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ORIGINAL ARTICLE

Subclinical crystal arthropathy: a silent contributor to inflammation and functional disability in knees with osteoarthritis—an ultrasound study

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Abstract

Purpose This study aimed at investigating the prevalence of crystal deposits with knee osteoarthritis (OA) by ultrasonography and measure the inflammatory burden associated with crystal deposits in OA using WOMAC score.

Methods Adult patients with primary knee OA diagnosed according to the American College of Rheumatology criteria were included. Participants were subjected to history taking, clinical examination, knee US, and plain radiography. The EULAR and the OMERACT ultrasonography definitions and scanning protocols were used.

Results Fifty-three patients (44 females, 9 males) were enrolled. Mean values were 53.5 years ± 8.3 SD for age and 42.5 months ± 49.5 SD for disease duration. Crystals were detected by US in 73/106 knees (68.9%). Plain radiography revealed chondrocalcinosis in three patients. Mean values for WOMAC pain, stiffness, and disability scores were 14.38 ± 3.99, 4.93 ± 2.06, and 49.61 ± 13.06, respectively, with insignificant differences relative to presence of crystals ($P > 0.05$). Regression analysis revealed a 4.1-fold increase in the incidence of sonographic crystals with bursitis (OR = 4.13, CI = 1.5–11.2, $p = 0.01$) and a 3.2-fold increase in the incidence of sonographic crystals with synovial effusion (OR = 3.16, CI = 1.34–7.44, $p = 0.01$).

Conclusion Subclinical crystals were detected in a considerable number of patients with primary knee OA. The incidence of crystal deposits was significantly higher in patients with bursitis and knee effusion.

Keywords Osteoarthritis · Subclinical crystal deposition disease · Chondrocalcinosis · Clinical predictors

Introduction

Osteoarthritis (OA) is a slowly progressive degenerative disease that affects joint components from cartilage to meniscus and subchondral bones. It is a complex process that remains poorly understood and is definitely multifactorial. The disease is regarded as one of the five leading joint pathologies contributing to significant physical disability in the elderly worldwide [1, 2]. Radiographic estimates for the prevalence of knee OA in different studies yielded figures that ranged from 25 to 30% of the population aged 45–64 years, 60% of those older than 65 years to more than 80% of those older than 75 years. OA is expected to rank the fourth amongst the leading causes of disability worldwide by 2020. In spite of being a degenerative process, an inflammatory element of variable intensity has been significantly reported, adding to the disease burden and raising concerns regarding the need for regular use of oral nonsteroidal anti-inflammatory drugs and the benefits of possible addition of colchicine, as well as local corticosteroid injections [3].

Crystal arthropathies refer to a group of joint diseases related to abnormal intra-cartilaginous precipitates of crystals. The disease is a relatively common articular pathology fostering a higher prevalence with advancing age. This form of arthritic disorders has been clinically associated with acute periarthritis as well as chronic destructive joint disease. The most commonly reported forms of crystals are monosodium urate monohydrate (MSU), calcium pyrophosphate dehydrate (CPPD), and calcium phosphate (CPP) crystals. Multiple recent evidence illustrated the existence

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of such crystal deposits in synovial joints with OA, with a tendency towards a joint-specific pattern; for example, CPPD and gout tend to be associated with knee and ankle OA more than hip OA [4, 5].

Despite the frequent coexistence of mixtures of different types of these crystals in synovial fluid analyses and biopsies in OA joints [4], the interpretation of such findings, the underlying pathogenic theories, and their contribution to the existence/severity of the inflammatory degenerative process in OA awaits in-depth understanding and evidence-based clarifications. A number of explanations have been postulated. Most commonly accepted is the one about inflammasomes and crystals [6]. MSU and CPP crystals can directly stimulate the innate inflammatory cells like macrophages promoting inflammasome activation leading to the subsequent downstream production and secretion of active inflammatory cytokines such as IL-18 and IL-1β, a finding that strongly correlated with OA severity [7, 8].

Intraarticular calcific crystal deposits frequently go underdiagnosed, being largely dependent on physicians' knowledge and judgment, compounded by the lack of reproducibility of plain radiography in CDD, another shortcoming of radiographic diagnosis. Diverse reports revealed a high discordance between clinical criteria of pain, stiffness, and functional disability and radiographic changes in knee OA, while magnetic resonance imaging stood out as an accurate yet an expensive and time-consuming alternative. Joint aspiration and polarized microscopic examination are considered the gold standard measure for diagnosis of crystal arthropathies. Although not a difficult procedure, the use of joint aspiration on a routine basis remains limited, being a relatively invasive procedure that requires sufficient training, practice, and patient acceptance, particularly in the absence of significant effusion. Such a challenge to perfect practice and diagnosis emphasized the need for an alternative approach to achieve diagnosis of intraarticular crystal deposits aimed at improving standards of care, particularly in OA with an inflammatory element [9–12]. With the recent inclusion of ultrasound (US) as a bedside radio-imaging modality in the diagnosis of articular and periarticular pathologies, rheumatologists are experiencing a paradigm shift that has effectively improved daily practice towards an earlier diagnosis, decision-making, and follow-up of a particular pathology.

