara, Turkey

Hemimelia is the term used to describe the congenital skeletal abnormality characterized by the absence or underdevelopment of one side of the distal half of a limb. Occurring in approximately 1 per 150,000 live births, ulnar hemimelia is a very rare form where the ulna is totally or partially absent [1]. The reason for its rarity compared with other skeletal anomalies is speculated to be its relatively early development in embryonic life. The critical embryonic period in the development of ulnar deficiency (24–26 days) is earlier than those of other skeletal anomalies and it corresponds to a period of high mortality [2, 3]. Ulnar hemimelia is more common in men, with a male to female ratio of 3:2. It is reported to be unilateral in about 70 % of cases, and is mostly right-sided and incomplete. Some shortening of the forearm, radial bowing and tendency of the hand to drift to the ulnar side of the wrist usually accompany ulnar hemimelia. Other skeletal anomalies such as humeroradial synostosis, radial head dislocation, carpal or metacarpal coalition, and digital abnormalities may also be seen in cases of ulnar hemimelia. Different from the radial deficiencies, ulnar deficiency is mostly nonsyndromic and is most commonly seen in skeletal dysplasias. The radius is typically longer than the ulna in patients with achondroplasia, and in patients with mucopolysaccharidosis, the distal ulna and radius can be hypoplastic and may slope toward each other [4, 5]. Ulnar hemimelia may also present with Poland syndrome, Goltz–Gorlin syndrome, Cornelia De Lange syndrome, or femur fibula ulna syndrome [1, 6].

Patients with ulnar hemimelia may be asymptomatic in the presence of isolated mild ulnar deficiency. On the other hand, cases of prominent ulnar deficiency accompanied by complex upper limb abnormalities leading to severe disability may also be observed. Herein, we present four patients with varying degrees of ulnar hemimelia. Our first case had an isolated ulnar hemimelia, whereas the other three had additional upper limb abnormalities of different types.

Case Reports

Case 1

A 34-year-old woman presented with the complaint of a mild intermittent pain in her left elbow for the last few months. There was no history of trauma to her left arm during her childhood or later years. On physical examination, no loss of function was recorded in her left upper limb.

Anteroposterior (AP) radiograph of both forearms including the hands and the elbows were obtained. The right forearm, elbow joint and hand were radiographically normal (Fig. 1). AP and lateral (L) radiographs of the left forearm revealed partial absence of the distal portion of the ulna (Fig. 2a, b). There was some periarticular sclerosis consistent with mild osteoarthritis in the left humeroulnar joint (Fig. 2c). No anomaly was noted in the left hand.

Case 2

A 20-year-old man presented with pain and restriction of movement of his left elbow. He stated that he had been suffering from elbow pain for the last few years, but the restriction of elbow motion had begun only a few months ago. There was no trauma or any significant feature in his childhood or later history. On physical examination, the third digit of the left hand was short, and the left elbow extension was painful (Fig. 3a).

Anteroposterior and lateral radiographs of both forearms (including hands) were obtained. The right forearm and hand were radiographically normal (Fig. 3b). The radiographs of the left forearm revealed the partial absence of the distal portion of the ulna and radial bowing. Camptodactyly in the third digit, accompanied by the bowing of the third metacarpal, was evident in the left hand radiographs (Fig. 4a, b). There were intense periarticular sclerosis and prominent narrowing in the left humeroulnar joint consistent with severe osteoarthritis (Fig. 4c, d).

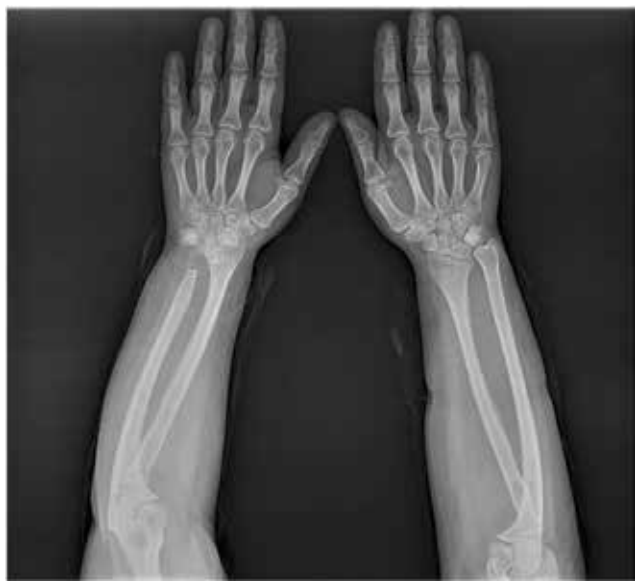


Fig. 1: Anteroposterior radiograph of both forearms including the hands and the elbows. The right forearm, right elbow joint, and both hands are radiographically normal. However, the distal portion of the left ulna is partially absent.

Case 3

A 26-year-old woman presented with a limited range of motion of her elbows and cosmetic disturbance concerning her upper limbs. She stated that her both arms had been curved, but had functioned well since childhood. She had been offered surgery when she was about 10; however, she could not undergo surgery because of financial difficulties. She had no systemic complaints other than the two upper limb deformities. On physical examination, the pronation and supination of the radioulnar joint and elbow movements were restricted on both sides. No sensory deficit was noted (Fig. 5).

Anterior radiographs of both forearms, including both elbows, along with AP radiographs of both hands, were obtained. The distal half of both ulnar bones were absent, and there was fixed flexion of about 45° of both elbow joints. Dislocation of the radial heads, bilateral radial bowing, and mild ulnar-sided drift of the hands were demonstrated (Fig. 6a, b). Fixed flexion of varying degrees of the digits was observed on the radiographs of both hands (Fig. 6c, d).

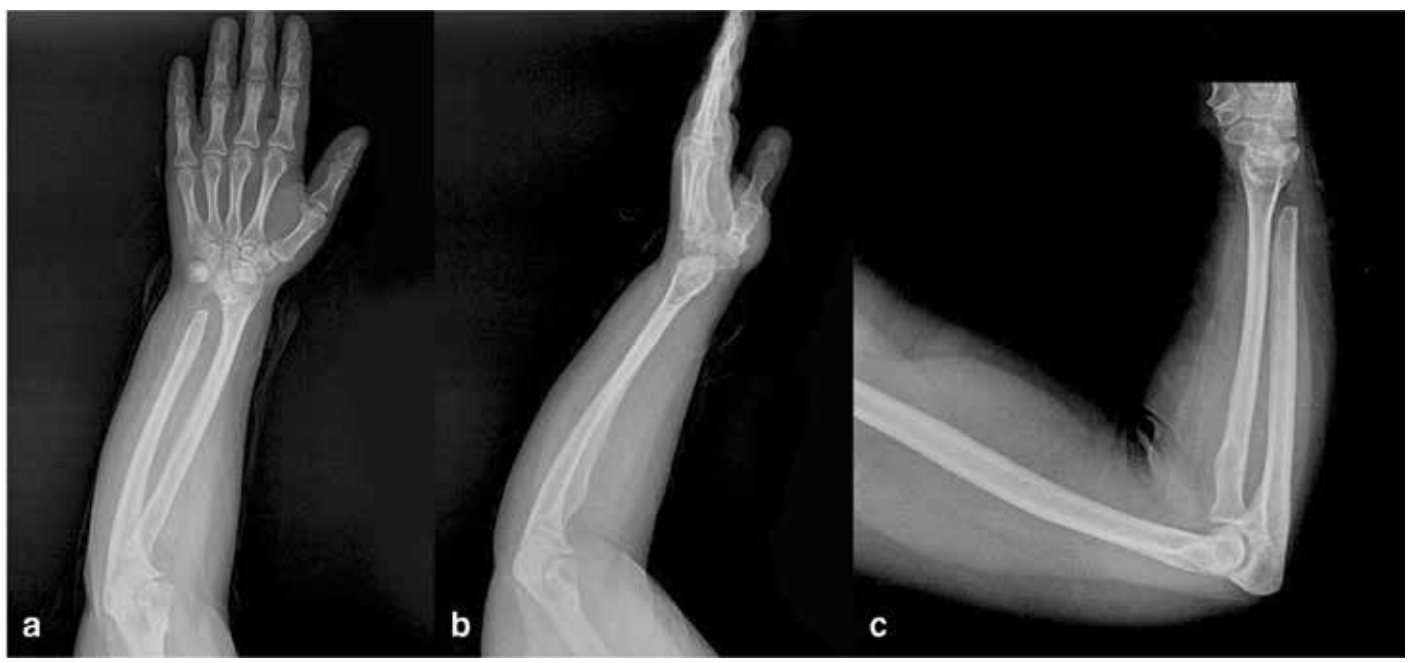


Fig. 2: **a** Anteroposterior and **b** lateral radiographs of the left forearm demonstrate partial absence of the distal portion of the ulna. **c** Lateral radiograph of the left elbow joint depicts some periarticular sclerosis consistent with mild osteoarthritis in the humeroulnar joint.

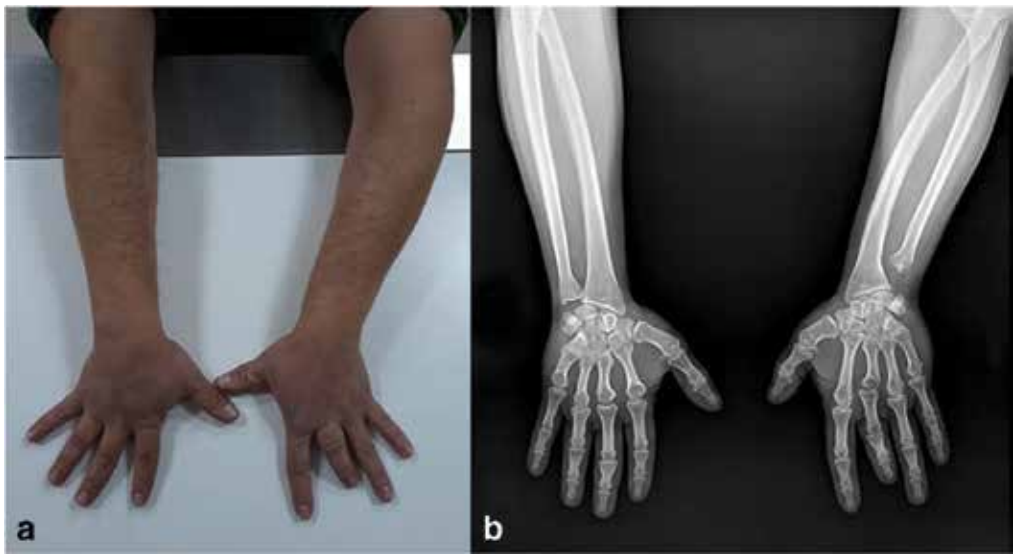


Fig. 3: **a** Clinical photograph and **b** anteroposterior radiograph of both forearms, including both hands, show that the right forearm and hand are normal, whereas the third digit of the left hand is short. Partial absence of the distal portion of the left ulna, and left radial bowing is evident on the radiograph (**b**).

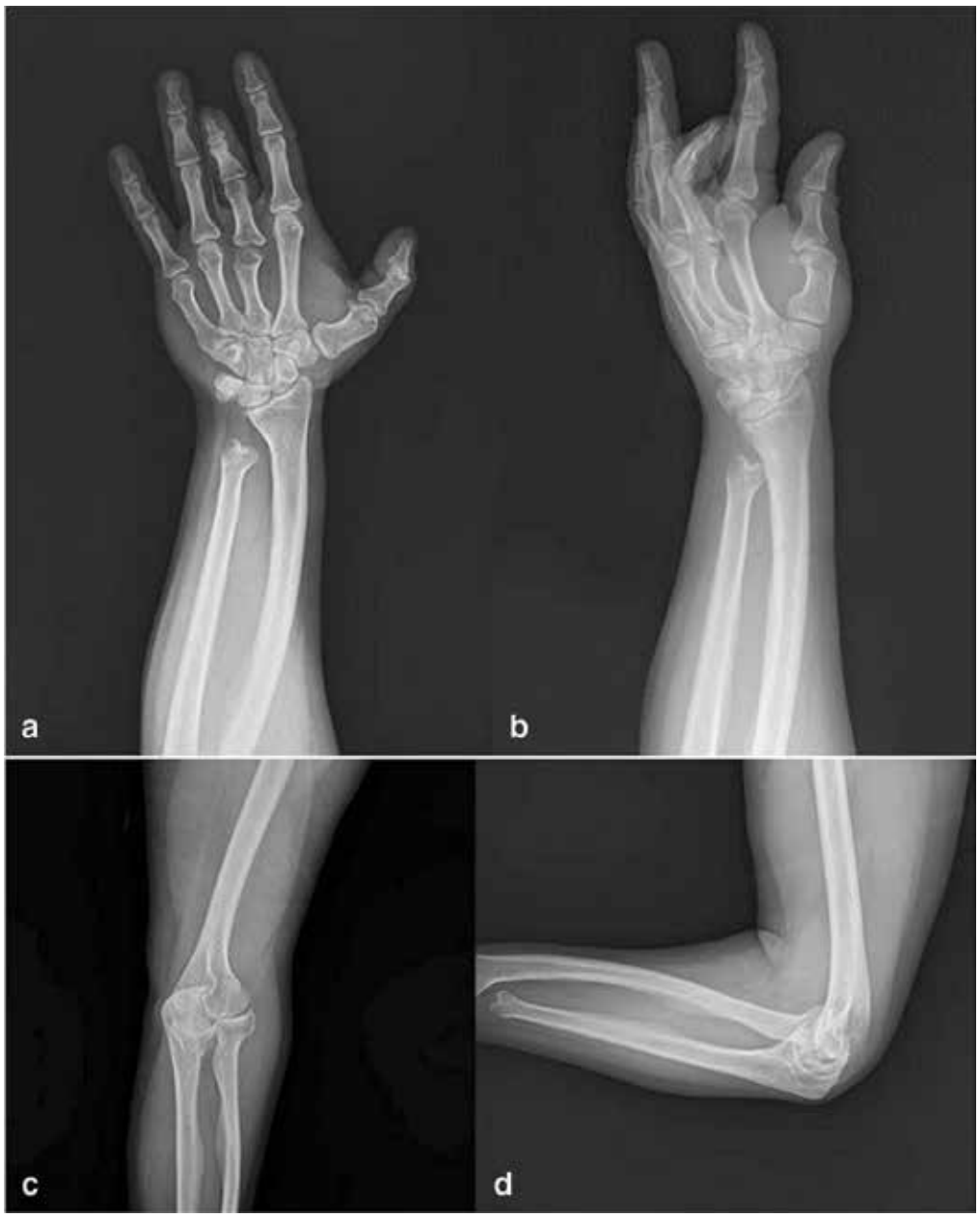


Fig. 4: **a** Anteroposterior and **b** lateral radiographs of the left forearm depict the partial absence of the distal portion of the ulna, and radial bowing. Camptodactyly in the third digit, accompanied by the bowing of the third metacarpal, is evident in the lateral radiograph (**b**). **c** Anteroposterior and **d** lateral radiographs of the left elbow joint show intense periarticular sclerosis and prominent narrowing in the humeroradial joint consistent with severe osteoarthritis.

