THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Original Research

Ultrasound-detected inflammation is more common in clinically manifest hand osteoarthritis than in painless bony enlarged finger joints: subanalysis of the population-based Bruneck study

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Ther Adv Musculoskel Dis

2022, Vol. 14: 1–11

DOI: 10.1177/1759720X221096382

Abstract

Purpose: The aim of this article is to examine the extent of structural and inflammatory lesions by ultrasound in elderly subjects with hand osteoarthritis (HOA) fulfilling the ACR classification criteria (Group A), in subjects with painless enlarged finger joints (Group B), and in individuals without clinical abnormalities at hands (Group C).

Methods: This study was nested within the population-based, prospective Bruneck study; 293 subjects of ⩾65 years of age were assessed. Clinical and ultrasound assessment was conducted at wrists and finger joints. Gray scale synovitis (GSS), Power Doppler (PD), osteophytes, and erosions were scored semiquantitatively (0–3). The Short Form Score for the Assessment and Quantification of Chronic Rheumatic Affections of the Hands (SF-SACRAH), the Health Assessment Questionnaire (HAQ), and the Functional Index for Hand Osteoarthritis (FIHOA) were retrieved.

Results: Most subjects had ⩾1 ultrasound abnormality, of which osteophytes were the most prevalent finding in all groups (Group A: 100%, Group B: 99.4%, and Group C: 93.9%). GSS and PD-signals were more common in Group A than in Group B (94% *versus* 67% and 33% *versus* 13%, respectively). In Group C, GSS was observed in 39.4% of subjects. In subjects with HOA, the SF-SACRAH correlated with osteophyte scores ($corr_{coeff}$ = 0.48), and the FIHOA correlated with the osteophyte ($corr_{coeff}$ = 0.42) and PD scores ($corr_{coeff}$ = 0.33).

Conclusion: GSS and PD were more frequent in patients with symptomatic HOA than in cases with painless bony enlargements and subjects without clinical joint abnormalities. Functional restriction in HOA is associated with structural and inflammatory ultrasound changes.

Keywords: hand osteoarthritis, osteophytes, pain, ultrasound

Received: 26 May 2021; revised manuscript accepted: 28 March 2022.

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Introduction

Hand osteoarthritis (HOA) is one of the most common rheumatic joint diseases worldwide. It negatively affects the quality of life of patients, which are mainly elderly women, and its vast socio-economic impact must not be underestimated.[1–3] To maintain the activities of daily living, early detection and diagnosis of HOA is crucial.

The definition of HOA is still uncertain.[4] Joint pain is the hallmark of the disease, and it is one of the entry domains for the American College of Rheumatology (ACR) classification criteria.[5] These

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criteria have been developed for classification of patients in clinical studies, but they are also applied, with some limitations, in clinical practice to confirm HOA in patients with finger pain.[6] Conventional radiography is the gold standard imaging tool for osteoarthritis (OA), and the combination of pain, aching, and stiffness together with characteristic x-ray findings is often used to diagnose HOA in clinical routine.[7]

Ultrasound is increasingly utilized for the assessment of HOA.[8] It is more sensitive than radiography for the detection of structural changes and enables the detection of soft tissue inflammation which is common in HOA.[9] Ultrasound-verified synovitis has been linked to pain and structural damage, and ultrasound may be used to distinguish HOA from other diseases in case of unclear joint symptoms.[10,11]

In clinical practice, we also observe subjects with bony thickening of joints and characteristic radiographic changes of HOA who do not have (and often never develop) clinical symptoms of OA.[12] Whether these individuals are still considered 'healthy' and joint changes reflect normal aging or whether these subjects suffer from subclinical HOA is unclear. Previous studies indicated that ultrasound can be a valuable tool in these patients to investigate the presence of joint inflammation and to exclude potential differential diagnoses.[13]

In this study, which was conducted as a part of the prospective, population based Bruneck study, we compared ultrasound findings between patients with clinically symptomatic HOA, individuals with bony joint enlargements but no symptoms of HOA, as well as subjects without pain and joint thickening.