This study aimed to investigate the following The primary aim was to investigate the prevalence of calcific crystal deposits in patients with knee OA using ultrasonography. Secondary aims were to clinically and radiographically measure the added inflammatory burden associated with the sonographic diagnosis of crystals and its impact on pain and functional disability in OA using WOMAC score.

Materials and methods

Study design

In this single-center cross-sectional study, a total of 60 adult patients diagnosed according to the criteria set forth by the American College of Rheumatology (ACR) for the classification of knee OA were enrolled. The ACR clinical and laboratory diagnostic criteria for OA of the knee joint included the following: Knee pain plus at least five of the following nine criteria: age > 50 years; stiffness < 30 min; crepitus; bony tenderness; bony enlargement; no palpable warmth; ESR < 40 mm/hour; RF < 1.40; synovial fluid signs of OA. The ACR clinical and radiographic diagnostic criteria for knee OA: Knee pain plus osteophytes, plus at least one of the following three criteria: age > 50 years; stiffness < 30 min; crepitus [12].

Inclusion criteria

All patients who satisfied the requirements of ACR criteria and gave consent were included. *Exclusion criteria* (i) Patients with inflammatory joint disease other than OA, such as rheumatoid arthritis, spondyloarthritis, and/or connective tissue disease. (ii) Patients with advanced degenerative changes (Kellgren-Lawrence radiographic score of 4). (iii) Patients with diagnosis of gout or calcium pyrophosphate deposition disease (CPPD). (iv) Patients with history of knee joint surgery and/or severe knee previous injury. (v) Patients with history of previous intraarticular steroid injection for the knee joint [13, 14]. The Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) questionnaire was used for quantitative scoring of pain, stiffness, and disability in the studied patients [15].

Participants were all subjected to history taking, general and musculoskeletal clinical examination, and laboratory workup including complete blood count, erythrocyte sedimentation rate, serum uric acid, lipid profile, liver and kidney function tests, and urinalysis. All the patients underwent knee bilateral plain radiography and US examination. Patients with knee effusion were also subjected to synovial fluid aspiration and crystal analysis whenever possible. Clinical, laboratory, radiographic, and US assessments were all performed within the same week of inclusion to secure integrity and homogeneity of data. The study was approved by the institutional review board of ethics.

Musculoskeletal ultrasound examination methodology and protocol

Examination of the knee joint for all patients was done by a rheumatologist who was blind to clinical and laboratory data prior to ultrasound examination. The knee structures were scanned both in gray-scale and power Doppler mode [16–18]. The exam was conducted using a real-time Logic p5 ultrasound machine (General Electric Medical Systems, Chicago, United States) with a multi-frequency linear transducer (7–13 MHz).

Table 1 shows the US scanning technique adopting the standard scans for the assessment of knee cartilage described in the EULAR guidelines for musculoskeletal ultrasound in rheumatology [15–17].

The US examination focused on the detection of crystal deposits and inflammatory features (e.g., synovial hypertrophy, synovial fluid), identified according to the international definitions provided by OMERACT/EULAR definitions for respective sonographic findings [16–19].

The presence of the following US inflammatory features was investigated

1. *Effusion* Defined as an abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intraarticular material that is displaceable and compressible, but does not exhibit a Doppler signal.
2. *Synovial hypertrophy* Defined as an abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intraarticular tissue that is non-displaceable and poorly compressible, and may exhibit a Doppler signal.
3. *Bursitis* Defined as an abnormal hypoechoic/hyperechoic material within the bursa causing its enlargement.
4. *Crystal deposits* According to the literature and previous reports [18–20], CPP and MSU crystals were distinguished based on their peculiar topographic distribution. Parameters of gray-scale gain were adapted to enhance crystal recognition (crystal deposits maintain high reflectivity, similar to the bony cortex, even at low level of gain value). Meniscal fibrocartilage is an almost exclusive target of CPP crystal deposits. Both MUS and CPP crystals may deposit at the hyaline cartilage. CPP crystals were identified as hyperechoic deposits of varying size, which may or may not generate a posterior acoustic shadowing, localized within the meniscal fibrocartilage, the hyaline cartilage, and the synovial/bursal fluid. MSU crystals were identified as a hyperechoic band over the superficial margin of the knee articular hyaline cartilage ("double contour" sign) and as intraarticular/intrabursal circumscribed hyperechoic foci (tophi) or heterogeneous hyperechoic foci [17].