Case 4

A 24-year-old man presented with severe pain and restriction of movement of his left shoulder. Both upper limbs were short, and bilateral hand oligodactyly was present. He stated that he had never undergone surgical or nonsurgical treatment for the deformities involving his upper extremities. He had no systemic complaints other than musculoskeletal deformities and shoulder pain. Physical examination revealed fixed extension of both elbow joints, and left shoulder instability.

Anteroposterior and lateral radiographs of both forearms, including hands and both elbows, were obtained, along with the AP radiographs of both shoulders. Bilateral ulnar hypoplasia accompanied by bilateral shortening of the limb, humeroradial synostosis, radial bowing, massive carpal coalition, and tridactyly were depicted. The limb shortening was more prominent on the left side (Fig. 7a, b). In both hands, the proximal phalanges of the third digits were bifid, and the medial and distal phalanges of the third digits were duplicated. There was fixed flexion of varying degrees of the digits of both hands (Fig. 7c, d). AP radiograph of the right shoulder was normal. AP radiograph of the left shoulder revealed glenohumeral dysplasia of the shoulder with a dysplastic and hypoplastic glenoid, a small humeral head, a small scapula and arm, a blunted coracoid process, and muscular atrophy in the arm. Minor rotoscoliosis with the curve convex to the right, L4 butterfly vertebra, and spinal dysraphism at the T12 level were also noted (Fig. 8).

Discussion

We presented four patients with ulnar hemimelia, two of whom were admitted with relatively mild clinical complaints of pain and restricted motion of a single elbow joint, whereas the other two were suffering from severe disability of both upper limbs and serious cosmetic discomfort. The severity of the ulnar deficiency and the presence or absence of the accompanying skeletal anomalies determine the time of presentation and the clinical course of ulnar hemimelia. The two main complaints of the patients are disability of the limb and cosmetic disturbance. The limitation of the extension of the elbow joint to approximately 90° is a frequent finding among patients with ulnar hemimelia. In severe cases, fixed flexion of the joint up to 160° may be present [1]. In

Fig. 5: Clinical photographs of both **a** forearms and **b** hands show that both arms are curved inwards, and there is a mild ulnar-sided drift of the left hand. There are also varying degrees of fixed flexion of the digits of the left hand.

our third case, there was fixed flexion of about 45° of both elbow joints, whereas our fourth case presented bilateral humeroradial synostosis with bilateral fixed extension of the elbow joints. Fixed flexion or extension of the elbow joint is reported to occur in cases with accompanying humeroradial synostosis. Congenital bilateral humeroradial synostosis is a rare skeletal disorder associated with ulnar hypoplasia and is classified according to the position of the forearm. Class I is sporadic and comprises patients with fixed extension, whereas Class II is familial and comprises patients with fixed flexion. Class II is reported to be associated with multiple systemic anomalies [7, 8]. Humeroradial synostosis of our patient (Case 4) was of Class I, and caused severe disability of both upper limbs of this young man. However, the reason for bringing the patient to the doctor was the recurrent pain in his left shoulder. Shoulder radiography revealed glenohumeral dysplasia, implying the presence of shoulder instability. To our knowledge, this is the first case reported to have glenohumeral dysplasia associated with ulnar hemimelia. Tridactyly in both hands of this unfortunate patient increased the severity of his disability.

Ulnar hemimelia may be associated with complex carpal, metacarpal, and digital abnormalities. Carpal abnormalities including aplasia, hypoplasia and fusion may accompany ulnar deficiency. The triquetrum and the capitate are commonly absent in these patients [9]. In addition, the absence of postaxial (ulnar-sided) metacarpal and digital bones are frequent findings in patients with ulnar hemimelia. The most common hand anomaly associated with the disorder is three-fingered hand (tridactyly), closely followed by monodigital hand [2, 9]. Our fourth case presented all these mentioned features. The number

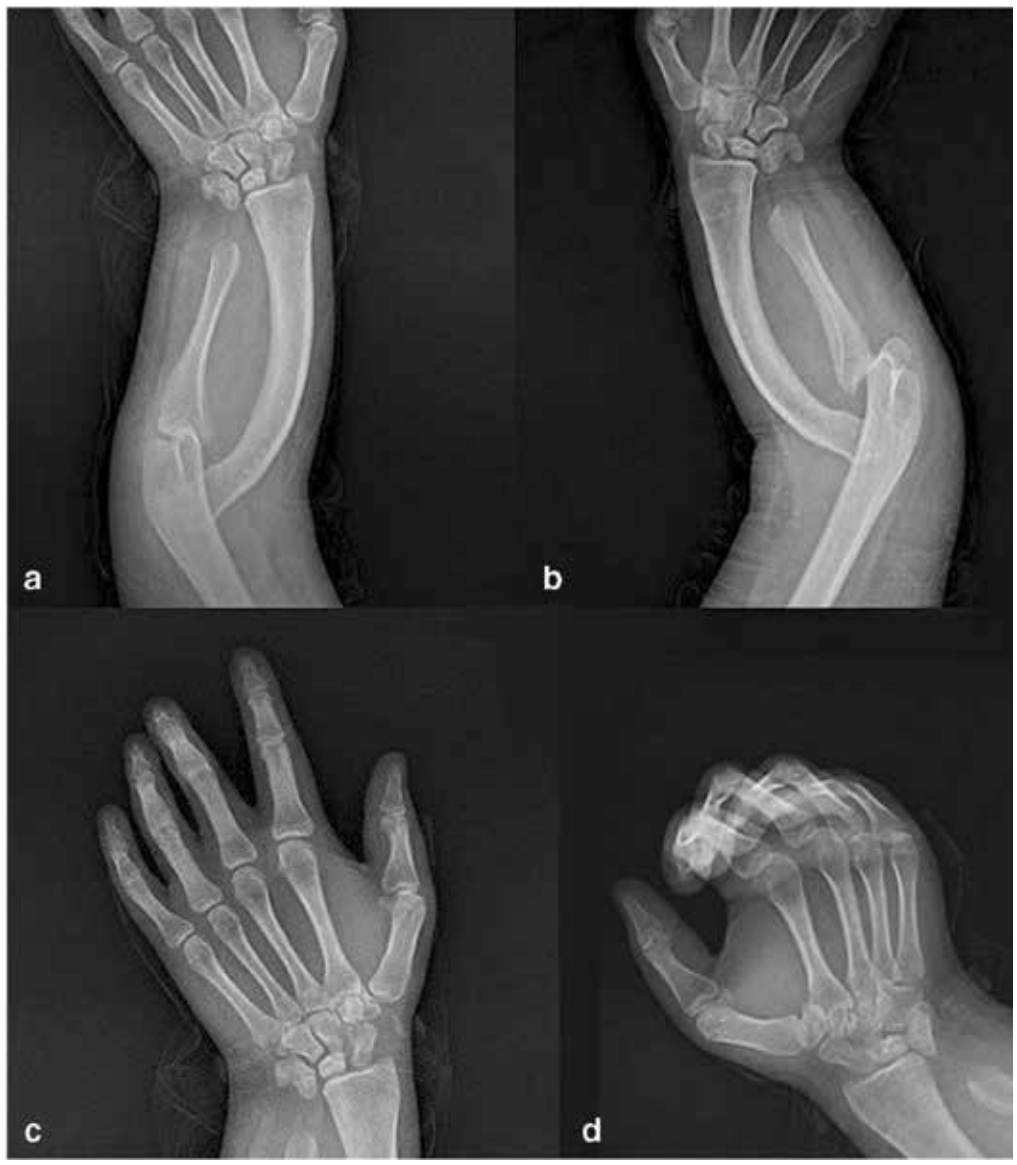


Fig. 6: Anteroposterior radiographs of **a** the right and **b** the left forearm, and anteroposterior radiographs of **c** the right and **d** the left hand. The distal halves of both ulnar bones are absent, and there is fixed flexion of about 45° of both elbow joints. Dislocation of both radial heads, bilateral radial bowing, and mild ulnar-sided drift of the hands are also evident (**a**, **b**). Fixed flexion of the digits of varying degrees is seen (**c**, **d**).

of the deficient digits and the presence or absence of additional digital abnormalities such as syndactyly and camptodactyly (fixed flexion deformity of the interphalangeal joints) closely affect the functionality of the hand [2, 6]. Camptodactyly was present in our second case, and fortunately did not cause serious disability, as the neighboring digits functioned well. In syndromic cases of ulnar hemimelia, the clinical course and the prognosis are reported to depend on the severity of the syndrome [10]. In none of the patients in our series was ulnar hemimelia associated with a syndrome.

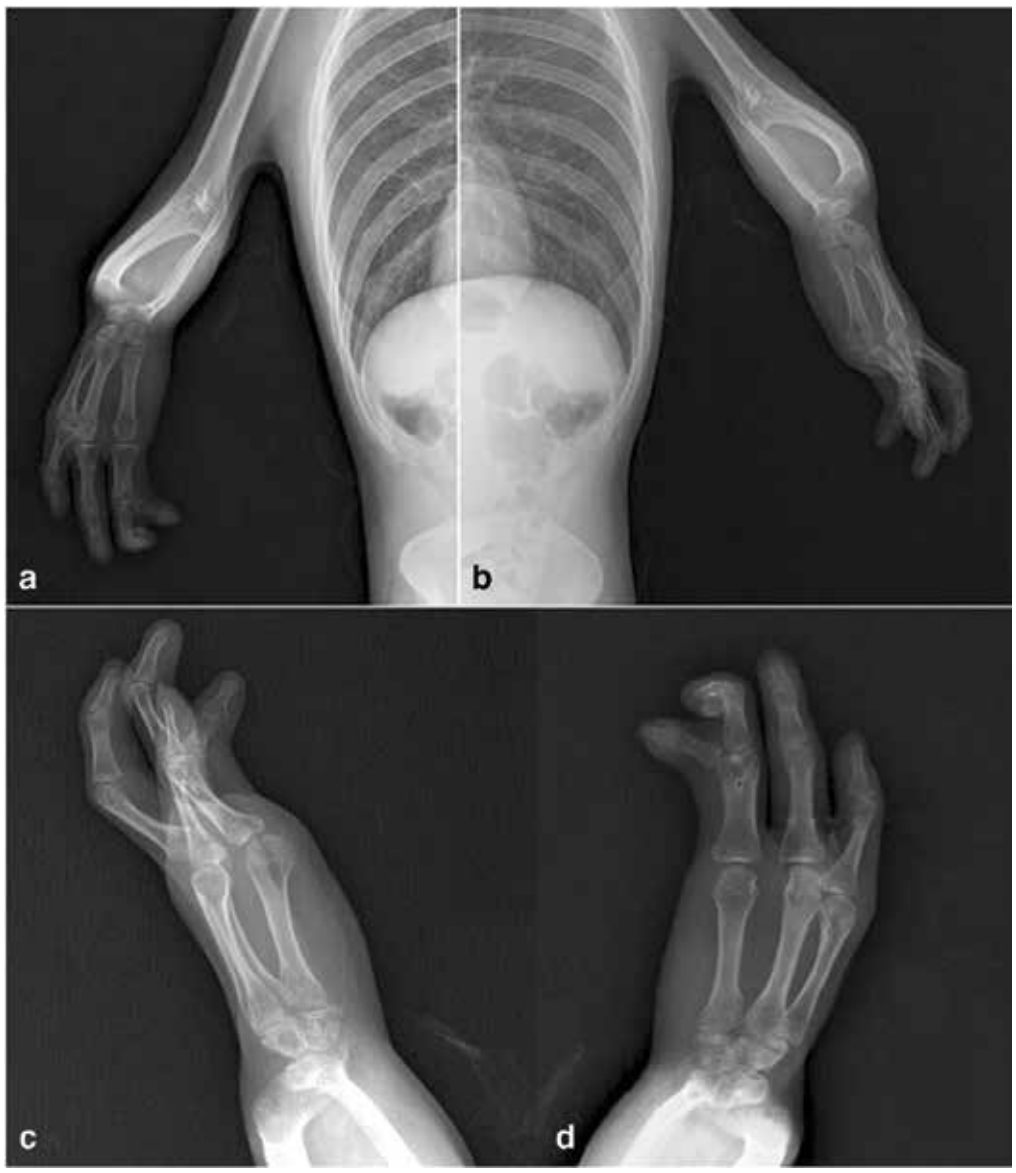


Fig. 7: Anteroposterior radiographs of **a** the right and **b** the left forearm, and anteroposterior radiographs of **c** the right and **d** the left hand. Bilateral ulnar hypoplasia accompanied by bilateral shortening of the limb, humeroradial synostosis, radial bowing, massive carpal coalition, and tridactyly are depicted. Note the limb shortening is more prominent on the left side (**a**, **b**). In both hands, the proximal phalanges of the third digits are bifid, and the medial and distal phalanges of the third digits are duplicated. There is fixed flexion of the digits of both hands of varying degrees (**c**, **d**).

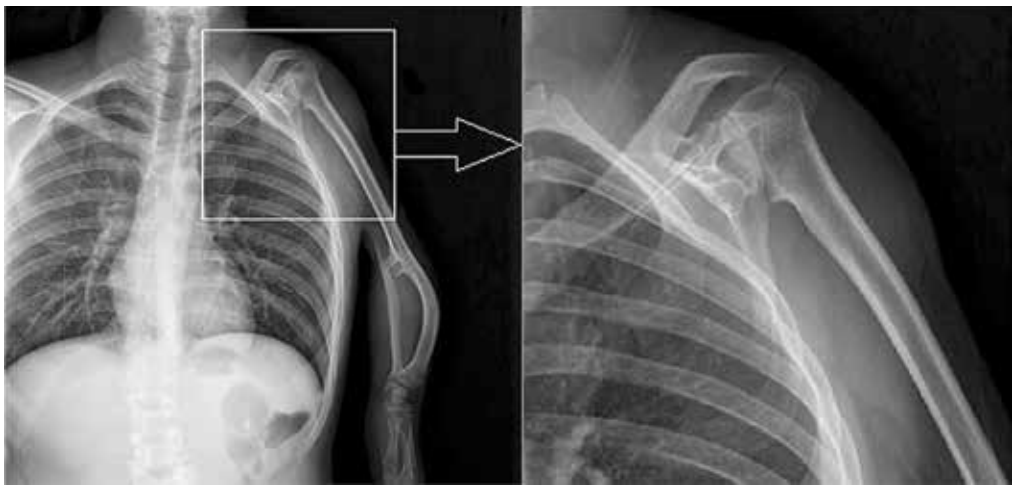


Fig. 8: Anteroposterior radiograph of the left shoulder joint demonstrates glenohumeral dysplasia of the shoulder with a dysplastic and hypoplastic glenoid, a small femoral head, a small scapula and arm, a blunted coracoid process, and muscular atrophy in the arm. Minor rotoscoliosis with the curve convex to the right, L4 butterfly vertebra, and spinal dysraphism at the T12 level are also evident.