Methods

Subjects

This study was nested within the 'Bruneck study', a prospective study of 1000 individuals from the city of Bruneck, Italy. All subjects were first recruited in 1990 from the official population register by random sampling. To create a representative sample, stratification for age and sex was performed with 125 individuals per sex and each decade of age from the fifth to eighth decade. A re-evaluation of the 1000 subjects was performed every 5 years (1995, 2000, 2005, 2010), and participation rates exceeded 90% (of subjects alive) for each visit. The current investigation focuses on 353 subjects who returned for the fifth follow-up conducted between April and May 2016. The majority of participants not showing up at the current visit were either deceased or in such bad health conditions that participation in the study was impossible. The Bruneck study was approved by the local institutional review board, and each patient provided written informed consent.

Clinical examination and clinical scores

Each subject underwent full medical history and clinical examination conducted by a trained medical student (N.G.). Medical history included questions concerning previous and current pain at hands, knees, hips, and spine; joint replacement surgery; and the items of the ACR classifications criteria for HOA.[5] Pain level was further evaluated using a visual analog scale (VAS) (ranging from 0 to 10 cm, 10 = worst). Clinical examination was performed in order to evaluate the presence of bony (hard) joint enlargements, (soft) joint swelling, and tenderness at the following joints: wrists, carpometacarpal joint (CMC) 1, metacarpophalangeal joint (MCP) 1–5, proximal interphalangeal joints (PIP) 1–5, and distal interphalangeal joints (DIP) 2–5. All study participants were asked to complete the Short Form Score for the Assessment and Quantification of Chronic Rheumatic Affections of the Hands (SF-SACRAH, range: 0–10),[14] the Health Assessment Questionnaire (HAQ, range: 0–3.0),[15] and the Functional Index for Hand Osteoarthritis (FIHOA, range: 0–30).[16]

We defined the following groups: Group A were patients who fulfilled the ACR criteria for HOA.[5] Group B were individuals who had at least one bony joint enlargement, which was defined as a hard, non-deformable swelling at finger joints but did not fulfill the ACR criteria for HOA and did not report current or previous pain, aching, tenderness, or soft tissue swelling at hands. Group C included all subjects that had neither clinical joint abnormalities nor symptoms suggesting HOA. Thirty-three patients presented with swelling, pain, aching, or tenderness of ≥ 1 joint of the hands but did not fulfill the ACR criteria and were therefore not included in any of the groups. The study flowchart is depicted in Supplementary Figure 1. X-rays of hands were not performed because it was not consented by the ethical committee.

Ultrasound examination

Ultrasound evaluation was conducted by one of two rheumatologists experienced in musculoskeletal sonography (C.D.: 8 years of experience, A.A.: 5 years of experience). The sonographers were unaware of the clinical history and group allocation. The participants were in a sitting position opposite to the examiner with the hands resting on a horizontal examination table in a darkened room. The hands were held in a neutral position, and the duration of each examination was around 20 min. Ultrasound was performed in transverse and longitudinal scans of the dorsal side of the wrists and the palmar and dorsal sides of CMC 1, MCP 1–5, PIP 1–5, and DIP 2–5 joints. We used a GE Logic E ultrasound device with a 20-MHz and a 12-MHz probe. For gray scale (GS), imaging parameters were adjusted to maximize the contrast between examined structures. Power Doppler (PD) settings were standardized accordingly: frequency: 14.3 or 7.7 MHz, respectively; pulse repetition frequency: 700 Hz; and medium flash filter. The PD-gain was optimized by increasing the gain until noise appeared and then reducing it just enough to suppress the noise. The following abnormalities were assessed by GS ultrasound: erosions, osteophytes, and gray scale synovitis (GSS) using previous definitions.[17] In addition, PD sonography was conducted. We used the following semiquantitative grading system for GSS and PD-signals: 0 = no change, 1 = mild, 2 = moderate, 3 = severe, in accordance with prior publications.[17,18]

Erosions were graded from 0 to 3 with 0 = no change, 1 = horizontal cortical break of 0–1 mm, 2 = horizontal cortical break of 1.1–2 mm, and 3 = horizontal cortical break >2 mm.

The OMERACT score[17] was used to assess osteophytes. Osteophytes were defined as step-up bony prominence at the bony margins that is visible in two perpendicular planes and were graded semiquantitatively with 0 = none, 1 = minor, 2 = moderate, and 3 = major size of osteophytes. The ultrasound atlas of osteophytes developed by Mathiessen *et al.*[19] was used as a reference. Osteophytes and erosions were not investigated at the wrist.