Plain radiographic examination

Conventional weight-bearing (standing) antero-posterior and lateral view knee radiographs were taken. The radiographs were evaluated by the radiologist. The traditional K-L was used as the scoring tool to assess the severity of knee OA on plain radiograph [ranging from 0 = no OA to 4 = severe OA] [22].

Statistical analysis

Data were coded and summarized using SPSS version 16 for Windows. Quantitative variables were described using mean ± standard deviation (SD), and categorical data by using frequency and percentage. Mann–Whitney, χ^2 tests, and analysis of variance were used to calculate statistically significant differences between clinical and ultrasound variables. P value of < 0.05 was considered statistically

Table 1 The US scanning technique adopted for the standard scans for the assessment of knee cartilage described in the EULAR guidelines for musculoskeletal ultrasound in rheumatology [15–17]

Scanning planes adopted	Position of the patient	Anatomical structures scanned
Anterior transverse and longitudinal scans	Patient in supine with knee in neutral extended position and knee semi-flexed at 45	Suprapatellar patellar pouch, quadriceps, patellar tendon and entheses
Anterior suprapatellar transverse and longitudinal scan	Patient supine with knee in maximal flexion > 90	Hyaline cartilage of the femoral trochlea and the anterior portion of the femoral condyles
Anterior para-patellar transverse and longitudinal scan	Patient supine with knee in maximal flexion > 90	The lateral portion of the hyaline cartilage of the femoral condyles
Lateral and medial transverse and longitudinal scans	Patient supine with the knee in neutral extended position and with the knee in maximal flexion > 90	The external portion of the menisci
Posterior transverse and longitudinal scan	Patient prone with the knee in neutral extended position	Hyaline cartilage of the posterior portion of the femoral condyles. Gastrocnemius-semimembranosus bursa

Table 2 The clinical and demographic data of the study population with knee OA

Parameters	Range	Mean ± SD
Age 44 females (83%) 9 males (17%)	38–67 years	53.5 ± 8.3
Disease duration	1–240 months	42.5 ± 49.5
BMI	24.2–53.3	34.9 ± 6.3
Serum uric acid (2.4–5.7 mg/dl)	1.7–8.5	5.2 ± 1.4

significant. Regression analysis models were employed to examine the relationship between the presence of crystals as identified by US (dependent variable) and various potential predictors, i.e., age, patient gender, presence of dyslipidemia, chronic medical illnesses such as diabetes mellitus and hypertension, clinically detected knee effusion, limitation in range of motion, sonographic loose bodies, osteophytosis, and synovial hypertrophy (independent variables).

Results

A total of 60 adult patients were enrolled, with 53 patients (44 females (83%) and 9 males (17%)) satisfying the inclusion criteria. Mean values were 53.5 years ± 8.3 SD for age, 42.5 months ± 49.5 SD for disease duration, and 34.9 ± 6.3 SD for body mass index. All patients were on interrupted courses of NSAIDs for pain and stiffness (variable formulae and combinations) (Table 2).

Plain radiographic examination revealed joint space narrowing in 43 patients (81.1% of the study population) with K-L radiographic score for degenerative changes of 2–3. Plain radiography revealed chondrocalcinosis in three patients.

Results of knee ultrasonographic scanning: Crystal deposits were sonographically diagnosed in 73 knees (68.9%). Sonography revealed calcifications in the hyaline cartilage, fibrocartilage, recesses, and bursa in 49.05%, 6.60%, and 19.81% of the scanned knees, respectively. A double contour pattern on the surface of the articular cartilage denoting MSU was observed in 31.1%, whereas sonography detected punctate intra-cartilagenous calcific deposits of CPPD pattern within the hyaline cartilage and menisci in 63.2%, and a picture of mixed crystal deposits was found in 5.7% of the cases.

Results for WOMAC scores for pain, stiffness, and functional disability indices revealed WOMAC pain scores that ranged from 4.00 to 20.00 with a mean value of 13.21 ± 4.96, WOMAC stiffness scores that ranged from 0 to 8 with a mean of 5.05 ± 2.05, and WOMAC disability scores that ranged from 14 to 67 with a mean value of 49.92 ± 13.25.

Results showed insignificant differences between OA patients as regards the mean pain score (14.03 ± 3.98 without crystals, 14.42 ± 3.99 with crystals) and mean disability score (48.82 ± 12.44 without crystals, 50.41 ± 13.66 with crystals), with p value > 0.05 and 95% CI = − 7.12 to 3.82, − 2.01 to 1.2, in respect of the sonographic diagnosis of crystal deposits.