The disability caused by ulnar hemimelia and associated anomalies deteriorates in adulthood as disuse atrophy and osteoarthritis are added to the clinical picture. We detected severe osteoarthritis in the humeroradial joint of our second case who was only 20 years old. Early diagnosis and applying an appropriate treatment of ulnar hemimelia is essential, and the diagnosis can be based solely on radiography. Management of the disorder is challenging, and should be highly individualized. The most important factors determining the treatment approach are the severity and complexity of the abnormality, the age of the patient, and the uni-/bilaterality of the disorder. Continuous physiotherapy and training should be given from infancy to avoid disuse atrophy and to obtain maximum functioning of the limb. For the improvement of function in patients with varying degrees of ulnar hemimelia, several nonsurgical management approaches, including elbow prothesis, are available from puberty [1, 2]. In our first and second cases, regular and continuous physiotherapy was applied. In both patients, successful results were obtained in terms of both pain relief and improvement of function. In cases with bilateral involvement and significant reduction in the range of motion, surgical intervention is indicated. Different surgical approaches including Z-plasty, elbow disarticulation, and humeral derotational osteotomy may be performed to improve the range of motion of the elbow joint [1, 2]. A humeral rotational osteotomy was planned for our third case to achieve cosmetic and functional improvement. For our fourth case, glenoid augmentation (bone graft) surgery was performed to create a blocking effect for the patient's instability; however, restriction of movement and pain of the shoulder joint developed early after the surgical intervention.

References available on request
Healthcare.India@springer.com

Source: Özdemir, M., Turan, A. & Kavak, R.P. *Skeletal Radiol* (2019) 48: 1137. https://doi.org/10.1007/s00256-019-3167-x. © ISS 2019.

Joint space narrowing evaluation is the “gold standard” in daily practice and has been recommended as the best available method for assessment of joint-damage progression due to osteoarthritis.

CLINICAL UTILITY AND POTENTIAL OF ULTRASOUND IN OSTEOARTHRITIS

Tadashi Okano[1], Kenji Mamoto[1], Marco Di Carlo[2], Fausto Salaffi[2]

Marco Di Carlo (✉)
dica.marco@yahoo.it

Tadashi Okano
ma1sa3ru@med.osaka-cu.ac.jp

Kenji Mamoto
mamoto7@hotmail.com

Fausto Salaffi
fausto.salaffi@gmail.com

[1] Department of Orthopedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan

[2] Rheumatological Clinic, Università Politecnica delle Marche, Ospedale “C. Urbani”, Via Aldo Moro, 25, 60035 Jesi, Ancona, Italy

Osteoarthritis (OA) is the most common disorder of human joints. OA generates chronic musculoskeletal pain and mobility disability, especially in older people. OA of the knee and hip is diagnosed in 40 % of people aged > 65 years in the UK, and pain is the major symptom of OA causing disability (e.g., difficulty in walking and climbing stairs) [1]. Thus, early detection of OA is necessary to maintain the activities of daily living. In recent years, imaging has aided the detection, prediction and follow-up of OA features [2].

Conventional radiography is used widely for the diagnosis of OA. To assess the damage wrought by OA to knee joints, the radiologic extent of joint space narrowing (JSN) and osteophyte size are the mainstay features. Severity of knee OA is assessed commonly using the Kellgren–Lawrence system, which is a composite score combining osteophyte presence and JSN for the whole knee [3]. JSN evaluation is the “gold standard” in daily practice and has been recommended as the best available method for assessment of joint-damage progression due to OA [4]. However, conventional radiography is not sensitive to early degenerative changes of cartilage (which are already occurring before radiographic reduction of the joint space) and structural alterations visible on conventional radiography (osteophytes and JSN) appear only at the relatively late stages of OA [5, 6]. In contrast to grading using the Kellgren–Lawrence system, feature-oriented atlas-based compartmental radiographic grading according to standards set by the Osteoarthritis Research Society International is becoming deployed more frequently in clinical research [7]. JSN continues

to be applied widely as an indirect indicator of thinning of tibiofemoral cartilage. However, radiographic JSN reflects cartilage thinning and meniscal extrusion and does not demonstrate morphologic damage to cartilage and menisci directly [8, 9].

Currently, magnetic resonance imaging (MRI) is being used increasingly to visualize cartilage and intra-articular structures directly. MRI is the gold standard for assessing the knee joint and is considered to be the most accurate imaging modality for assessment of knee OA [2, 10]. Advantages of MRI include its noninvasiveness, multiplanar capability and excellent soft tissue contrast. Despite its high sensitivity, however, MRI is not usually employed as an initial imaging method for knee OA and is not readily available for serial evaluation of cartilage status due to practical reasons and expense [11]. Thus, MRI is not widely available for routine clinical practice.

The number of OA patients is so large that convenient diagnostic imaging methods are useful. Ultrasound (US) has been less well studied, but recent high-resolution US, which can be dynamic and offer multiplane visualization, has become of great interest in OA research and daily clinical practice. Morphologic changes in the bone surface, menisci and femoral cartilage can be depicted reliably and assessed semiquantitatively and/or quantitatively as single features upon US examination [12–14]. Moreover, US has advantages over other imaging modalities in the ability to visualize structures (e.g., femoral hyaline cartilage) and inflammatory abnormalities. Additionally, US examination is relatively inexpensive, does not involve ionizing radiation and, overall, there are no contraindications to its use [15, 16]. Thus, evidence of the validity of US in comparison with traditional imaging modalities used for OA is increasing [12, 17, 18]. Such evidence supports the idea of deploying US as one of the first-line modalities for detection of the morphologic changes in knee OA. In this review, we describe the specific findings and utility of US for OA assessment.

Ultrasound Findings in Osteoarthritis

Synovitis

Osteoarthritis is regarded widely as being primarily a degenerative disorder of articular cartilage, but which is associated with synovial inflammation. Accurate assessment of synovial inflammation is important for the early diagnosis and evaluation of disease activity not only in inflammatory arthropathies, such as rheumatoid arthritis (RA), but also in OA. In addition to physical and laboratory examinations, evaluation of inflamed tissues using noninvasive imaging in daily clinical practice is important. Although conventional radiography shows lesions affecting bone structure, detection of synovial inflammation using radiography is difficult.

> “ ***Ultrasonography and magnetic resonance imaging have been recognized as valuable imaging tools to evaluate inflammation severity in synovial tissues.***

Ultrasonography (US) and magnetic resonance imaging (MRI) have been recognized as valuable imaging tools to evaluate inflammation severity in synovial tissues [19, 20]. The Outcome Measures in Rheumatology (OMERACT) US Working Group defined “synovial hypertrophy” as abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular tissue (Fig. 1a) that is nondisplaceable and poorly compressible and which may exhibit a Doppler signal [21]. The power Doppler (PD) signal in ultrasound (PDUS) can visualize the degree of synovial inflammation (Fig. 1b). For example, in RA, a high PDUS is associated with pathologic findings of active synovitis, including neovascularization and intensive infiltration of inflammatory cells such as macrophage-like synoviocytes and T-helper-17 cells [22]. Positive PDUS findings illustrate more faithfully active synovitis defined by histopathology than MRI, but the distinct features of both modalities for clinical assessment of chronic joint diseases are important [23].

Synovial Fluid

The OMERACT US Working Group defined “synovial fluid” as abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular material that is displaceable and compressible, but does not exhibit a Doppler signal [21] (Fig. 2a). The appearance of synovial fluid with anechoic or inhomogeneous hypoechoic intra-articular material is dependent upon its composition and the presence of intra-articular debris and proteinaceous or calcified material (Fig. 2b). The amount of synovial fluid tends to correlate with the inflammatory activity in that joint. US can also be used as a guide for fluid aspiration as soon as it is found in the joint. Fluid aspiration is very important for resolving pitfalls in differential diagnoses.

Cartilage

Ultrasound assessment of cartilage has limitations since the acoustic window has only a small area of cartilage available for imaging [24]. For example, some part of the femoral cartilage is visible, but most parts of tibial and patellar cartilages in the knee joint are not visible. Moreover, the scanning technique (e.g., maintenance of the probe angle perpendicular to the underlying structures) is important to visualize the cartilage layer. However, normal hyaline cartilage is imaged clearly by US as a homogeneously anechoic layer lining the bony cortex and having a superficial and deep margin that appears thin, sharp, continuous and regularly hyperechoic (Fig. 3a). “Pathologic change of cartilage” in US is defined as loss of sharpness and/or irregularities of the superficial/deep margin, loss of the normal anechoic echostructure, as well as focal and asymmetric thinning up

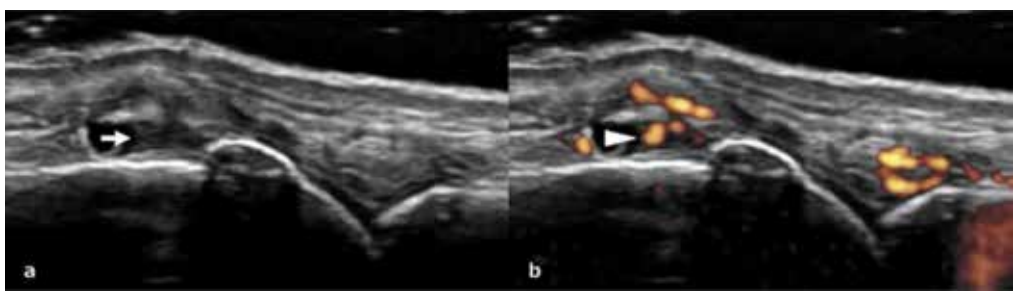


Fig. 1: **a** Synovial hypertrophy (*arrow*) is observed in metacarpophalangeal joint. **b** Power Doppler signal in the synovial tissue (*arrow head*) indicates inflammatory synovitis. **a**, **b** Longitudinal scans.

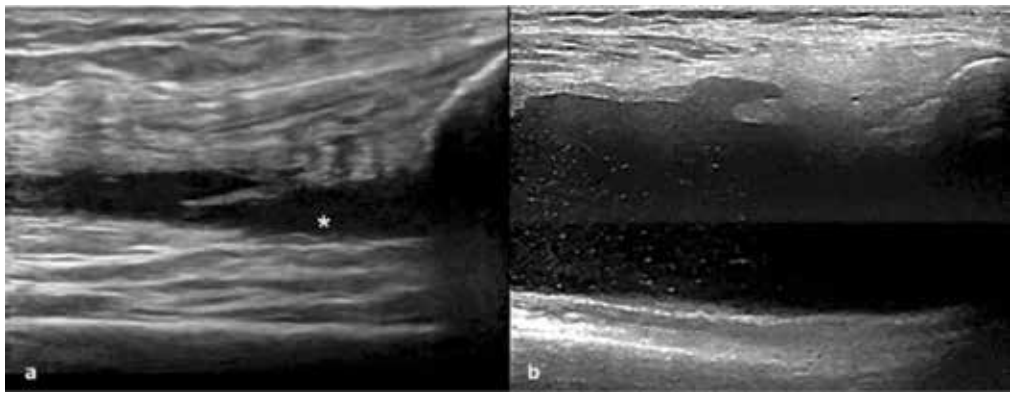


Fig. 2: **a** Synovial fluid as abnormal anechoic area (*asterisk*) in knee joint. **b** Multiple calcified materials are observed in knee synovial fluid of patient with calcium pyrophosphate deposition disease. **a**, **b** Longitudinal scans.

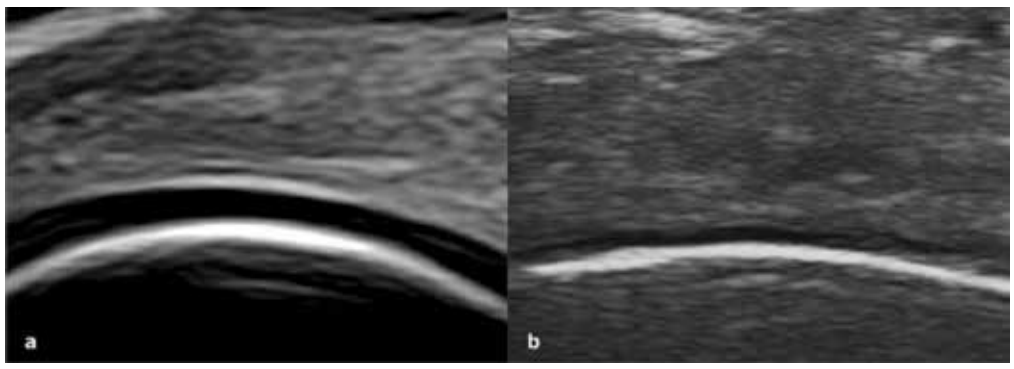


Fig. 3: **a** Normal hyaline cartilage is visualized as a homogeneously anechoic layer (Aplio i800 with 24-MHz probe "ultra-high-frequency transducer," Canon Medical Systems). **b** Damaged hyaline cartilage. **a**, **b** Transversal scans.

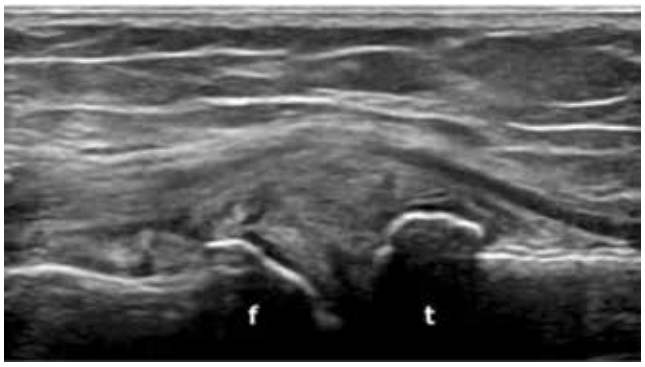


Fig. 4: Osteophytes in both distal medial femoral condyle (f) and proximal tibia (t) in knee joint. Longitudinal scan.

to the complete absence of the cartilaginous layer [25] (Fig. 3b).

Osteophytes

An osteophyte is defined as a step-up of the bony prominence at the end of the normal bone contour or at the margins of the joint seen in two perpendicular planes, with or without an acoustic shadow [25] (Fig. 4). Usually, on US, an osteophyte has a posterior acoustic shadow, and the size of the osteophyte correlates with the severity of joint damage and duration of OA. US has been shown to be more sensitive for the detection of osteophytes, even of minimal size, than conventional radiography [25, 26]. US found 20 knees with medial femoral osteophytes in 46 knees in which conventional radiography did not detect any osteophytes and 26 knees with lateral osteophytes in 66 knees for which conventional radiography did not detect any osteophytes [26]. Acquisition of multiplanar US images allows for visualization of even tiny, hidden osteophytes.

Erosion

An erosion is defined as an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes in US [25] (Fig. 5). Typical findings in OA are breakdown of joint cartilage as well as increased bone formation and increased numbers of osteophytes around the joint. Thus, bone erosion seems to be an opposite finding in OA. However, erosive OA (sometimes called "inflammatory OA") with more inflammatory signs, such as synovial hypertrophy, PDUS and effusion, is recognized an important subtype of hand OA. In the latter, it has been reported that the PDUS (but not synovial hypertrophy) is associated with erosive progression on conventional radiography [27].

Knee Osteoarthritis

Ultrasound Findings in Knee Osteoarthritis

Although OA can affect one or more joints in the body, knee OA is the most common and involves the entire joint tissues: menisci, ligaments, subchondral bone, capsule, synovium and periarticular muscles [28]. Prevalence of knee OA in older populations is increasing and leads to a lower quality of life and working disability, which has major implications for health care and the overall economy [29, 30]. Degeneration of articular cartilage and menisci, formation of osteophytes, bone erosion, effusion and synovial inflammation are structural and compositional hallmarks of knee OA. High-resolution US can be employed to assess the superficial structures in a knee joint, such as synovial tissue, cartilage, menisci, osteophytes and popliteal cysts (Baker's cyst).