Statistical analysis

All statistical analyses were done using R [R Core Team (2016), Vienna, Austria (https://www.r-project.org/)].

Descriptive statistics were used to summarize the data. Possible correlations of clinical factors including the three questionnaires (SF-SACRAH, FIHOA, and HAQ), the number of joints with bony enlargement, the number of joints with soft swelling (SJC), and the number of joints with tenderness (TJC) with ultrasound findings including GSS sum score (0–48), the PD sum score (0–48), the osteophyte sum score (0–48), and the erosion sum score (0–48) were investigated using the Spearman's rank correlation test or the Pearson's test as appropriate. The ultrasound sum scores were calculated per patient by summing up all semiquantitative gradings (for each joint, the higher value of palmar or dorsal scans was used).

Inter-observer and intra-reader variability of ultrasound was investigated on 67 stored images from 18 patients using Kappa index with linear weighting.

Results

Demographic data

Out of the 353 subjects studied, 17 individuals were excluded because of incomplete data and 10 individuals were excluded because of inflammatory rheumatic diseases [rheumatoid arthritis ($n = 5$), polymyalgia rheumatica ($n = 2$), psoriatic arthritis ($n = 1$), and collagenous colitis ($n = 2$)]. Of the remaining 326 patients, 87 were classified as HOA according to the ACR criteria (26.7%, Group A), 173 individuals had bony enlargements at finger joints without symptoms of HOA (53.1%, Group B), and 33 subjects had neither bony enlargements nor pain (10.1%, Group C). Thirty-three patients (10.1%) did not meet the criteria for any group and were excluded from subsequent analyses; hence, 293 subjects in Groups A–C were proceeded for further analysis (see Supplementary Figure 1 for flowchart).

Demographic data are depicted in Table 1. There were more women in Group A than in Group B (62% *versus* 42%). There was no considerable difference between groups concerning type of previous work (white collar/blue collar), previous replacement surgery of any joint, or prevalence of hip, knee, or spinal pain.

Comparison of ultrasound findings between individuals with and without clinical symptoms of HOA

Ultrasound findings at the population level. All 87 study subjects in Group A yielded at least one

Table 1. Demographic and clinical data.

	Group A (*n* = 87)	Group B (*n* = 173)	Group C (*n* = 33)
Age, mean (SD)	76.7 (6.7)	75.8 (7.2)	72.4 (7.5)
Female, *n* (%)	54 (62.1)	72 (41.6)	12 (36.4)
Former blue-collar worker, *n* (%)[a]	42 (77.8)	70 (68.6)	11 (61.1)
Any previous joint replacement, *n* (%)	15 (17.2)	16 (9.3)	2 (6.1)
Number of enlarged joints per patient, mean (SD)	8.2 (4.6)	4.9 (3.5)	–
Hip pain, *n* (%)	12 (13.8)	15 (8.7)	2 (6.1)
Knee pain, *n* (%)	27 (31.0)	35 (20.2)	5 (15.2)
Chronic back pain, *n* (%)	34 (39.1)	61 (35.3)	13 (39.4)
Pain level hand, median (IQR)	0 (0–3)	–	–
Pain level hand, min, max	0, 8		
SF-SACRAH, median (IQR)	1.4 (1.0–1.8)	–	–
SF-SACRAH, min, max	0.0, 6.8		
FIHOA, median (IQR)	0 (0–5)	–	–
FIHOA, min, max	0, 16		
HAQ, median (IQR)	0 (0–125)	–	–
HAQ, min, max	0, 2375	–	–

FIHOA, Functional Index for Hand Osteoarthritis; IQR, interquartile range; SD, standard deviation; SF-SACRAH, Short-Form Score for the Assessment and Quantification of Chronic Rheumatic Affections of the Hands.
Group A: subjects with clinically manifest hand osteoarthritis; Group B: subjects with painless bony joint enlargements; Group C: individuals with apparently normal joints at hands.
[a]130 out of 326 subjects did not state their former occupation.

Table 2. Percentage of subjects with at least one ultrasound abnormality.