Significant differences were found in the mean stiffness score (4.97 ± 1.59 without crystals, 5.08 ± 2.23 with crystals), with $p < 0.01$ and 95% CI = − 0.96 to − 0.74.

The mean WOMAC pain score was significantly higher in patients with crystal deposits and bursitis (15.56 ± 3.57

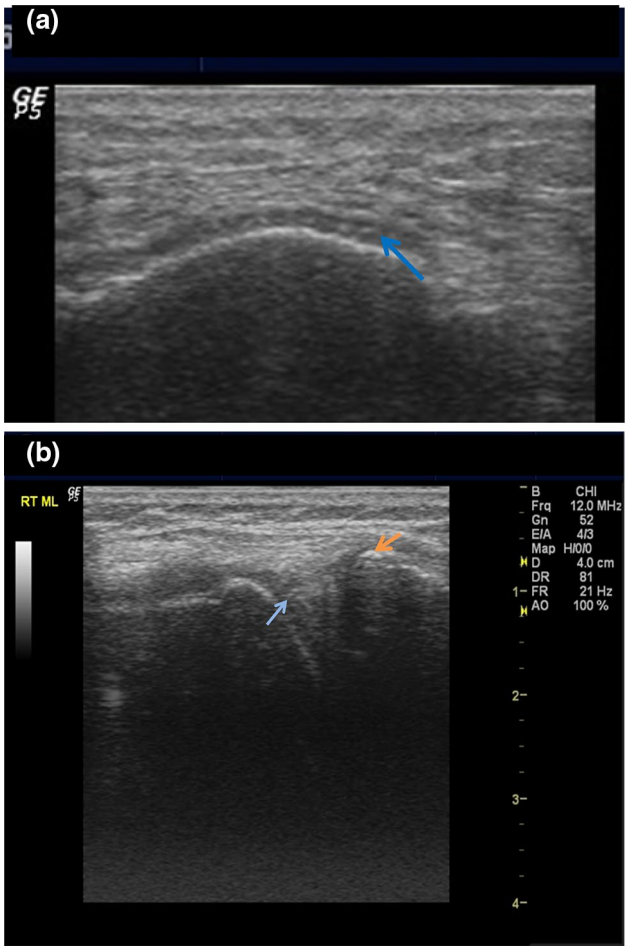

Fig. 1 **a** Medial transverse (short) scan of the medial condylar surface of the right knee joint in flexion using a linear probe (8–13 MHz). The image reveals intra-cartilagenous hyperechoic calcific deposits (speckled pattern, blue arrow) denoting CPPD deposits within articular cartilage substance. **b** Medial longitudinal scan of the right knee joint in flexion using a linear probe (8–13 MHz) showing intra-meniscal hyperechoic calcific fine deposits suggestive of CPPD associated with intra-meniscal small degenerative cyst (blue arrow) and minimal osteophytic lipping (orange arrow)

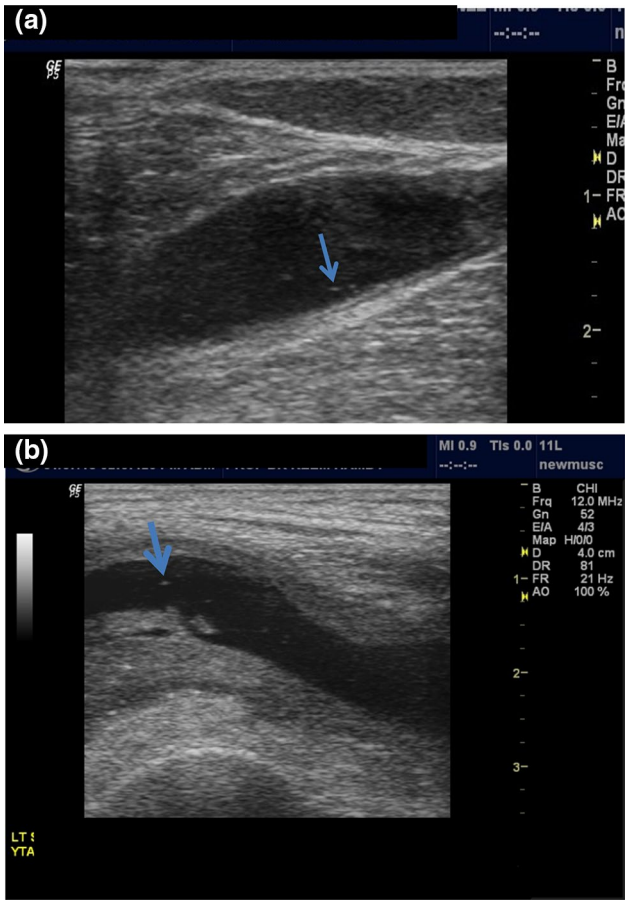

Fig. 2 **a** A posterior longitudinal scan of the knee joint using a linear probe (8–13 MHz) showing bursitis with snowflake-like hyperechoic floating calcific crystals in Baker's cyst (the snowflake pattern goes more with MSU) (blue arrow). **b** Anterior transverse short scan of the left knee joint in extension using a linear probe (8–13 MHz) showing suprapatellar bursitis with minute floating calcific bodies suggestive of intra-bursal crystal deposits (blue arrow) with effusion