Synovitis in Knee Osteoarthritis

Synovial proliferation in knee OA is usually low grade, which can be visualized with/without synovial fluid and/or PDUS, though some patients have severe synovitis as the same as in RA. In RA patients, the degree of PDUS has been found to predict development of joint damage such as erosions. A prospective study provided evidence that OA synovitis also generates joint-damage progression, and that US-detected effusion is a predictor of the requirement of total knee arthroplasty [31]. Thus, US-detected synovitis of knee OA can be a target of treatment, as well as demonstrating that US may be a useful outcome measure for studies involving inflammation treatment.

Cartilage in Knee Osteoarthritis

Establishing clinical measurements of cartilage health and identifying changes in cartilage status are very important for evaluating the effectiveness of protocols to reduce the risk of the development and progression of knee OA [32]. Although evaluation of knee cartilage by US can be limited due to the depth and lack of adequate visualization, some diseases can be detected clearly

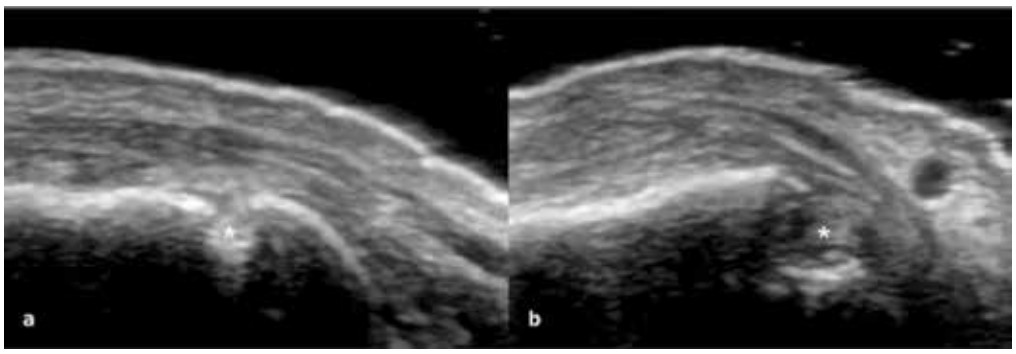


Fig. 5: An ultrasound-detected bone erosion (*asterisk*) is discontinuity of the bone surface that is visible in two perpendicular planes at metacarpal head, longitudinal dorsal scan (**a**) and transverse dorsal scan (**b**).

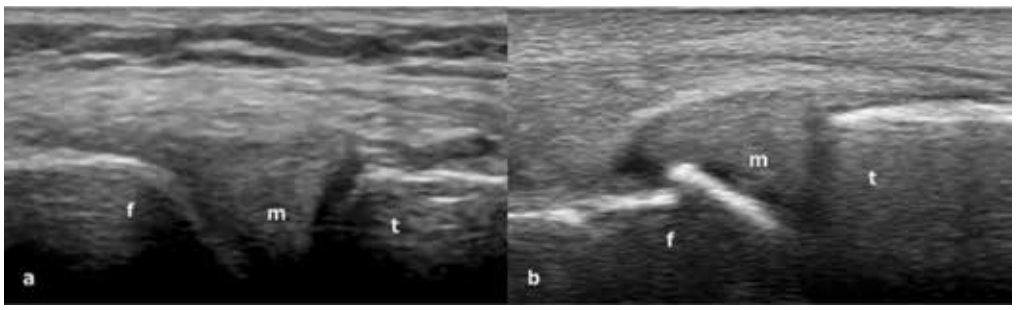


Fig. 6: **a** Normal position of medial meniscus. **b** Medial meniscal extrusion with small osteophyte in femoral bone in OA patient. f: Medial femoral condyle, t: proximal tibia, m: medial meniscus. **a**, **b** Longitudinal scans.

by high-resolution US. Using US, the normal hyaline articular cartilage is visualized as a hypoechoic layer, typically 1.5–2 mm in thickness [33]. Cartilage thickness is an important measure to detect the onset and progression of OA because structural changes in the development and progression of clinical OA are characterized by thinning and loss of cartilage. Patients with knee OA have less tibiofemoral cartilage compared with healthy people [34, 35]. It has been suggested that the center of the medial femoral cartilage should be assessed to evaluate changes in cartilage morphology at the early stage of knee OA [36]. Therefore, accurate and effective tools to measure medial femoral cartilage thickness could be clinically useful and necessary to detect cartilage defects and monitor the treatment effects for them. In diagnostic assessment of cartilage thickness, US can be an alternative measure as a clinically available and cost-effective imaging method for articular cartilage of the knee [37]. We reported that US-assessed damage to the medial femoral cartilage correlated strongly with radiographic narrowing of the medial tibiofemoral joint, and that US was a sensitive imaging method for detecting cartilage damage even in the early radiographic stages of knee OA [26]. In a comparison between US and MRI for measuring cartilage thickness in the medial femoral condyle, Randy *et al.* reported that transverse and longitudinal US measurements were significantly positively correlated with MRI measurements and, thus, US could be used to assess cartilage thickness in medial femoral regions (middle and posterior) [38].

Menisci in Knee Osteoarthritis

Medial and lateral menisci are visualized by US as hyperechoic triangular-shaped structures between the femur and tibia (Fig. 6a). Although the peripheral aspects of menisci are visualized clearly, the inner regions are often poorly identified and, in particular, overall visualization of the lateral meniscus tends to be limited [39]. Meniscal injuries are common in athletes and require an optimal protocol for the diagnosis. It has been reported that the sensitivity and specificity of US examination for the diagnosis of a meniscal tear are 88 % and 85 %, respectively [39]. In another report, US could be used to identify medial and lateral meniscal injuries with an accuracy comparable with that of MRI [40]. Conversely, it is often difficult to differentiate internal meniscal degeneration by US, so MRI is warranted for detection and further assessment. However, some studies have reported that US assessment is a more accurate imaging method for the detection of medial meniscal extrusion (Fig. 6b) (which is caused by knee OA and related to knee pain and radiographic medial JSN) than radiographic assessment [18]. Moreover, dynamic US assessment of menisci in the unipodal weight-bearing position before and after walking 50 m might be a reproducible method for the assessment of meniscal subluxation [41].

> *Ultrasound was found to be a sensitive imaging method for detecting tiny osteophytes even in the early radiographic stages of knee osteoarthritis.*

Osteophytes in Knee Osteoarthritis

Ultrasound is easy to visualize osteophyte. Thanks to the multiplanar scanning technique. Excellent agreement was found between ultrasound observers for the presence of osteophytes in knee OA [42]. Koski *et al.* [12] demonstrated that semiquantitative US was more sensitive than radiography for identification of osteophytes in the medial compartment of a knee joint with OA. We revealed significantly positive correlations between the radiographic and US grades of femoral osteophytes for medial and lateral sides. Moreover, US was found to be a sensitive imaging method for detecting tiny osteophytes even in the early radiographic stages of knee OA [26].

Baker's Cyst

A Baker's cyst refers to a fluid-filled swelling in the posterior side of the knee that causes stiffness and pain (Fig. 7). A Baker's cyst is considered one of the inflammatory signs of knee OA. US examination of the popliteal fossa can detect a Baker's cyst more often than clinical examination even in patients without symptoms at the popliteal fossa [43]. A prospective cohort study showed accelerated radiologic progression in patients with knee OA with a Baker's cyst at baseline evaluated by US over 2 years [44]. Cyst aspiration with US-guided corticosteroid injection from the posterior side of the knee yielded clinical improvement and cyst-volume reduction in patients with a Baker's cyst secondary to knee OA [45]. Intra-articular corticosteroid injections in patients with knee OA have been shown to reduce the dimensions and wall thickness of a Baker's cyst [46]. Thus, US examination of the popliteal fossa should be undertaken to detect a Baker's cyst to prevent advancement of knee OA.

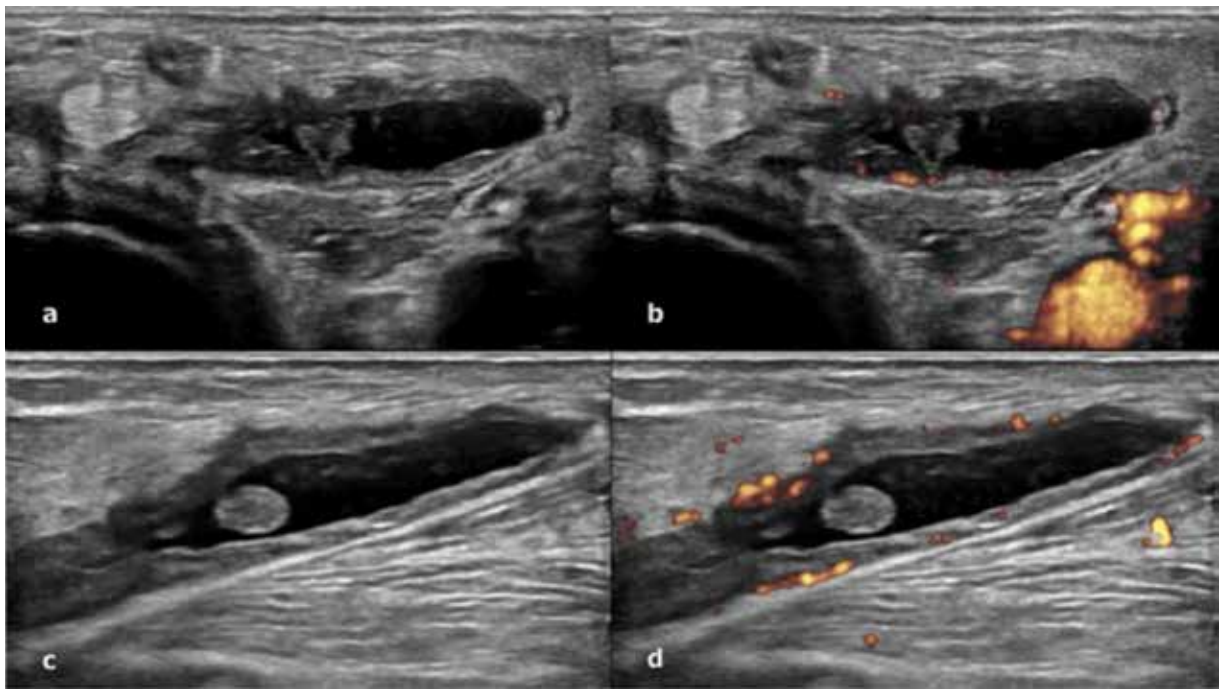


Fig. 7: Baker's cyst in the posterior aspect of the knee. Power Doppler signal is positive in the proliferative tissue inside the cyst (**b, d**). **a**, **b** Transverse scans and **c**, **d** longitudinal scans.

Differential Diagnoses in Knee Osteoarthritis

Other diseases that should be differentiated from knee OA are crystal-induced arthropathies such as gout and calcium pyrophosphate deposition disease (CPPD). Typical US findings in articular cartilage can be detected in both diseases.

In the knee of the patients with gout, crystals of monosodium urate may appear as hyperechoic lines on the surface of the hyaline cartilage ("double contour sign" [DCS]) [47] (Fig. 8). In one study, DCS identification indicated gout with 83 % sensitivity and 76 % specificity and disappeared when the serum level of uric acid was < 6 mL/dL [48]. The DCS is differentiated from the normal cartilage interface in that of the latter as a smooth, less bright continuous interface identified only if the cartilage surface is perpendicular to the transducer sound beam. The DCS of gout should be differentiated from chondrocalcinosis (which is seen in CPPD and other conditions), which appears as hyperechoic calcific foci within the hyaline cartilage [47, 49]. CPPD is characterized by intra-articular and/or periarticular deposition of CPP crystals [50]. Deposits of CPP crystals can be found in the hyaline cartilage (Fig. 9a) and fibrocartilage of the knee [51]. US is very useful for detecting CPP crystals in the knee joint and has a key role in the diagnosis of CPPD. Gutierrez *et al.* reported that "spots" on the hyaline cartilage were detected by US in ≥ 1 knee in 59.5 % of patients with CPPD,

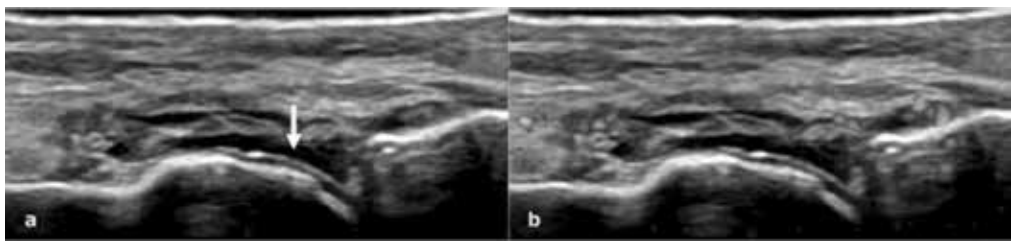


Fig. 8: **a** Double contour sign (*arrow*) on metatarsal head in patient with gout. **b** Low-grade inflammation was observed. **a**, **b** Longitudinal scans.