	Group A (*n* = 87)	Group B (*n* = 173)	Group C (*n* = 33)
⩾1 US abnormality, *n* (%)	87 (100.0)	172 (99.4)	32 (97.0)
Osteophytes, *n* (%)	87 (100.0)	172 (99.4)	31 (93.9)
GSS, *n* (%)	82 (94.3)	116 (67.1)	13 (39.4)
Power Doppler, *n* (%)	29 (33.3)	22 (12.7)	1 (3.0)
Erosion, *n* (%)	15 (17.2)	24 (13.9)	0 (0.0)

GSS, gray scale synovitis; US, ultrasound.

ultrasound abnormality (Table 2). Osteophytes were the most frequent finding occurring in 100% of subjects, followed by GSS and PD-signals, which were observed in at least one joint in 94% and 33% of subjects, respectively. Erosions were the least common pathology (17% of the examined subjects in Group A). In Group B, 99% of the subjects revealed at least one abnormal ultrasound finding. Osteophytes (99%) and erosions (14%) occurred to a similar frequency as in Group A, whereas GSS (67%) and PD-signals (13%) were less common. In Group C, the prevalence of ultrasound findings was still high (97%): 94% of individuals had osteophytes, and GSS was observed in 39%. There was only one subject with PD-signals (3%) and none with erosions.

Results of semiquantitative scoring is depicted in Table 3. Almost half of the subjects in Group A (46.0%) had at least one grade 3 osteophyte as compared with 23.1% in Group B. Only a small proportion of individuals yielded grade 3 GSS (Group A: 12.6% *versus* Group B: 2.9%), grade 3

Table 3. Prevalence of grades 1–3 ultrasound abnormalities.

		Osteophytes	GSS	Erosion	Power Doppler
Group A (*n* = 87)	None	0 (0)	5 (5.7)	72 (82.8)	58 (66.7)
	Grade 1	14 (16.1)	43 (49.4)	4 (4.6)	11 (12.6)
	Grade 2	33 (37.9)	28 (32.2)	9 (10.3)	16 (18.4)
	Grade 3	40 (46.0)	11 (12.6)	2 (2.3)	2 (2.3)
Group B (*n* = 173)	None	1 (0.6)	57 (32.9)	149 (86.1)	151 (87.3)
	Grade 1	58 (33.5)	75 (43.4)	11 (6.4)	12 (6.9)
	Grade 2	74 (42.8)	36 (20.8)	12 (6.9)	10 (5.8)
	Grade 3	40 (23.1)	5 (2.9)	1 (0.6)	0 (0.0)
Group C (*n* = 33)	None	2 (6.1)	20 (60.6)	33 (100)	32 (97.0)
	Grade 1	20 (60.6)	10 (30.3)	0 (0.0)	0 (0.0)
	Grade 2	9 (27.3)	2 (6.1)	0 (0.0)	1 (3.0)
	Grade 3	2 (6.1)	1 (3.0)	0 (0.0)	0 (0.0)

GSS, grey scale synovitis.
The number (percentage) of subjects with no (none), or at least one grade 1, 2, or 3 ultrasound abnormality is depicted.

erosions (2.3% *versus* 0.6%), and grade 3 PD findings (2.3% *versus* 0%) in both Groups A and B.

In Group C, grade 3 changes were observed in <10% of individuals for all abnormalities (see Table 3).

Ultrasound findings at the joint level. The prevalence of abnormal ultrasound findings in different joint groups (DIPs, PIPs, MCPs, wrists) is detailed in Table 4. DIPs were more frequently affected in Group A as compared with Group B (98.9% *versus* 85.0%, respectively), particularly osteophytes at DIPs were more often observed in the former than in the latter group (98.9% *versus* 83.2%). In Group B, PIPs were the most frequently involved joint group (89.0%). GSS (72.4% *versus* 40.5%, respectively) and PD-signals (12.6% *versus* 2.3%, respectively) were nevertheless more common at PIPs from group A than from Group B patients. Erosions were mainly observed at MCPs in both groups (A: 11.5% *versus* B: 11.0%).

The most commonly affected individual joint was the DIP2 (83.3% of the examined DIP2s in Group A and 50.6% in Group B yielded at least one ultrasound abnormality), as detailed in Supplementary Table 1.

In Group C, osteophytes were most commonly observed at PIPs; GSS, PD-signals, and erosions were rare in all joints. The most commonly affected individual joint in this group was PIP1.