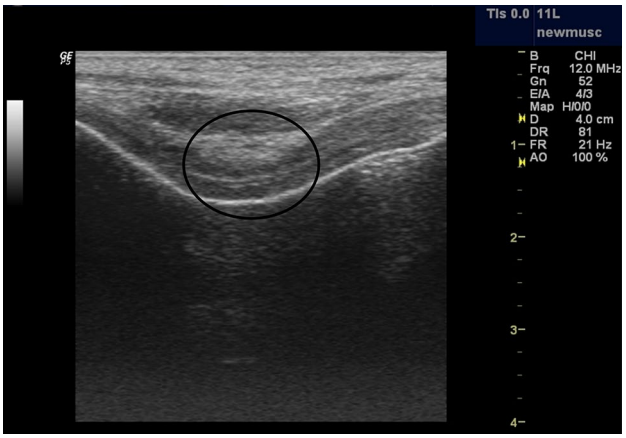

Fig. 3 An anterior transverse scan of the left knee joint in full and 30-degree flexion using a linear probe (8–13 MHz) illustrating a triple contour pattern, which is a combined image of MSU deposit over the surface of the articular cartilage giving the double contour pattern, and intra-cartilagenous calcific punctate deposits going with CPPD with degenerative changes in the articular cartilage

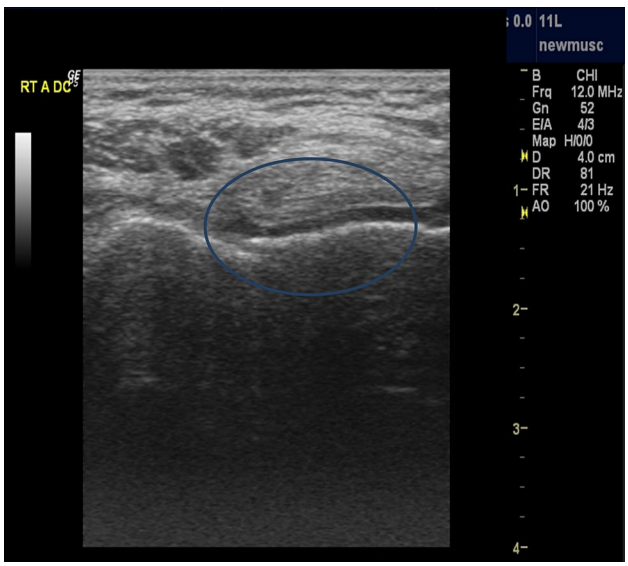

Fig. 4 An anterior transverse scan of the right knee joint in full and 30-degree flexion using a linear probe (8–13 MHz) illustrating a triple contour pattern, which is a combined image of MSU deposit over the surface of the articular cartilage giving the double contour pattern, and intra-cartilagenous calcific punctate deposits going with CPPD with degenerative changes in the articular cartilage

with vs 12.03 ± 3.83 without, $p < 0.05$) (Figs. 1, 2, 3, 4, Table 1, 2, 3, 4).

Results of regression analysis

Regression analysis models were employed to examine the relationship between the presence of crystals as identified by US (dependent variable) and various potential predictors, i.e., age, patient gender, presence of dyslipidemia, chronic medical illnesses such as diabetes mellitus and hypertension, clinically detected knee effusion, limitation in range of motion, US loose bodies, osteophytosis, and synovial hypertrophy (independent variables).

The presence of crystal deposits as identified by US significantly correlated with the presence of knee effusion and bursitis by US. Forest plot test revealed a 4.1-fold incidence of sonographic crystal deposition in patients with sonographic bursitis versus those without (OR = 4.13, CI = 1.5–11.2, $p = 0.01$) and a 3.2-fold incidence of crystal deposition in patients with sonographic effusion versus those without (OR = 3.16, CI = 1.34–7.44, $p = 0.01$), as shown in Table 5 and Fig. 5.