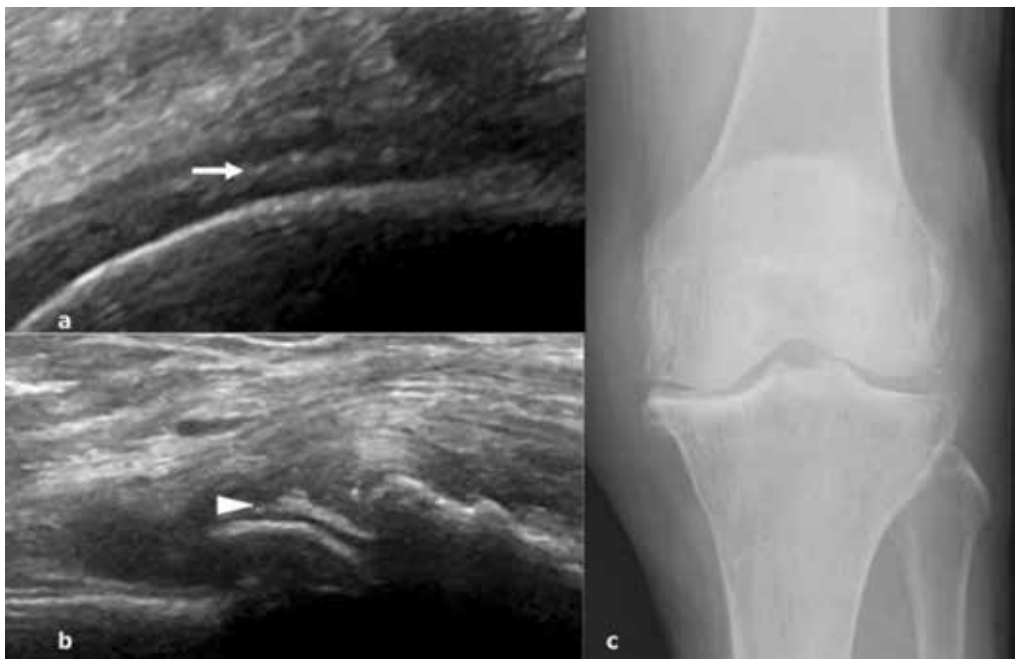


Fig. 9: **a** Calcification in medial meniscus in patient with calcium pyrophosphate deposition disease (*arrow*). **b** Calcification in femoral hyaline cartilage (*arrow head*). **c** Conventional radiography in this patient. **a**, **b** Longitudinal scans.

whereas radiography detected hyaline-cartilage spots in 45.9 % of them ($P < 0.001$). They reported that US was an accurate and reliable imaging method for detection of calcification of articular cartilage in the knee joint in patients with CPPD [52]. CPPD may also involve menisci (Fig. 9b), appearing as an internal hyperechoic area [53]. In one study, US was used to detect meniscal fibrocartilage calcifications in 90.5 % of CPPD patients,

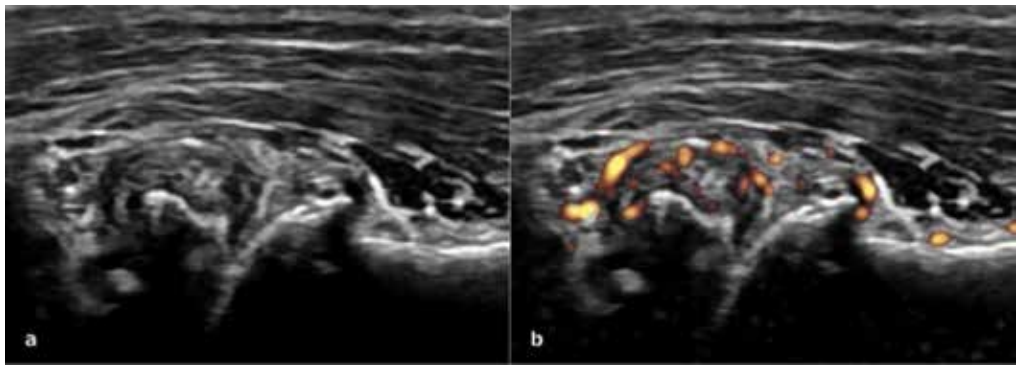


Fig. 10: **a** Osteophyte and synovial proliferation in the first carpometacarpal joint. **b** Power Doppler signal was found in the proliferative synovial tissue. **a**, **b** Longitudinal scans.

whereas conventional radiography detected calcifications in 83.7 % of them ($P = 0.011$). US can be a more accurate imaging tool to detect calcifications in menisci than radiography [52] (Fig. 9c).

Hand Osteoarthritis

Ultrasound Findings in Hand Osteoarthritis

Hand OA is a prevalent disease causing considerable pain and disability [54]. Haugen *et al.* reported a prevalence of hand OA in 44 % of women and 38 % of men aged 40–84 years using radiography [55]. However, the prevalence of hand OA using radiography is not known because of the considerable variation between studies, which may be due to differences in types of populations, disease definitions and/or risk factors (e.g., genetic background or environmental exposures) across study cohorts [56]. Hand OA is found frequently in the first carpometacarpal joint and 2–5 distal interphalangeal (DIP) joints, but is also found in 1–5 proximal interphalangeal joints and 1–5 metacarpophalangeal joints. High-resolution US can be used to assess the superficial structures in finger joints, such as synovial tissue, cartilage and osteophytes.

Cartilage in Hand Osteoarthritis

Ultrasound assessment of cartilage in the finger joints is done upon maximal flexion of the joint (Fig. 3a). The OMERACT US Working Group proposed a semiquantitative scoring system using US for cartilage abnormalities in hand OA [57]. This four-point scale was: 0 = normal cartilage (anechoic structure, normal margins of cartilage); 1 = loss of anechoic structure and/or focal thinning of the 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 the cartilage layer and irregularities and/or loss of sharpness of at least one cartilage margin; 3 = focal absence or complete loss of the cartilage layer. High-frequency probes can clearly show the detail of the finger cartilage even with minimal (e.g., 0.1 mm) change. This advanced technology will be useful for detailed observation of cartilage degeneration in longitudinal studies and for verification of some disease-modifying OA drugs.

Osteophytes in Hand Osteoarthritis

Osteophytes are also representative findings in hand OA. Radiographic- and US-detected osteophytes in finger joints have been demonstrated to be related to pain [58]. US has been shown to be more sensitive than clinical examination or radiography for the detection of finger osteophytes [59] (Fig. 10a). Mathiessen *et al.* [60] reported good agreement between osteophytes detected by US and MRI, which could be due to the demonstration of multiplanar joints by US. Acquisition of multiplanar US images allows for visualization of even tiny, hidden osteophytes.

Synovitis in Hand Osteoarthritis

High-quality US is a promising tool for detecting OA synovitis. OA has demonstrated a high prevalence of synovitis in painful hand joints with OA. Sustained synovitis generates articular erosions which are frequently found in RA. Mathiessen *et al.* [56] reported that US-detected grayscale synovitis (Fig. 10a) and PDUS (Fig. 10b) were associated significantly with radiographic progression after 5 years. US can also confirm the response to synovitis treatment. Klauser *et al.* [61] undertook US-guided intra-articular injections of hyaluronic acid in patients with hand OA, and a decrease in joint thickening and PDUS was found.

Differential Diagnoses in Hand Osteoarthritis

Psoriatic arthritis (PsA) is an inflammatory arthritis that develops in 5–40 % patients with psoriasis [62]. One of the characteristics of PsA is periosteal proliferation in the joints and inflamed entheses. PsA affects the DIP joint frequently, and arthritis in the DIP joint can be confused with OA, and periosteal proliferation at the level of the DIP joints goes into differential diagnosis with OA osteophytes. High-resolution, peripheral, quantitative computed tomography (CT) has shown the differences between osteophytes and periosteal proliferation in these two diseases [63]. The overall number and size of proliferative changes and osteophytes were similar in patients with PsA and cases with hand OA. However, localization of lesions within individual joints is substantially different between patients with PsA and those with hand OA. US can also be used to show differences in the shape and location of osteophytes in patients

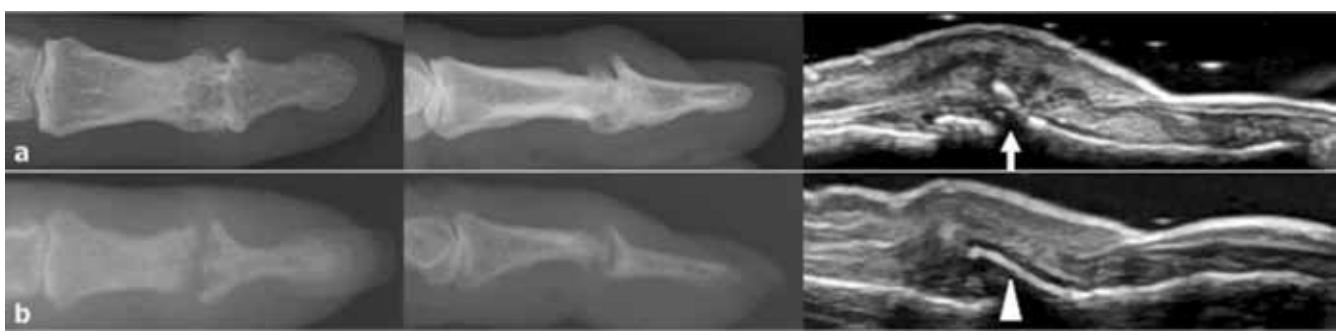


Fig. 11: **a** The osteophyte observed in hand OA nearly perpendicular to the joint space (*arrow*). **b** The periosteal proliferation in patients with psoriatic arthritis (*arrow head*), in a joint with associated erosive changes. **a**, **b** US images are longitudinal scans of the distal interphalangeal joints.

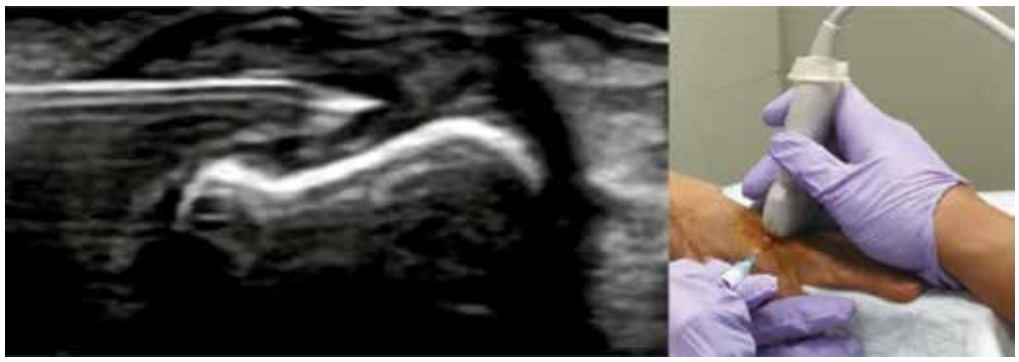


Fig. 12: Ultrasound-guided injection in metacarpophalangeal joint. Transversal scan.

with inflammatory conditions. The osteophytes were observed in hand OA nearly perpendicular to the joint space because they are due to OA (Fig. 11a). Conversely, the proliferative changes seen in PsA due to enthesitis are usually parallel to the tendon fiber, capsule and ligament (Fig. 11b).

Ultrasound-guided Injections in Osteoarthritis

Intra-articular injections of corticosteroids have been used for several decades for the management of inflammatory and degenerative joint conditions such as OA and RA if first-line conservative therapies (rest, ice and anti-inflammatory medications) cannot provide adequate relief from symptoms. Intra-articular corticosteroid injections provide short-term benefit and clinical efficacy for chronic knee pain [64]. More recently, various injectable hyaluronic acid agents have become available and gained clinical acceptance as effective treatments for knee OA. These agents are indicated for treatment of the pain associated with knee OA in patients who do not respond adequately to conservative therapies.

Traditionally, intra-articular injections have been carried out using anatomic landmarks to identify the correct trajectory for needle placement. However, different anatomic-guided methods of injection have yielded inconsistent positioning of the needle. This has been due, in large part, to the fact that the treating physician cannot visualize the area of interest directly, and variations in anatomy are common. Incorrect placement of the needle has been attributed (at least in part) to variable clinical outcomes [65]. Furthermore, inaccurate corticosteroid injections in the knee, for example, can result in post-injection pain, crystal synovitis, hemarthrosis, joint sepsis, atrophy of articular cartilage, as well as systemic effects (e.g., fluid retention or exacerbation of hypertension or diabetes mellitus) [66]. Therefore, identification of methods and appropriate training to aid correct placement of the needle during these procedures are warranted.

> *The sonographer should recognize the advantages and disadvantages of each imaging modality, normal anatomy of the structures and the appropriate examination method to maximize the potential of ultrasound.*

Fluoroscopy, CT and MRI can be used to improve the accuracy of intra-articular injections. However, musculoskeletal US is very practical because it is rapid, safe, relatively inexpensive, emits no ionizing radiation and can be undertaken in the outpatient clinical setting [67]. US enables identification of vascular and nervous structures and demonstrates needle movement in real time [68]. David *et al*. reported that US guidance resulted in better accuracy than anatomic guidance (95.8 % vs 77.8 %, $P < 0.001$) in knee injections, and that the enhanced accuracy of injection achieved with US-based needle guidance improved patient-reported clinical outcomes and cost-effectiveness directly [69]. Accuracy of the injection is more important in smaller joints (Fig. 12), and US-guided injection is also quite useful in hand OA.

Conclusions

Imaging is the mainstay for OA patients management in daily clinical practice, and conventional radiography remains the gold standard. Nevertheless, in comparison with radiography, US performs at least equally or even better for identification of osteophytes and morphologic degeneration of cartilage. US provides relevant additional diagnostic information on pathologic changes in soft tissue (e.g., synovitis, meniscal injuries and Baker's cyst), not detectable by conventional radiography. Consequently, the use of US as a complementary imaging tool along with radiography (especially if MRI is not justified) could enable more accurate and cost-effective diagnostics of knee OA at the primary-healthcare level.

In recent decades, MRI has become the gold standard imaging modality for different knee diseases, but US offers some advantages over MRI. US equipment is, in general, less expensive than MRI devices. US allows dynamic examination—the sonographer can observe visualized tissues during active and passive motion. Hence, US could be used to detect a range of pathologic processes of the knee and complement MRI, especially if the knee is evaluated dynamically. However, the major limitation of US in OA assessment is that only superficial tissues can be visualized. Hence, subchondral bone-marrow lesions and cysts, which can be shown by MRI can, therefore, not be detected using US. The sonographer should recognize the advantages and disadvantages of each imaging modality, normal anatomy of the structures and the appropriate examination method to maximize the potential of US.

Compliance with ethical standards

Conflict of interest: The authors declare no conflicts of interest.

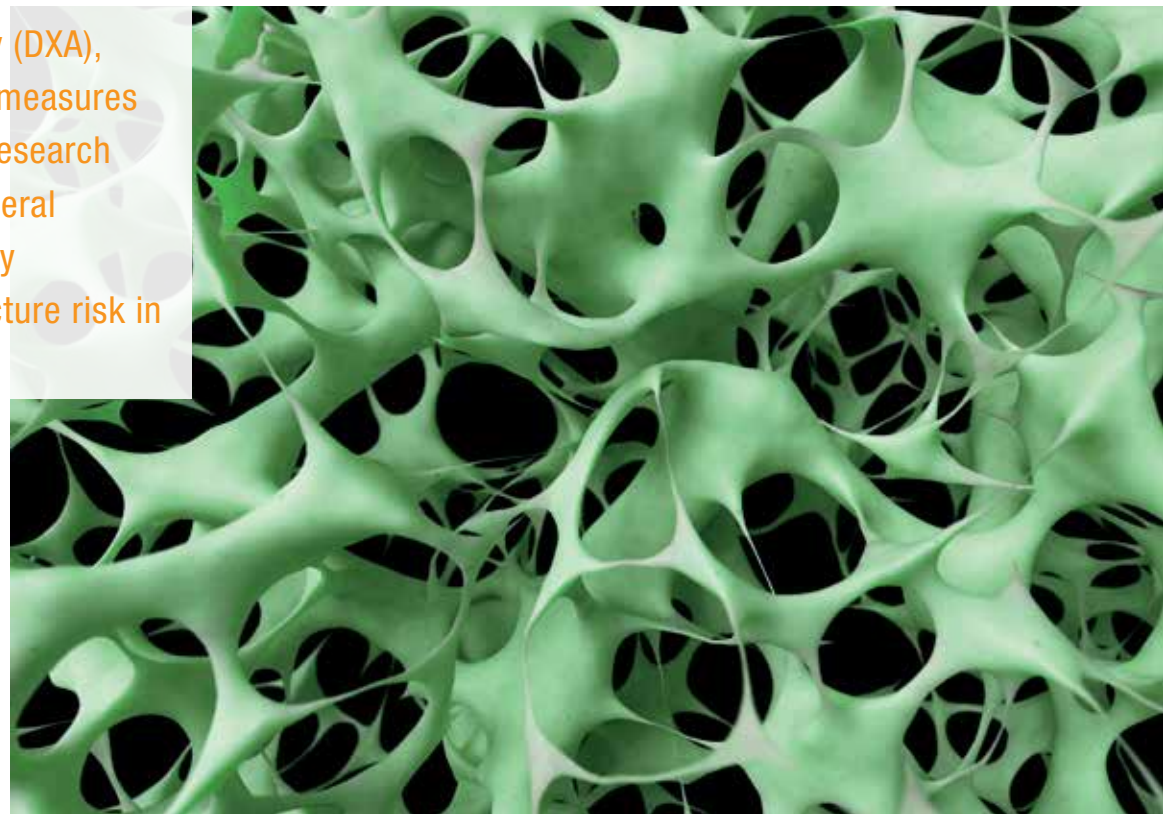
Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

Publisher's Note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References available on request
Healthcare.India@springer.com

Source: Okano, T., Mamoto, K., Di Carlo, M. *et al. Radiol med* (2019). https://doi.org/10.1007/s11547-019-01013-z.