Association between ultrasound and clinical findings

Correlation analyses were conducted in order to investigate the association between ultrasound findings and functional impairment. For patients with HOA (Group A), there was a moderate correlation of the osteophyte sum score with the SF-SACRAH ($corr_{coeff} = 0.48$). Also, the osteophyte sum score and the PD sum score correlated moderately with the FIHOA ($corr_{coeff} = 0.42$ and $corr_{coeff} = 0.33$) and hand pain ($corr_{coeff} = 0.38$ and $corr_{coeff} = 0.34$). The HAQ did not correlate with any of the ultrasound parameters. For Group B, no correlations were found between ultrasound scores and any of the questionnaires. In Group C, moderate correlations were found of the osteophyte

Table 4. Ultrasound findings according to joint regions.

		⩾1 US abnormality	Osteophyte	GSS	Erosion	PD	GSS + PD
Group A (*n* = 87)	Wrist	22 (25.3)	NA (NA)	22 (25.3)	NA (NA)	5 (5.7)	5 (5.7)
	CMC	70 (80.5)	69 (79.3)	24 (27.6)	4 (4.6)	14 (16.1)	12 (13.8)
	MCP	72 (82.8)	68 (78.2)	47 (54.0)	10 (11.5)	9 (10.3)	9 (10.3)
	PIP	82 (94.3)	82 (94.3)	63 (72.4)	0 (0.0)	11 (12.6)	11 (12.6)
	DIP	86 (98.9)	86 (98.9)	40 (46.0)	2 (2.3)	6 (6.9)	6 (6.9)
Group B (*n* = 173)	Wrist	23 (13.3)	NA (NA)	21 (12.1)	NA (NA)	5 (2.9)	3 (1.7)
	CMC	113 (65.3)	109 (63.0)	18 (10.4)	2 (1.2)	8 (4.6)	5 (2.9)
	MCP	139 (80.3)	127 (73.4)	57 (32.9)	19 (11.0)	11 (6.4)	10 (5.8)
	PIP	154 (89.0)	148 (85.5)	70 (40.5)	5 (2.9)	4 (2.3)	2 (1.2)
	DIP	147 (85.0)	144 (83.2)	48 (27.7)	2 (1.2)	2 (1.2)	1 (0.6)
Group C (*n* = 33)	Wrist	3 (9.1)	NA (NA)	3 (9.1)	NA (NA)	0 (0.0)	0 (0.0)
	CMC	12 (36.4)	12 (36.4)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
	MCP	24 (72.7)	23 (69.7)	8 (24.2)	0 (0.0)	1 (3.0)	1 (3.0)
	PIP	26 (78.8)	24 (72.7)	6 (18.2)	0 (0.0)	1 (3.0)	1 (3.0)
	DIP	21 (63.6)	20 (60.6)	3 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)

DIPs, distal interphalangeal joints; GSS, grey scale synovitis; MCPs, metacarpophalangeal joints; PD, Power Doppler; PIPs, proximal interphalangeal joints; US, ultrasound.
The number (percentage) of subjects with ⩾1 ultrasound abnormality in each joint region is depicted.

score with the SF-SACRAH ($corr_{coeff}$ = 0.41) and the HAQ ($corr_{coeff}$ = 0.49).

There was no association between the number of joints with bony enlargements and pain.

The osteophyte sum score revealed low to moderate correlations with the number of joints with bony enlargement in Group A ($corr_{coeff}$ = 0.36) and Group B ($corr_{coeff}$ 0.51), respectively, while other ultrasound scores revealed no relevant correlations (see Supplementary Table 2).

Weak correlations were also found between the GSS sum score and the SJC ($corr_{coeff}$ = 0.370) as well as between the osteophyte sum score and the TJC ($corr_{coeff}$ = 0.457) in Group A (Group B had per definition no tenderness or soft swelling of the joints).

Group C was not included in this analysis because of the absence of clinically evident bony enlargements, tenderness, or swelling of the joints.

Reliability exercise

Inter-rater reliability was good with a linear weighted kappa index of 0.83 [95% confidence interval (CI) = 0.78–0.88] for semiquantitative scoring of all lesions. Kappa for GSS was 0.72 (95% CI = 0.57–0.86), for osteophytes was 0.69 (95% CI = 0.58–0.80), for PD-signals was 0.96 (95% CI = 0.88–1.0), and for erosions was 1.0 (95% CI = 1.0–1.0).