Table 3 Sonographic findings in the study cohort showing the differences between knee OA patients with sonographic evidence of crystal deposits versus knee OA patients without detectable crystals by ultrasound

Ultrasound findings	Total (106 knees)	Percentage
Osteophytosis	104	98.1%
Joint effusion	59	55.7%
Bursitis	41	38.7%
Anserine bursitis	6	5.7%
Supra-patellar bursitis	4	3.8%
Pre-patellar bursitis	2	1.9%
Baker's cyst	33	31.1%
Synovial hypertrophy	2	1.9%
Meniscal degeneration	16	15.1%
Loose bodies	13	12.33%
Calcifications by US	Total (106 knees)	Percentage
Calcification within the hyaline cartilage	52	49.05%
Surface calcific deposits on Hyaline cartilage	22	20.75%
Synovial fluid calcific aggregates	16	15.09%
Meniscal calcifications	7	6.60%
Calcifications within Bursa and recesses	21	19.81%

Table 4 Differences in the demographic and clinical features of the studied patients with knee OA and sonographic evidence of CDDs versus those without

	OA with CDD (Mean ± SD)	OA without CDD (Mean ± SD)	*t* value *p* value (Significance)	Confidence interval 95%
Age (in years)	54.3 ± 7.5 (38–67)	51.8 ± 9.7 (40–67)	$p > 0.05$	CI = − 5.82 to 1.03
Disease duration (months)	37.8 ± 41.7 (1–180)	52.9 ± 62.4 (2–240)	$p > 0.05$	CI = − 0.83 to 0.32
WOMAC pain score	14.42 ± 3.99	14.03 ± 3.98	$p > 0.05$	CI = − 7.12 to 3.82
WOMAC stiffness score	5.08 ± 2.23	4.97 ± 1.59	$p < 0.05$	CI = − 0.96 to − 0.74
WOMAC disability score	50.41 ± 13.66	48.82 ± 12.44	$p > 0.05$	CI = − 2.01 to 1.2

*p value < 0.05 was considered significant

Table 5 Reported risk factors associated with the sonographic diagnosis of crystal deposits in the population studied with primary knee OA

Risk factors	Knees with sonographic crystals (Total: 73 knees)	Knees without sonographic crystals (Total: 33 knees)	Odds ratio	95% CI	*p* value (significance)
Male Gender	15	3	2.6	0.7–9.6	0.16
Female Gender	58	30	0.4	0.1–1.4	0.16
Dyslipidemia	38	16	1.2	0.5–2.6	0.73
Chronic medical illness as Diabetes mellitus and hypertension	20	10	0.9	0.4–2.1	0.76
Clinically detected knee effusion	7	2	1.6	0.3–8.4	0.55
Limitation in ROM	36	10	2.2	0.9–5.4	0.07
Bursitis by sonography	35	6	4.1	1.5–11.2	0.01*
Effusion by sonography	47	12	3.2	1.3–7.4	0.01*
Total (fixed effects)	430/1022	156/462	1.9	1.4–2.6	0.23
Total (random effects)	430/1022	156/462	1.9	1.3–2.8	