Dual-energy X-ray absorptiometry (DXA), clinical assessment, biochemical measures of bone remodeling, and, from a research standpoint, high-resolution peripheral quantitative computed tomography (HRpQCT) can help determine fracture risk in rheumatoid arthritis (RA) patients.



OSTEOPOROSIS PATHOPHYSIOLOGY, EPIDEMIOLOGY, AND SCREENING IN RHEUMATOID ARTHRITIS

Giovanni Adami[1,2], Kenneth G. Saag[1] (✉)

Kenneth G. Saag
ksaag@uabmc.edu

[1] Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, 510 20th Street South, Faculty Office Tower 820D, Birmingham, AL 35294, USA

[2] Rheumatology Unit, University of Verona, Pz Scuro 10, 37135 Verona, Italy

This article is part of the Topical Collection on *Rheumatoid Arthritis*

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by local and systemic bone loss [1]. Osteoporosis (OP) is one of the major comorbidities of RA and is caused by a number of complex pathophysiologic processes. Bone fragility in RA results from a mix of systemic inflammation, circulating autoantibodies, and pro-inflammatory cytokine secretion that collectively have deleterious effects on bone. Glucocorticoids, used more for the treatment of RA than for any other inflammatory disease, also play a crucial role in the development of OP in RA. Even with adequate OP primary prevention strategies, through appropriate calcium and vitamin D dietary supplements and acceptable physical exercise, most RA patients will develop OP during the progression of the disease. OP screening strategies are crucial for fracture prevention in RA patients since they have unique risk factors relative to the general population. Dual-energy X-ray absorptiometry (DXA), clinical assessment, biochemical measures of bone remodeling, and, from a research standpoint, high-resolution peripheral quantitative computed tomography (HRpQCT) can help determine fracture risk in RA patients.

Pathogenesis of Bone Loss in Rheumatoid Arthritis

Although there is mechanistic overlap, we separately discuss local bone loss (at the joint level) and systemic bone loss.

Local Bone Loss

Periarticular osteopenia results from the reduction of bone trabeculae, both in number and in dimension. Periarticular osteopenia is the consequence of cortical bone thinning at the insertion of the inflamed synovium, the predominant site of bone erosions in RA [1]. RA patients have increased cortical porosity with lower volumetric bone mineral density (BMD) at both trabecular and cortical site [2, 3]. Local bone loss is an early change in

RA patients associated with development of aggressive systemic disease [4]. Bone marrow edema, an early sign of periarticular bone loss [5] and the decline in hand bone mineral density [6], is independently associated with the development of bone erosions. Moreover, peripheral bone mineral density loss is a hallmark of pre-clinical arthritis [7]. The pathogenesis of local bone loss is multifactorial. Not surprisingly, traditional pro-inflammatory cytokines play an important role in the development of periarticular osteopenia. Lower BMD and microstructural deterioration of the bone are related to systemic inflammation and cytokine release (e.g., tumor necrosis factor [TNF] and interleukin 6 [IL-6]) [2, 3]. In addition, T cell–derived receptor activator of nuclear factor kappa-B ligand (RANKL) [8, 9] and autoantibodies against citrullinated proteins (ACPA) are determinants of bone loss [10, 11]. Interestingly, metacarpal bone loss, detected with HRpQCT, was seen in ACPA-positive RA and not in ACPA-negative RA or in other inflammatory diseases such as psoriatic arthritis or inflammatory bowel disease [12]. In addition, ACPA-mediated detrimental activity on periarticular bone loss was also found in sporadic (5.3 %) ACPA-positive psoriatic arthritis patients [13]. The latter evidence supports the recent hypothesis of a direct and independent effect produced by ACPA on osteoclasts [14], an effect potentially mediated by IL8-dependant osteoclast activation [15] that, in turn, confers a particular susceptibility of periarticular bone loss in ACPA-positive RA patients.

Systemic Bone Loss

Systemic bone loss leads to OP with an increased risk of fragility fractures. In RA patients, systemic bone loss seems to start early in disease development and in some patients even before the clinical onset of RA [16••]. Both trabecular and cortical bone are affected but cortical sites (i.e., femoral neck and distal radius) appear to be more susceptible to OP [17]. The pathogenesis of systemic and local bone loss in RA is similar. Several studies attest to the critical role inflammation plays in the development of systemic OP in RA. For example, cytokines such as TNF, IL6, IL1, and immune cell-derived RANKL had a detrimental effect on osteoblastogenesis and a positive effect on osteoclastogenesis [18]. Furthermore, RA patients with low BMD displayed high level of circulating senescent CD4+CD28− T cells, cells that expressed RANKL to a greater extent than CD28+ T cells and more efficiently induced osteoclastogenesis [9]. In addition, autoantibodies directed against osteoprotegerin (OPG), a decoy receptor of RANKL, have been discovered in RA patients and are related to higher levels of bone resorption markers [19]. Another important factor in the development of OP in RA is Dickkopf-related protein 1 (Dkk-1), a Wnt signaling inhibitor, that is a key regulator of joint remodeling in RA [20••] that plays a significant role in systemic bone [21]. A 2018 meta-analysis on 1305 patients and 504 controls showed significant elevation of Dkk-1 serum levels in RA patients [22].

> “
> ***Osteoporosis is one of the most common comorbidities associated with rheumatoid arthritis (RA). Data from the UK Clinical Practice Research Datalink (CPRD) showed that the incidence ratio of osteoporosis in RA patients who were not taking glucocorticoids was 7.5 per 1000 person-years, compared to 4.1 per 1000 person-years in healthy controls, with an estimated incidence rate ratio of 1.8.***

Similarly to periarticular bone loss, ACPA are associated with systemic bone loss, with a titer-dependent effect on BMD [23]. The deleterious role of ACPA on bone density may pre-date the onset of clinical arthritis by years, even at systemic level [16]. Glucocorticoids are widely prescribed for the treatment of RA and, at higher doses, have a well-known detrimental effect on bone [24–26, 27•]. Nevertheless, the role of low-dose and short-term treatment with glucocorticoids is controversial [28]. Indeed, reducing systemic inflammation with lower dose glucocorticoids might counteract their unfavorable effects on bone with a resulting null or even positive net bone outcome. In accordance with this hypothesis, many studies and meta-analyses demonstrated that low-dose glucocorticoid users affected by active RA do not experience significant BMD changes compared to controls [29–31]. In contrast, even low-dose glucocorticoid and intra-articular glucocorticoids may not be entirely innocuous to bone [32, 33]. A thoughtful case–control study of hip fractures suggested that both RA and glucocorticoids are likely independent risk factors to bone [34].

The etiopathogenesis of systemic and periarticular bone loss overlaps and shares a common pathway. Moreover, periarticular bone loss is enhanced by the post-menopausal state, present in many RA patients [35], raising the interesting possibility that OP might increase the susceptibility to bone erosions in RA [36]. Indeed, the systemic bone loss that occurred in nearly 60 % of early-RA patients is a strong predictor of radiographic joint damage [4]. Another study indicated a possible association between low systemic BMD and the occurrence of atlantoaxial subluxation, a fearsome complication of RA [37]. In this scenario, systemic OP might be a key factor and not a mere spectator of the pathogenesis of RA-associated erosive changes [36].

Epidemiology of Bone Loss in Rheumatoid Arthritis

The epidemiology of bone loss in RA can be divided into epidemiology of OP, epidemiology of fractures, and epidemiology of OP screening and fracture prevention in RA.

Epidemiology of Osteoporosis in Rheumatoid Arthritis

Osteoporosis is one of the most common comorbidities associated with RA. Data from the UK Clinical Practice Research Datalink (CPRD) showed that the incidence ratio of OP in RA patients who were not taking glucocorticoids was 7.5 per 1000 person-years, compared to 4.1 per 1000 person-years in healthy controls, with an estimated incidence rate ratio of 1.8 (95 % CI, 1.7, 2.0) [38]. BMD decline was related to disease duration (i.e., the longer the duration, the lower the BMD) but not with ongoing RA treatment [39]. Cortical sites (distal radius and femoral neck) appeared more susceptible to OP than trabecular site (lumbar spine) in RA, an effect independent of age or positive antibody status [40]. Other studies have indicated that about one-third of post-menopausal RA patients have OP with a twofold increased frequency of OP at all ages, compared with the general

population [40, 41]. A 2014 study showed that the prevalence of OP in RA is approximately 30 % [42]. More recently, among a large Korean cohort of post-menopausal women with RA, nearly 50 % of patients had OP [43]. Data on the prevalence of OP in pre-menopausal RA women is sporadic. A 2016 study reported that, among women with RA, the proportion of pre-menopausal patients with OP was 13 % compared to 0 % of healthy and age-matched controls [44]. Compared with healthy women, these pre-menopausal patients with RA had a relative risk of osteopenia of 3.6 (95 % CI, 1.6, 8.0) and 14.0 (95 % CI, 4.4, 44.6) at lumbar spine and femoral neck, respectively [44]. It was similarly demonstrated that men with RA had an increased risk of having OP, compared with age-matched healthy individuals (22.4 % vs 10.5 %, $p = 0.049$) [45].

Epidemiology of Fractures in Rheumatoid Arthritis

A systematic review of 25 studies published in 2018 reported that patients with RA have a greater risk of fragility fracture (1.6, 95 % CI 1.4–1.8) [46]. The pooled incidence of fragility fractures was 33.0 per 1000 person-years, ranging from 7.0 to 86.3 per 1000 person-years across the selected studies, with greater risk among women. Clinical vertebral fracture incidence was 4.3 per 1000 person-years, but as high as 42.4 per 1000 person-years when defining fractures using radiographic screening. Despite this, the latter systematic review did not show an increasing temporal trend in the incidence of fractures. A more recent Spanish longitudinal analysis, not included in the latter review, of almost 7000 hip fractures in RA patients, showed that incidence of hip fractures increased from 1999 to 2015 [47]. In this analysis, the osteoporotic hip fracture rate increased every year during follow-up, but to a lesser extent in women (3.1 %) compared to men (3.5 %).

Epidemiology of Osteoporosis Screening and Fracture Prevention in Rheumatoid Arthritis

Dual-energy X-ray Absorptiometry Epidemiology in Rheumatoid Arthritis

In 2013, the American College of Rheumatology (ACR) published a list of five medical procedures at risk of overuse in daily practice; DXA scans were one of the five listed [48]. Nevertheless, epidemiological data on DXA usage in RA varies. An international cross-sectional study showed that DXA had been performed in about 60 % of RA patients [49], and the rate ratio of DXA utilization was 1.8 (95 % CI, 1.6–62.0) in RA patients, compared to the general population [50]. The National Data Bank for Rheumatic Diseases (NDB) longitudinal prospective observational study found that OP screening measures (defined as undergoing BMD measurement) were reported in close to an identical proportion of RA patients [51]. In contrast, a retrospective cohort study revealed that only 30 % of women with RA received an incident DXA during a 4-year period (2006–2010) [52]. During an overlaying time frame (2008–2014), there was also a declining trend of BMD measurement and OP treatment from in RA with no improvement observed after release of the 2010 ACR glucocorticoid-induced OP treatment guidelines [51]. In addition, among just over 8000 RA patients followed over a 2-year period (2008–2009), the rate of DXA scans per beneficiary was 0.7 per year while peripheral joint X-rays per beneficiary was 2.6 per year [53]. Notably, 49 % of the population under this analysis (81.3 % women aged ≥ 65 years) never received a DXA scan during the period; yet 47 % received ≥ 2 peripheral joint radiograph and 16 % underwent 5 or more radiographs [53]. It is possible that some of these downward temporal trends are associated with a decrease in the reimbursement levels for DXA tests in the U.S.A., making the test financially infeasible for some clinicians to perform in their offices [54]. In summary, DXA does appear to be overused, at least in RA, and its utilization is declining.

Epidemiology of Osteoporosis Treatment in Rheumatoid Arthritis

Studies that directly address the epidemiology of OP therapies in RA are sparse. In an observational study of RA patients, 44.4 % were receiving vitamin D supplementation at the time of the study visit [49]; the mean daily calcium intake in RA was estimated around 800 mg [42]. Bisphosphonates are widely used for post-menopausal OP and are probably the most prescribed anti-osteoporotic drug in RA. In an analysis from the Veterans Affairs Rheumatoid Arthritis (VARA) registry, 41.5 % of RA patients overall took bisphosphonates, with an average length of treatment around 40 months. Not surprisingly, the number prescribed bisphosphonates was over 25 % greater (68.4 %) for RA patients who were glucocorticoid users [55]. A large observational study on subjects followed from 2003 to 2014 revealed that two-thirds of RA patients never received any OP treatment, and among those who were treated with an OP medication, 16.9 % received bisphosphonates [51], a proportion largely lower than the one seen in the VARA study and in other post-menopausal OP studies [55, 56, 57]. In summary, OP treatment in RA seems to be underused and largely driven by glucocorticoid use.

Laboratory Evaluation and Imaging Assessment of Osteoporosis in Rheumatoid Arthritis

Who Should be Screened for Osteoporosis in Rheumatoid Arthritis?

In 2016, a task force of the European League Against Rheumatism (EULAR) published a set of recommendations for the daily practice screening of comorbidities in inflammatory rheumatic diseases [58]. The guideline group encouraged screening for risk factors of OP (including body mass index < 19, physical inactivity, glucocorticoid exposure, alcohol intake, family history of femoral neck fracture, and secondary OP and BMD). They advocated that the FRAX global risk score be calculated where applicable (a statement based on individual cohort study and low-quality randomized controlled trials). The EULAR task force, however, did not produce recommendations for specific RA sub-populations, such as ACPA-positive patients or post-menopausal women, groups that might deserve more aggressive screening strategies. However, the frequency of BMD evaluation or the threshold for intervention with anti-osteoporotic medications was not included in these EULAR recommendations. In 2017, the ACR released an updated guideline for the prevention and treatment of glucocorticoid-induced osteoporosis [59]. This guideline, albeit specific to chronic glucocorticoid use, advocates anti-osteoporotic treatment in all individuals ≥ 40 years of age with a moderate-to-high risk of fracture (assessed with glucocorticoid adjusted FRAX) and in those < 40 years of age at high risk factor for osteoporosis (history of fragility fracture

and/or high dose glucocorticoid treatment). Moreover, ACR recommended to reassess clinical fracture risk every 12 months and do BMD testing every 1–3 years, depending on ongoing anti-osteoporotic medication, risk factors, glucocorticoid dose, and age. Similar recommendations can be applied to RA patients who are taking glucocorticoids and might be even considered for RA patients who are not on glucocorticoids. Figure 1 summarizes the ACR recommendation on glucocorticoid-induced osteoporosis reassessment in adults, with proposed considerations for RA patients.