Intra-reader reliability of ultrasound findings ranged from moderate to good. Linear weighted kappa indices were 0.94 (95% CI = 0.91–0.98) and 0.81 (95% CI = 0.76–0.86) for all lesions,

0.78 (95% CI = 0.65–0.91) and 0.79 (95% CI = 0.68–0.90) for GSS, 0.98 (95% CI = 0.96–1.0) and 0.59 (95% CI = 0.46–0.72) for osteophytes, 1.0 (95% CI = 1.0–1.0) and 1.0 (95% CI = 1.0–1.0) for PD-signals, as well as 1.0 (95% CI = 1.0–1.0) and 1.0 (95% CI = 1.0–1.0) for erosions according to the raters C.D. and A.A., respectively.

Discussion

Our study suggests a possible link of structural changes and inflammation, which can both be detected by ultrasound, with symptomatic HOA. GSS and PD were more common in the group fulfilling the ACR criteria for HOA than in individuals with painless bony enlargements and subjects with apparently normal fingers.

The prevalence of structural findings was comparable in Groups A and B, and still, >90% of subjects without any clinical symptoms at finger joints had osteophytes with or without other ultrasound abnormalities. This observation further stimulates the discussion about whether every osteophyte can be considered a pathology, that is, OA, or whether it simply makes part of health aging, at least to a certain degree, particularly when it is not associated with pain, aching, or functional restrictions.[20] The alternative hypothesis is that OA (assuming that osteophytes detected by imaging would be sufficient for a diagnosis of OA) affects the vast majority of the elderly people becoming clinically manifest only in a proportion of them, namely, in those with joint inflammation and a high extent of structural damage, which might be determined by genetic and other factors. It has previously been shown that radiographic features of HOA are very common, but only some of these people develop symptoms. In the Framingham study, for example, the prevalence of radiographic HOA was similarly high in women and men (94,4% *versus* 88.6%), while symptoms occurred twice as common in women.[21]

In our study, we also observed that the majority of patients with symptomatic HOA were women, while the majority of people with painless bony enlargement were men. This might be related to the fact that in the overall study population, there was male predominance but could also indicate that painless bony enlargement of joints is distributed differently between sexes than symptomatic HOA.

We moreover observed that the number of joints with bony enlargement correlated with the sonographic osteophyte score. Ultrasound-verified osteophytes further correlated with joint tenderness, which is in line with earlier research.[22]

GSS, PD, and osteophyte grades but not the prevalence of osteophytes were higher in Group A than in Group B (see Tables 2 and 3) suggesting that low-grade osteophytes may be painless, whereas the progression of bone formation from low to high grade is associated with or might even cause inflammation and aching. The observation that the number of clinically enlarged joints in Group A was nearly twice as high as in Group B further supports this conclusion. Another hypothesis is that structural changes precede clinically apparent HOA. This is supported by a recent study suggesting that ultrasound-verified osteophytes predicted the onset of radiographic and clinical HOA after 5 years.[23] A follow-up of the Bruneck study is already scheduled to shed more light on this issue. Whether structural changes in HOA itself cause synovitis by mechanical means promoting additional structural changes and pain also needs to be clarified by future studies. While we observed an association between pain, inflammation, and structural changes, the causal and temporal relationship (i.e. whether inflammation precedes structural damage or vice versa) can only be clarified by a longitudinal follow-up design.

A related issue is the possible relevance of GSS and PD findings in asymptomatic patients, as observed in up to two thirds of individuals in Groups B and C. It is conceivable that subclinical inflammation occurs along with (or precedes) joint degeneration as recently observed in a histological study of knee OA,[24] and this is also supported by the correlation of GSS/PD scores with structural damage in our cohort. In other studies, it has been concluded that low-grade inflammatory findings may occur in healthy subjects and are thus non-specific.[25] The majority of GSS and PD changes in our study were of grade 1. In accordance with previous publications, this could still be considered within the range of normal,[26,27] and maybe, the cut-off for abnormal GSS and PD scores has to be adjusted for age in future studies. Moderate- to high-grade synovitis, which might be more relevant for clinical and structural outcomes, has been observed in only one-fifth of subjects in Group B and in <10% of individuals in Group C.[28]