*p value < 0.05 was considered significant

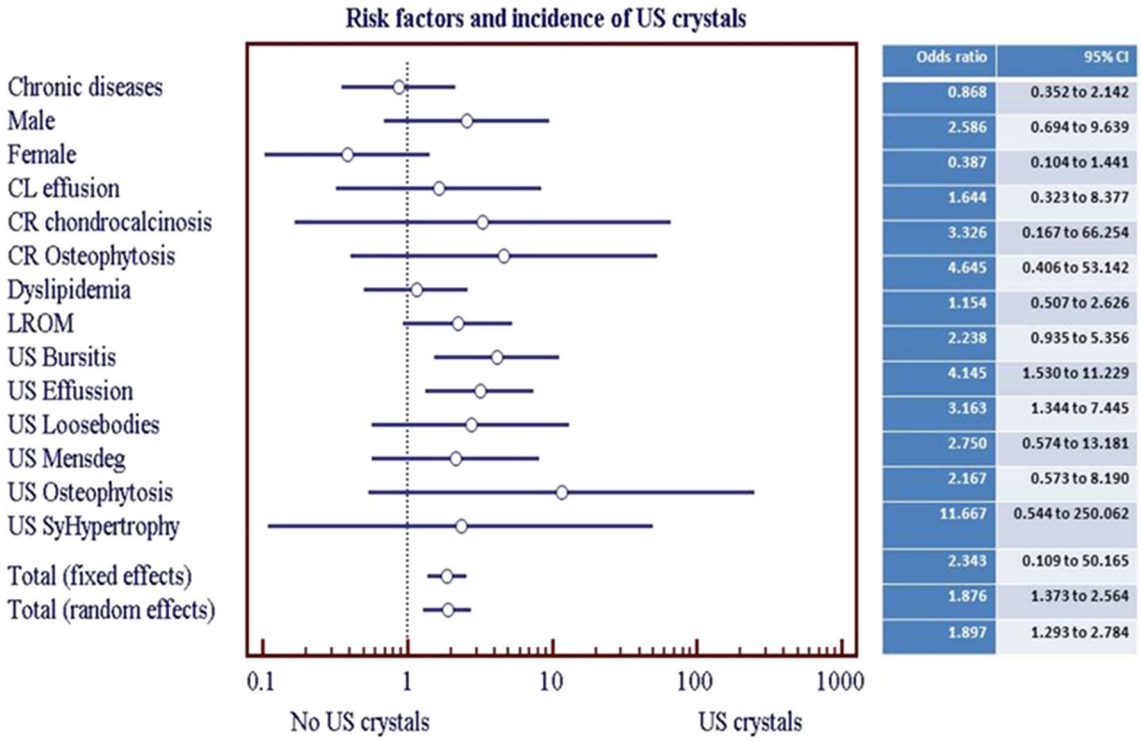

Fig. 5 Illustrates the forest plot curve for the results of regression analysis

Discussion

Crystal deposition disease is one of the most common arthropathies of the elderly. Similarly, OA is considered to be the most common joint pathology amongst the elderly population, usually associated with significant pain, disability, and even synovitis. The precipitation of crystals in joints with OA has been described in patients with OA. There is ample scientific support for the notion that calcium crystals can cause or worsen OA, with additional support for the notion that OA promotes intraarticular calcium crystal formation. In spite of recurring evidence, calcium crystal deposits are commonly underdiagnosed in OA [22]. The actual prevalence of crystal deposits as a pathologic finding that might contribute to symptomatic arthritis in patients with inflammatory knee pain or OA has been neither fully explored nor reliably measured to facilitate sound diagnosis in daily practice. An estimated prevalence rate ranging from 4% to over 50% has been suggested, possibly due to limits of both the survey methods and plain radiographic detection [21, 23–26].

According to the recommendations of the European League Against Rheumatism (EULAR) for the diagnosis of crystal deposition disease, synovial fluid (SF) analysis remains the gold standard [27–29]. Owing to the invasive nature and being dependent on the performing physician's expertise and the patient's consent, the inclusion of another easy-to-perform, noninvasive, and cost-effective bedside diagnostic alternative has been needed in daily practice. Recently, studies demonstrated the usefulness of US in identifying CPP crystal deposits in the hyaline cartilage and fibrocartilage at different joint sites. Meniscal fibrocartilage is one of the preferred targets of CPPD, which makes calcifications at meniscal fibrocartilage as well as hyperechoic spots (isolated, confluent, or linear) within the hyaline cartilage an almost exclusive feature of CPPD. The use of US in assessing patients with suspected CPPD has been recognized by the EULAR recommendations, which acknowledged US as a promising tool for the diagnosis of the disease. In 2014, the OMERACT US subtask force on CPPD was created to proceed with standardization of the technique and provide agreed-upon definitions for identifying CPPD by US [22–34]. The OMERACT US group acknowledged gaps regarding the use of US in CPPD, and established a well-defined consensus, the reproducibility of which was examined in a number of cases and yielded good results in terms of reliability in the assessment of the knee hyaline cartilage and fibrocartilage [21, 35–43]. In our study, US scanning using the OMERACT definitions and scanning technique could successfully detect calcifications in the hyaline cartilage, fibrocartilage, recesses, and bursa in 49.05%, 6.60%, and 19.81% of the scanned knees, respectively [17–19].

In the current study, the authors aimed to investigate the prevalence of subclinical crystal deposition in knee OA and

its contribution to clinical as well as sonographic indices of inflammation using musculoskeletal ultrasound. The study additionally investigated the impact of sonographically detected crystal deposits on pain, stiffness, and functional disability as practically recognized functional indicators of the existing inflammatory degenerative process in the study cohort with knee OA. The scanning rheumatologist was blinded to plain radiography and serum uric acid levels. Crystal deposits were sonographically detected in 68.9% of the study cohort, while plain radiography could detect chondrocalcinosis in three patients only. An obvious discrepancy between sonography and plain radiography has been reported in the current study, which might be attributed to a variety of factors. First, the bi-dimensional nature of the images obtained with plain radiography together with the superimposition of bones limits the whole cartilage assessment. Second, given the size and density of CPPD aggregates, conventional radiography may miss low-density CPPD aggregates, which are visible as hyperechoic spots using US. Third, any pathologic concomitant conditions, in this case knee OA, may impair the correct visualization of the cartilage because of the relevant joint space narrowing [25, 35, 43].

Addressing secondary outcomes, the study found insignificant differences between OA patients as regards the mean pain score (14.03 ± 3.98 without crystals, 14.42 ± 3.99 with crystals) and mean disability score (48.82 ± 12.44 without crystals, 50.41 ± 13.66 with crystals), with p value > 0.05 and 95% CI = − 7.12 to 3.82, − 2.01 to 1.2), in respect of the sonographic diagnosis of crystal deposits. This can be possibly attributed by the authors to the continuous use of local as well as systemic analgesics in addition to the interrupted use of NSAIDs by the population studied; furthermore, the majority of the population recruited and examined had mild to moderate OA changes in an attempt to minimize the effect of severe degenerative OA on the interpretation of clinical versus sonographic parameters used.