Efforts to improve the outcomes of comorbidities in RA including osteoporosis are badly needed. In a 6-month trial, patients were randomized to receive a nurse-led screening (consisting of a guided questionnaire) or a self-administered questionnaire focused on several comorbidities related to RA [60]. The number of OP testing and treatment strategies implemented differed significantly between the nurse-led arm and the self-assessment arm (1.08 vs 0.31, $p < 0.001$). Interestingly, the incidence rate ratio for anti-osteoporotic measures was 3.34 compared with 1.40, 1.77, and 1.60 for measures against other RA comorbidities including cardiovascular events, infectious diseases, and cancer, respectively (all corrected for glucocorticoid treatment). Another study indicated that a 1-day clinic screening for multimorbidities, including OP, is relevant and feasible in RA patients [61]. Therefore, screening strategies may be somewhat efficacious in modifying physician and patient behaviors towards OP prevention and treatment.

Dual-energy X-ray Absorptiometry in Rheumatoid Arthritis

Lumbar Spine and Hip Bone Assessment

Lumbar spine and total hip are sites typically evaluated for the assessment of OP. BMD measured at these sites have been used as clinical trial outcome for over three decades, and its reliability for fracture risk assessment is widely recognized [62]. Nevertheless, RA is an independent risk factor for fractures, and patients with RA experience fractures at a lower BMD threshold compared with controls [63]. Another important difference between general OP and RA patients is that the latter seem to be particularly prone to cortical bone OP, namely total hip and femoral neck.

Trabecular Bone Score

Trabecular bone score is an index derived from a computer analysis of lumbar spine DXA that helps to predict fracture risk [64]. The Manitoba BMD Registry analysis reported trabecular bone scores significantly lower in RA patients compared to non-RA patients. Trabecular bone score can be used to improve the sensibility of FRAX algorithm. Using the trabecular bone score adjustment to FRAX, the proportion of RA patients who were reclassified over the intervention cutoffs (major osteoporotic fractures ≥ 20 % and hip fractures ≥ 3 %) was 4.9, with an odds ratio for being reclassified of 1.7 (95 % CI, 1.2, 2.2) and 1.5 (95 % CI, 1.1, 1.9) for major osteoporotic fractures and hip fractures respectively [65]. In RA patients with at least a prevalent vertebral fracture, a negative correlation between trabecular bone score and FRAX was found, while lumbar spine BMD was not found to correlate with FRAX [66]. In addition, another study showed that trabecular bone score differed significantly between RA patients with or without a vertebral fracture, while lumbar spine BMD was not dissimilar [67]. In summary, trabecular bone score can be a helpful resource for the assessment of fracture risk in borderline patients. However, trabecular bone score requires specialized software that is not always available on all DXA machines.

Metacarpal Bone Assessment

Metacarpal bones are sites of great interest in the evaluation of BMD in RA. However, in destructive forms of RA, the value of these regions is more complicated. In 1994, a method for measuring mineral content an RA patients' hand was developed with the use of DXA [68]. The hand position and form (i.e., ulnar deviation) did not alter bone mineral content measurements but did alter BMD, which strictly depends on the area of the region explored. In this explorative study on 56 RA patients, the hand bone mineral content was inversely correlated with disease duration ($r = -0.62$, $p = 0.0003$), Larsen score ($r = -0.62$, $p = 0.0002$), and Sharp's score ($r = -0.69$, $p < 0.0001$). Other studies explored the significance of hand BMD in RA and the coefficient of variation at the hand ranged between 0.9 and 1.1 %, while at the spine and femoral neck, it was about 2.3 % and 2.7 %, respectively [69, 70]. A more recent study showed that metacarpal BMD loss could predict the progression of joint erosions [71]. In RA patients without erosive disease at baseline, an early BMD loss at the metacarpal site was the only independent predictor of subsequent articular radiographic

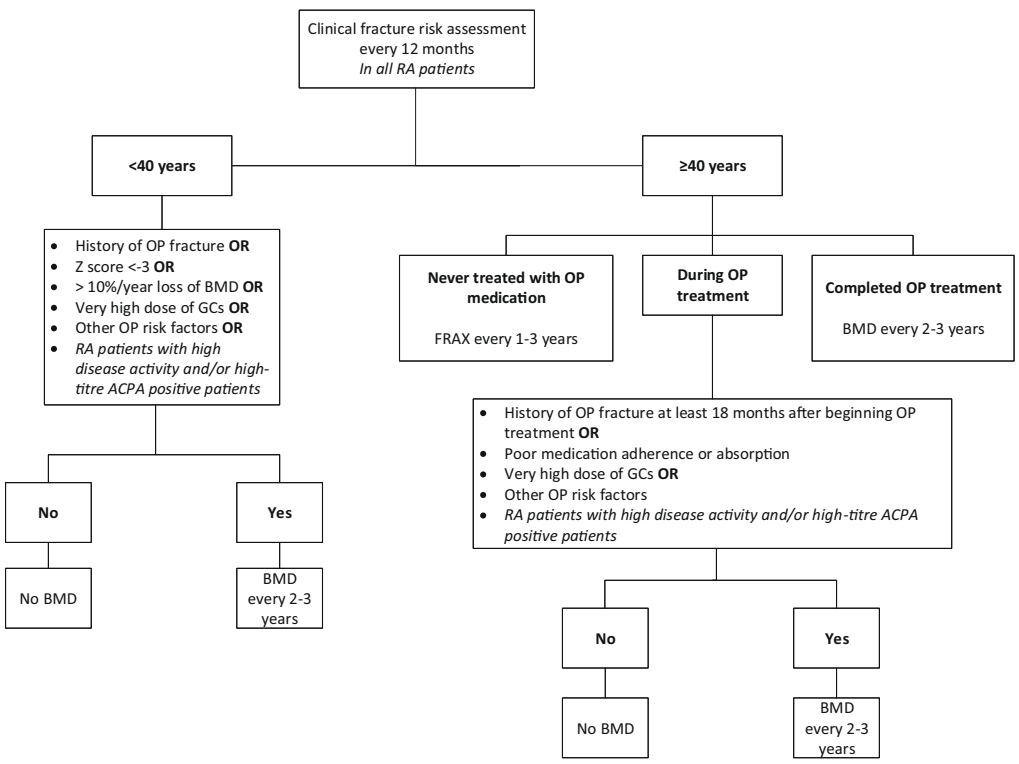


Fig. 1: American College of Rheumatology glucocorticoid-induced osteoporosis reassessment algorithm modified for rheumatoid arthritis patients. Reprinted with permission from 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis in Arthritis and Rheumatology published by John Wiley and Sons on June 6, 2017.

progression [71]. In another study, in RA patients who experienced BMD loss at the hand site, the odds ratios of erosive disease were 3.5 (95 % CI, 1.4, 8.8) and 3.5 (95 % CI, 1.4, 8.4) at 5 and 10 years respectively compared to those who did not experience such loss [72]. Moreover, total hand BMD loss was found as a strong predictor of RA development in patients with suspicious arthralgia [73]. While some data for metacarpal bone assessment has yielded positive results, the clinical utility remains unclear due to a paucity of evidence allowing fracture prediction based on this test alone.

FRAX

FRAX is a patented computer-based algorithm developed in 2008 in the UK that is used to calculate fracture risk at 10 years [63]. One of the dichotomous factors included for the estimation of fracture risk is the presence or absence of RA diagnosis, as well as the use of glucocorticoids. FRAX evaluates RA as a dichotomous variable and, as a FRAX limitation, does not includes RA disease activity and RA duration or the effects of ongoing treatment. In an example of a FRAX application [63], the 10-year probability of hip fracture for a woman with a BMI of 25 kg/m^2 aged 70 years in the absence of BMD measurement and any other risk factor is 2.3 % without RA and 4.1 % with RA (rising above the National Osteoporosis Foundation intervention threshold). From the analysis of combined clinical risk factors, a 65-year-old woman with RA would have a probability of major osteoporotic fracture of 12 % with a 26.3 % relative increase in fracture risk attributable to RA. In a cohort of RA patients (66.3 % taking glucocorticoids) followed for a median of 5.5 years, OP screening, with the use of FRAX, was performed in 67.4 % the patients, with an incidence rate of utilization of 35.6 per 100 person-years. The median 10-year risk factor calculated by FRAX was 10.5 % [51]. However, the UK Clinical Practice Research Datalink indicated that FRAX used without BMD might overestimate fracture risk in patients with RA; in proof of point, the mean predicted risk of major osteoporotic fracture at 10 years using FRAX was 13.3 %, compared with the observed 8.4 % [74]. Possible reasons for this overestimation might be the following: higher competing mortality and insufficient correction for disease severity or duration. In addition, ACPA-positive patients had a greater 10-year risk of major and hip fractures calculated by FRAX compared to ACPA-negative patients, a difference partly explained by higher smoking prevalence, lower femoral neck BMD, and higher rates of other comorbidities among ACPA-positive patients [75]. Nevertheless, FRAX does not currently incorporate the ACPA status of patients despite the growing body of evidence supporting an essential pathogenetic role these antibodies exert [14, 23, 76]. Despite these limitations, FRAX remains a valuable instrument to rapidly calculate the risk of fracture with or without BMD measurement.

Vitamin D Measurement

25-hydroxyvitamin D deficiency (a level < 20 ng/mL) has been widely reported in RA patients, with an estimated deficiency prevalence in about half of such patients [77]. The relationship between very low levels of 25-hydroxyvitamin D and low mineral density is well established in middle-aged and older adults [78], and, despite smaller populations under analysis, it seems to be true also for RA patients [79, 80]. Besides its effects on bone and calcium metabolism, vitamin D helps regulate immune response. Indeed, two meta-analyses, both published in 2016, reported that 25-hydroxyvitamin D was significantly associated with higher disease activity and greater predisposition to RA [77, 81]. Supporting the latter association, large doses of cholecalciferol ameliorated pain and functional disability in vitamin D-deficient RA patients [82, 83]. However, even if there is a strong biological rationale for the association between vitamin D deficiency and autoimmune diseases, the causal relationship between vitamin D deficiency and RA is yet to be determined. Nevertheless, for a variety of reasons, 25-hydroxyvitamin D measurement should be considered in most RA patients, especially in those who are at risk of having a very low level (e.g., older women and/or those with long standing RA).

Biochemical Markers of Bone Remodeling

Bone turnover markers (BTMs) in RA depend on both peripheral (i.e., bone erosions) and systemic (i.e., whole skeleton OP) osteoclast and osteoblast activity. Indeed, the utility of measuring BTMs can be twofold: monitoring RA activity itself and/or monitoring OP in RA. However, the interpretation of BTM values in RA can be challenging and vary considerably depending on disease activity, duration, and ongoing treatments (including glucocorticoids; with variable effects based on duration of therapy). Amino-terminal propeptide of type I procollagen (PINP), osteocalcin (OC), and bone alkaline phosphatase (BALP) are the most extensively studied markers of bone formation in RA while carboxy-terminal telopeptide of type I collagen (CTX), N-telopeptide (NTX), and carboxy-terminal telopeptide of type I collagen (ICTP) are the markers most studied for bone resorption. These markers not only have been investigated for predicting radiological damage, with convincing evidence [21, 84–86] but also were considered for the evaluation of bone loss in RA [84, 87–93]. BTMs are prone to change quickly in response to menopausal status, erosive changes, disease activity, and in response to modifications of RA-specific (i.e., biologics, glucocorticoids) and OP-specific (i.e., anti-resorptives) treatments. Variations in BTM levels might represent observed fluctuations of other confounding variables and not truly the effect of RA on bone. For this reason, BTMs should be evaluated only in select cases and be interpreted on a case-by-case basis.

High-resolution Peripheral Quantitative Computed Tomography

High-resolution peripheral quantitative computed tomography (HR-pQCT) is a relatively novel technique used to explore the microarchitectural structure of the bone for research purposes. HR-pQCT of the radius and femoral neck predicted the fracture risk better than DXA in post-menopausal women in one study [94]. HR-pQCT was first used in RA patients in 2010 [3, 95] and showed an extremely high capacity of discriminate articular damage with good inter-reader agreement for bone erosions [96]. A 2017 cadaveric study demonstrated that HR-pQCT is highly reliable for the assessment of metacarpal intra-articular bone structure and showed that RA patients had significant deterioration of both cortical and trabecular bone compared to healthy controls [35]. In addition, microfinite analysis at the distal radius of RA patients found that ACPA-positive patients had a significantly decreased bone strength that is associated with greater probability of low-impact fragility fractures [97]. HR-pQCT might be useful to investigate both articular

Cont'd. on page 31...

Serum Levels of Adiponectin and Vitamin D Correlate with Activity of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease in which numerous cells and mediators affect inflammatory conditions and disease severity. To compare the serum levels of adiponectin, vitamin D, copper, and zinc in patients with RA and to investigate the relationship between these parameters and RA severity. Ninety patients with RA and 30 healthy controls participated in this cross-sectional case-control study between November 2016 and April 2017; according to the ACR/EULAR criteria for RA. Serum levels of adiponectin were determined by ELISA; copper and zinc by colorimetric spectrophotometry; and vitamin D by HPLC. Kruskal-Wallis and Spearman tests were performed using SPSS software and data were depicted by GraphPad Prism software. Compared with healthy controls, the serum level of adiponectin was significantly

increased, whereas vitamin D was significantly decreased in patients with RA. Adiponectin and vitamin D levels were inversely correlated in RA subgroups ($P < 0.001$, $r = -0.410$). Adiponectin and vitamin D correlated with RA severity. Furthermore, no significant difference was found in copper and zinc levels between RA groups and controls. The definitive roles of adiponectin, vitamin D, copper, and zinc are not completely determined in RA development. Based on disease activity, these parameters can modulate inflammatory conditions, thus they have the potential to be used as promising therapeutic biomarkers to follow up the severity of disease, as well as the progression and treatment success in patients with RA.

Source: Khajoei, S., Hassanineviси, M., Kianmehr, N. *et al. Mol Biol Rep* (2019) 46: 2505. https://doi.org/10.1007/s11033-019-04682-1. © Springer Nature B.V. 2019.

Bone Marrow Lesion is Associated with Disability for Activities of Daily Living in Patients with Early Stage Knee Osteoarthritis

Osteoarthritis of the knee (knee OA) induces pain, loss of mobility and diminished activities of daily living (ADL). Although an understanding of the pathophysiology of early stage knee OA has been developed, the structural changes associated with disability for ADL in early stage knee OA are still unclear. The aim of the present study was to examine magnetic resonance imaging (MRI)-detected changes associated with disability for ADL in patients with early stage knee OA. One hundred and thirty-two patients with early stage medial knee OA (Kellgren–Lawrence grade ≤ 2) who first visited the outpatient clinic at our university hospital were included. They were also examined by 3.0-Tesla knee MRI. The OA-associated structural changes were scored using the Whole-Organ Magnetic Resonance Imaging Score (WORMS), and clinical manifestations were evaluated by the Japanese Knee Osteoarthritis Measure (JKOM). Median quartile regression was used for the analysis. Cartilage lesion, subchondral bone attrition and osteophytes were observed in all patients. Bone marrow lesions (BMLs) and synovitis were observed in 60 % and 55 % of the patients, respectively. Subchondral cysts and ligament changes were observed in 6 % and 17 % of the patients, respectively. Pain severity of the patients was associated with medial cartilage lesions (coefficient 2.50, 95 % confidence interval 0.61–4.40, $p < 0.01$). Disability for ADL of the patients was associated with BMLs in the medial side of the knee joint (0.82, 0.21–1.02, $p = 0.04$). BMLs in the medial side of the knee joint were associated with disability for ADL of patients with early stage medial knee OA.