In patients with clinically manifest HOA, osteophytes and PD-signals correlated with functional impairment and pain. Osteophytes furthermore also correlated with functional impairment in patients without pain or visible bony enlargements. This result is in line with previous publications extending our knowledge on the association between inflammation, damage, and patient-reported outcomes. Others reported that inflammation was more common at individual painful joints as compared with sites without tenderness, while the overall level of pain was not linked to global synovitis scores.[29–31] This might be explained by a limited sensitivity of global pain scores to detect inflammation as pain is influenced by comorbidities and other factors.[32]

The DIP2 was the most commonly affected individual joint which might be influenced by a higher mechanical load at this site.[33] Structural and inflammatory findings, however, were also common at MCPs, even if these joints are not typically affected clinically in patients with HOA. Erosions were frequent at MCPs (and in particular MCP2), underlining the previous observation that erosions at these sites are not always specific for rheumatoid arthritis.[34] An alternative hypothesis is that in some cases, two close osteophytes appearing like a breakage in the bone might have erroneously been classified as erosions (pseudo erosions) and that vessel channels at MCPs might have been misinterpreted as erosions.[35] A cadaver study comparing ultrasound, micro-computed tomography (μCT), and histology at PIP and DIP joints recently highlighted a low sensitivity (but high specificity) of ultrasound (and μCT) to detect erosions in HOA when histology was used as the gold standard.[36]

Subclinical involvement of MCPs in HOA might partially be determined by genetic factors. A linkage between variations in the *HFE* gene and HOA[37] has been described, and it is well known that hereditary hemochromatosis, caused by mutations in the *HFE* gene, commonly affects MCP2 and MCP3 with painful arthritis and extensive degenerative changes.[37] While our cohort was not tested systematically for any HFE mutation, our patients had no clinical or laboratory sign of hemochromatosis. Further research is required to better understand the possible association between polymorphisms in the HFE and other genes and the degree of clinical, structural, and inflammatory ultrasound findings in HOA.

The most important limitation of our study is the absence of radiographs to assess the grade of OA. Previous studies revealed a lower association of pain with radiographic as compared with ultrasound changes; however, we were unable to validate or refute this observation.[38] For the classification of HOA patients, we relied on the ACR criteria where x-ray data are not required but could not test alternative definitions of HOA.[7] For the detection of osteophytes, ultrasound seems to be much more sensitive than conventional radiography,[39] and the possible value of ultrasound for classification and diagnosis of HOA needs to be evaluated. We defined individuals who did not fulfill the ACR criteria as controls despite having ultrasound-verified structural changes, which might be debatable. As outlined above, almost 100% of individuals in all groups had at least one osteophyte; hence, the question remains open whether all these individuals should be diagnosed with HOA or whether low-grade structural changes, particularly in the absence of pain, can be considered as normal aging.

The difference in GS and Doppler measures between Groups A and B may be explained by the fluctuating nature of HOA, at least to some extent. Whether the classification of people with ultrasound-verified structural joint changes as HOA, as compared with traditional algorithms using clinical examination and radiography, might lead to earlier pharmacological interventions and better long-term outcomes has to be clarified by future studies.

Moreover, interobserver reliability was not conducted for clinical examination; however, exams were always performed by the same investigator who was specifically trained for the purpose of this study.

There has been significant attrition from the original cohort of the Bruneck study mainly because of death or declining health of people. This could certainly have led to a selection bias toward examination of those with healthy aging. Of note, the participation rate of each round of the Bruneck study exceeded 90%.

A further limitation concerning the group definition is that while patients were asked whether they had any history of joint pain, we cannot exclude that some patients did not recall or report correctly previous episodes of aching leading to

misclassification of some patients. On the other hand, it is likely that inflammatory findings at joints are more closely related to current rather than to any episodes of previous, self-limiting pain. For future phases of the Bruneck study, we plan multiple assessments at several time points to better map the temporal relation between pain and inflammation.

We did not include patients with joint symptoms but not fulfilling classification criteria for HOA. It might be that some of these patients later develop classic HOA, but some of them might also develop inflammatory arthritis. As the Bruneck study is scheduled as a follow-up study, we will have the opportunity to evaluate the outcome of these patients in the next round of this study.