However, the study found the mean stiffness score was significantly higher in the knee OA patients with crystal deposits (4.97 ± 1.59 without crystals, 5.08 ± 2.23 with crystals), with $p < 0.01$ and 95% CI = − 0.96 to 0.74, suggesting inflammation with crystal deposits.

The inflammatory element in patients with crystal deposits was also indirectly suggested by ultrasonography in this study via the results showing a significantly higher mean pain WOMAC score in patients with crystal deposits and bursitis (15.56 ± 3.57 with vs 12.03 ± 3.83 without, $p < 0.05$). Together with regression models and forest plot test yielding a 4.1-fold incidence of crystal deposition in patients with sonographic bursitis versus those without (OR = 4.13, CI = 1.5–11.2, $p = 0.01$) and a 3.2-fold incidence of crystal deposition in patients with sonographic effusion versus those without (OR = 3.16, CI = 1.34–7.44, $p = 0.01$), this can be explained by the fact that joint recesses and bursae could serve as a reservoir for intraarticular crystals and loose bodies, contributing to a higher incidence of inflammation in these sites, with special consideration to the fact that the sensitivity of ultrasound to visualize the characteristic shape of crystals whether stagnant or fluctuating within the synovial fluid in cases with effusion enables their differentiation from loose bodies. US could reveal signs of subclinical effusion and bursitis that were not detected on routine clinical examination in the study cohort. The investigators could understand from these findings that subclinical crystal deposits in knees with OA might be associated with a significantly higher inflammatory component.

Previous studies [43–45] including a recent meta-analysis by Gamon et al. in 2015 [46] have clearly illustrated that ultrasonography has excellent specificity (96.4%), good sensitivity (86.7%), a positive predictive value of 92%, and a negative predictive value of 93% for detecting CPPD compared to synovial fluid examination and is reported to perform better than CT. Furthermore, despite the fact that US is considered to be an operator-dependent technology with poor repeatability, it is reassuring to see that recent studies have established moderate to good inter-observer reliability [15, 16].

Review of these data potentially supports the use of ultrasonography as a better alternative to screen for crystal deposits aiming to properly address the magnitude of the problem in daily practice using a noninvasive, easy-to-perform radio-diagnostic technique. Furthermore, the use of ultrasound might safely guide researchers to properly investigate other alternatives including the selection of patients to go for invasive procedures like joint aspirations or high-cost radio-diagnostic procedures like magnetic resonance imaging.

The authors believe the present study is a practical model for the potential benefit of routine use of diagnostic musculoskeletal ultrasound in patients with knee joint pain that might serve to screen for crystal deposits within the knee joints aiming to guide therapeutic regimens and response to different therapies.

Conclusion

In this study, musculoskeletal US was able to diagnose more patients with crystal deposits compared to plain radiography in the studied group with knee OA. Sonographic diagnosis of crystal deposition significantly correlated to stiffness scores in the study group. The presence of crystal deposits has contributed to a higher level of inflammation in patients with knee OA. There was a significant relation between crystals identified by US and the presence of inflammatory components such as bursitis and effusion.

Study limitations

The small sample size and lack of facilities for microscopic analysis as well as patient refusal to undergo invasive procedures in the absence of clinical joint effusion were limitations to this study. Recommendations: The authors recommend performing a study in a larger population with knee OA to provide a better estimate of the magnitude of the problem. We encourage the use of MSUS for the detection of CDD in joints other than knees, arranging for combined assessment of those patients using MSUS and synovial fluid analysis for crystals, comparing MSUS to MRI in the radiographic evaluation of patients with OA and suspected crystal deposition, and arranging for follow-up of patients following the introduction of interventional modalities.

Author contributions Dr. RM was involved in the hypothesis and study design, performed ultrasound examinations of the patients, and was involved in statistical analysis of and interpretation of preliminary as well as final data, clinical assessment confirmation following ultrasound examination, review of plain radiography with a radiologist, and manuscript writing and revisions. Dr. ADM was involved in manuscript writing, interpretation of statistical data, and peer review for the manuscript. Dr. HK was involved as senior supervisor in the hypothesis, study design, and supervision and review of data collection and interpretation. Dr. AM was involved in patient recruitment, clinical assessment, and recording clinical data during the preliminary study.

Compliance with ethical standards

Conflict of interest There are no financial or other relations that could lead to a conflict of interest. Forms were submitted for all authors.

Ethical statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

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