Source: Sadatsuki, R., Ishijima, M., Kaneko, H. *et al. J Bone Miner Metab* (2019) 37: 529. https://doi.org/10.1007/s00774-018-0950-z. © The Japanese Society for Bone and Mineral Research and Springer Japan KK, part of Springer Nature 2018.

Etoricoxib and Diclofenac Diminish Risk of Dementia in Patients with Osteoarthritis

According to a study published in Dementia and Geriatric Cognitive Disorders, etoricoxib and diclofenac reduced the risk of dementia in patients with osteoarthritis.

Xue YH and colleagues performed a population-based cohort study to understand the link between dementia and osteoarthritis, and impact of non-steroidal anti-inflammatory drugs administration on risk of dementia.

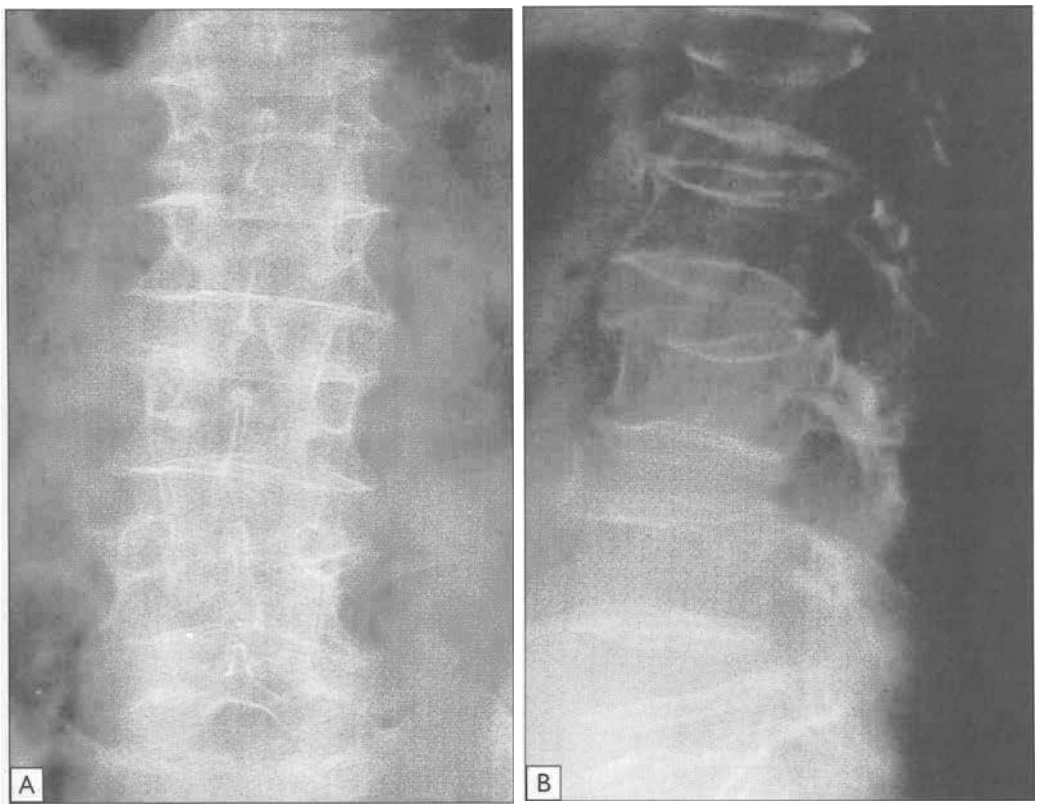
Patients were randomized into two groups; osteoarthritis group and non-osteoarthritis group. The following tests were performed: $\chi 2$ test, Student *t* test, Kaplan-Meier analysis, and Cox proportional hazard model.

It was noted that compared to patients without osteoarthritis, patients with osteoarthritis were at higher risk of dementia. The hazards ratio for dementia in osteoarthritis group was 1.42. In addition, administration of analgesics like etoricoxib and diclofenac helped in reducing the risk of dementia.

It was concluded that the risk of dementia is high in patients with osteoarthritis and administration of etoricoxib with diclofenac will help in minimizing the risk of dementia in this subgroup of patients.

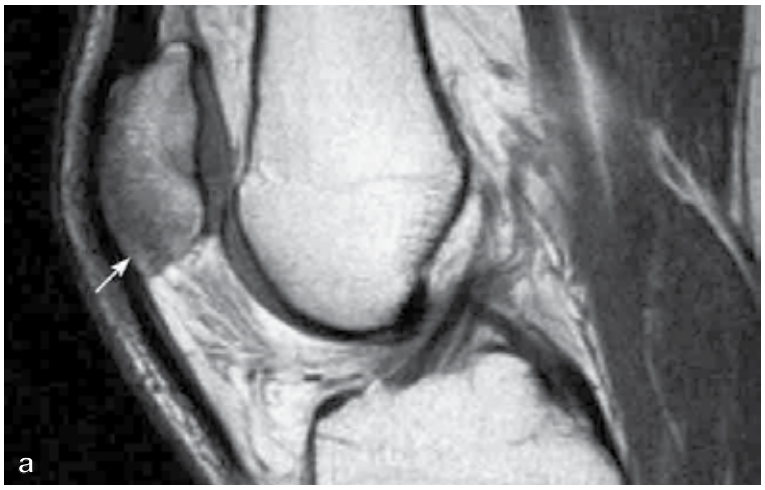
Source: Xue YH, Peng YS, Ting HF, *et al*. Etoricoxib and Diclofenac Might Reduce the Risk of Dementia in Patients with Osteoarthritis: A Nation-Wide, Population-Based Retrospective Cohort Study. *Dement Geriatr Cogn Disord*. 2018;45(5-6):262-271. DOI: 10.1159/000485176.

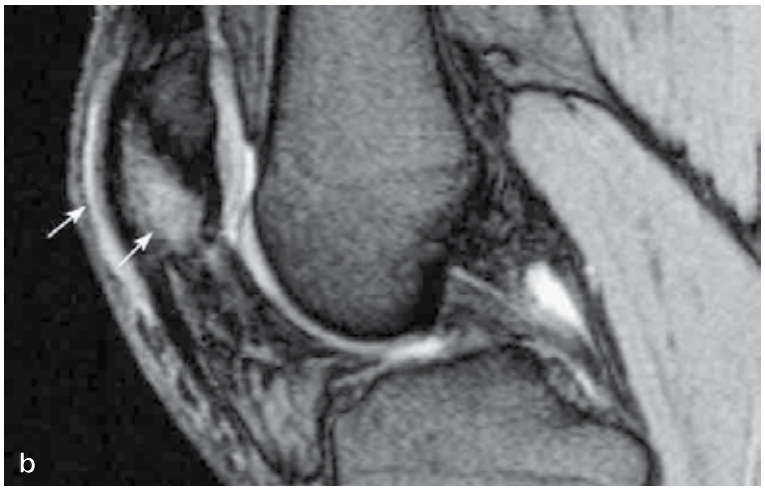
VERTEBRAL COMPRESSION FRACTURE

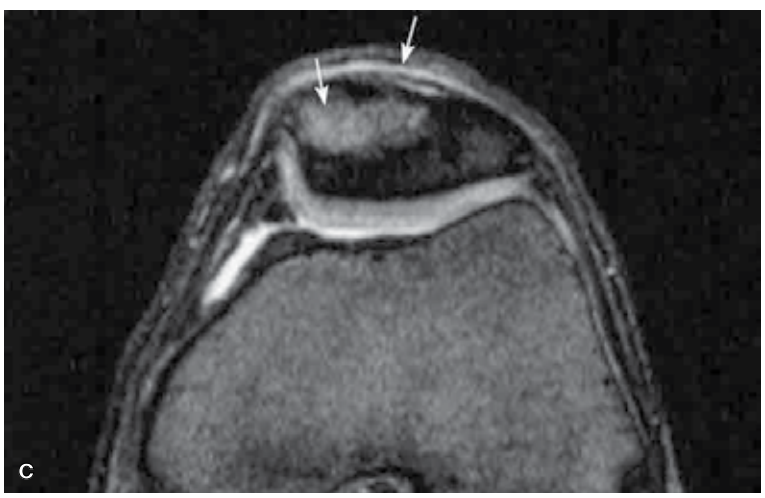


Multiple compression fractures, as seen on the anteroposterior (**A**) and lateral (**B**) views of the lumbar spine in a 76-year-old woman. Note generalized osteopenia with increased translucency of the vertebral bodies and thinning of the cortical and subchondral bone. Vertebral collapse has occurred at multiple levels. Severe compression of the fifth lumbar vertebra has resulted in a flattened vertebra. Partial collapse with loss of height and biconcave deformity is seen in the twelfth thoracic and the first three lumbar vertebrae. The height of the fourth lumbar vertebra is unchanged.

MICROFRACTURE OF ANTEROMEDIAL PATELLA



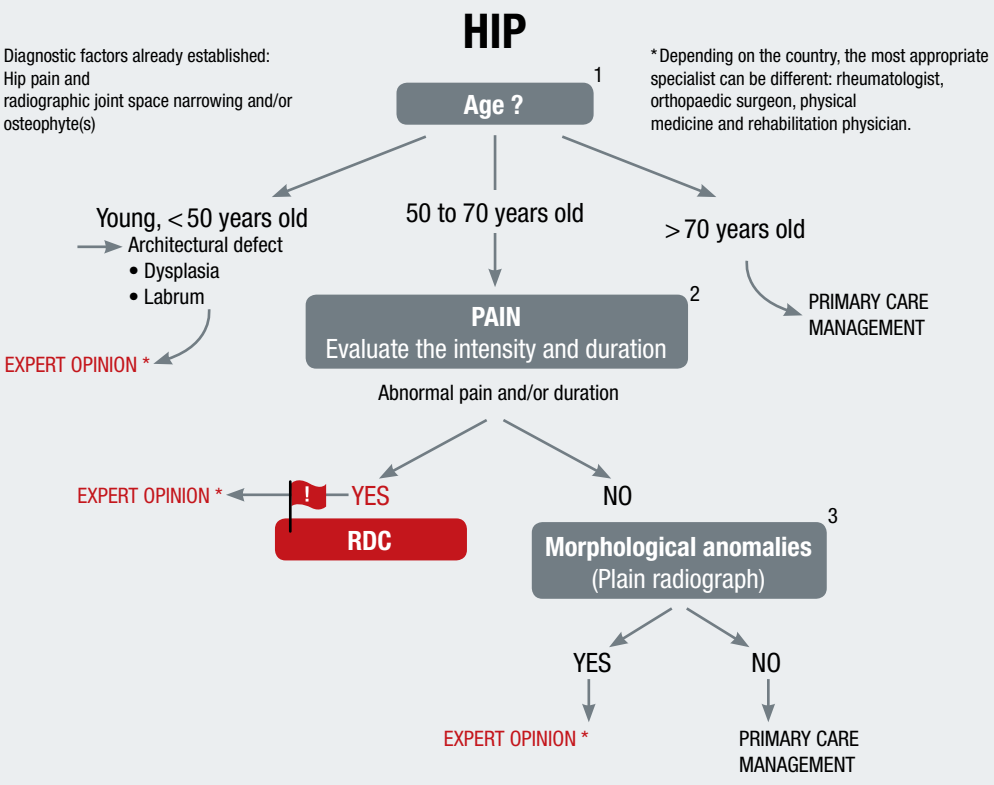




Microfracture of anteromedial patella – anterior knee contusion 3 weeks earlier (27-year-old male)

a. Sagittal T1: Mild signal decrease of anterobasal patella segments (*arrow*) **b.** Sagittal T2*; **c.** axial T2*: Both images show pronounced signal increase of anterobasal patella segments (*arrows*) and slight signal increase of subcutaneous structures in front of patella.

DIAGNOSTIC ALGORITHM OF HIP OSTEOARTHRITIS IN PRIMARY CARE



Guidelines for the diagnostic management of hip pain in primary care. Explanatory terminology and acronyms: abnormal pain: pain of an intensity or duration that is unusual for OA of the hip; VAS score >7 or duration longer than 10 days. RDC: rapidly destructive coxarthrosis or microfracture of the subchondral bone responsible for nocturnal pain and limping for which the only effective treatment is unloading body weight from the limb. Labral abnormalities: joint pain sometimes occurring with no radiographic or ultrasound abnormality, most common in young and/or athletic patients, requiring a specialist opinion. Situations requiring urgent expert opinion are denoted by red typeface.

Source: Martel-Pelletier, J., Maheu, E., Pelletier, JP. *et al. Aging Clin Exp Res* (2019) 31: 19. https://doi.org/10.1007/s40520-018-1077-8. © The Author(s) 2018.

...Cont'd. from page 28

bone damage and systemic bone loss, but it involves higher radiation exposure, higher costs, and in the absence of normative data, it is largely relegated to a research tool.

Conclusions

Osteoporosis represents the most common comorbidity of RA and might have important consequences, related to not only fragility fractures but also local bone loss. Systemic and local bone losses in RA start in early stages of the disease and, at least in part, even before the clinical onset of the disease. Initial and periodic OP screening using DXA is feasible and effective in RA, and scientific societies have endorsed initial systematic screening for OP risk in RA patients. Screening strategies should also include an OP risk factor assessment and FRAX calculation. In most RA patients, 25-hydroxyvitamin D should be measured and trabecular bone score as well as BTM measurement should be considered in selected patients. Furthermore, special considerations should be given to selected populations with RA, such as ACPA-positive patients, who are particularly susceptibility to systemic and local bone loss.

Compliance with Ethical Standards

Conflict of Interest: Giovanni Adami declares that he has no conflict of interest. Kenneth G Saag declares research grant from Amgen and Merck and consultant fee from Amgen, Lilly, Merck, Radius, and Roche.

Human and Animal Rights and Informed Consent: This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References available on request
Healthcare.India@springer.com

Source: Adami, G. & Saag, K.G. *Curr Rheumatol Rep* (2019) 21: 34. https://doi.org/10.1007/s11926-019-0836-7.

June 2019

Springer Healthcare

This edition is created in India for free distribution in India.
This edition is published by Springer Nature India Private Limited.
Registered Office: 7th Floor, Vijaya Building, 17, Barakhamba Road, New Delhi 110 001, India.
T: +91 11 4575 5888
www.springerhealthcare.com

Part of the Springer Nature group

In

Rheumatoid Arthritis,
Osteoarthritis & Acute Gouty Arthritis

℞

Etrik

Etoricoxib 60mg/90mg/120mg Tablets

Swift, Sure & Safe Relief

In

Acute Pain

℞

Etrik-P

(Etoricoxib 60mg + Paracetamol 325mg tablets)

The Extra Power to Pain Relief

In

Pain with Muscle Spasm

℞

Etrik MR

Etoricoxib 60mg + Thiocolchicoside 4mg

Beat Pain, Break Spasm

80040304 For the use of a Registered Medical Practitioner, Hospital or Laboratory only.