Another limitation is the fact that we had no reliable information on the onset of joint enlargements, because patients had difficulties to recall it. This precludes correlation analyses between the duration of joint changes and ultrasound findings.

Conclusion

In our study, we found GSS and PD inflammation as well as the extent of osteophytes to be higher in patients with HOA classified by the ACR criteria, as compared with those with painless bony enlargements of finger joints. In HOA, osteophytes and PD could be a possible link to functional restrictions and pain. Ultrasound-verified osteophytes and synovitis were also detected in our elderly subjects without clinically overt HOA.

Ethics approval and consent to participate

Institutional review board of the South Tyrol Health Trust. (Number 95 – 2015)

Consent for publication

Written consent was obtained.

Author contribution(s)

Nina Gasperi: Conceptualization; Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Nikolaus Schreiber: Conceptualization; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

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Antonella Adinolfi: Conceptualization; Writing – review & editing.

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Arno Gasperi: Conceptualization; Investigation; Methodology; Writing – review & editing.

Agnes Mayr: Data curation; Writing – review & editing.

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Acknowledgements

None.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study is part of the excellence initiative [Competence Centers for Excellent Technologies (COMET)] of the Austrian Research Promotion Agency FFG: 'Research Center of Excellence in Vascular Ageing – Tyrol, VASCage' (K-Project 843536) funded by the Federal Ministry for Transport, Innovation and Technology (BMVIT); Federal Ministry of Science, Research and Economy (BMWFW); Wirtschaftsagentur Wien; and Standortagentur Tirol. Funding was also provided by the South

Tyrol Health Trust. The funding organizations did not influence the design or conduct of the study; the collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Derived data supporting the findings of this study are available from the corresponding author C.D. on request.

Reporting of the study

The reporting of this study conforms to the STROBE statement.[40]

Supplemental material

Supplemental material for this article is available online.

References

1. Palazzo C, Nguyen C, Lefevre-Colau MM, *et al.* Risk factors and burden of osteoarthritis. *Ann Phys Rehabil Med* 2016; 59: 134–138.
2. Iagnocco A, Conaghan PG, Aegerter P, *et al.* The reliability of musculoskeletal ultrasound in the detection of cartilage abnormalities at the metacarpo-phalangeal joints. *Osteoarthritis Cartilage* 2012; 20: 1142–1146.
3. Lombnæs GØ, Magnusson K, Østerås N, *et al.* Distribution of osteoarthritis in a Norwegian population-based cohort: associations to risk factor profiles and health-related quality of life. *Rheumatol Int* 2017; 37: 1541–1550.
4. Haugen IK, Felson DT, Abhishek A, *et al.* Development of classification criteria for hand osteoarthritis: comparative analyses of persons with and without hand osteoarthritis. *RMD Open* 2020; 6: e001265.
5. Altman R, Alarcón G, Appelrouth D, *et al.* The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990; 33: 1601–1610.
6. Cibere J. Do we need radiographs to diagnose osteoarthritis? *Best Pract Res Clin Rheumatol* 2006; 20: 27–38.
7. Zhang W, Doherty M, Leeb BF, *et al.* EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. *Ann Rheum Dis* 2009; 68: 8–17.
8. Torralba K, Cannella A, Kissen E, *et al.* Musculoskeletal ultrasound instruction in adult rheumatology fellowship programs. *Arthritis Care Res* 2017; 12: 3218–3221.
9. Mancarella L, Addimanda O, Cavallari C, *et al.* Synovial inflammation drives structural damage in hand osteoarthritis: a narrative literature review. *Curr Rheumatol Rev* 2017; 13: 43–50.
10. Sakellariou G, Conaghan PG, Zhang W, *et al.* EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. *Ann Rheum Dis* 2017; 76: 1484–1494.
11. Mathiessen A, Slatkowsky-Christensen B, Kvien TK, *et al.* Ultrasound-detected inflammation predicts radiographic progression in hand osteoarthritis after 5 years. *Ann Rheum Dis* 2016; 75: 825–830.
12. Dahaghin S, Bierma-Zeinstra SMA, Hazes JMW, *et al.* Clinical burden of radiographic hand osteoarthritis: a systematic appraisal. *Arthritis Rheum* 2006; 55: 636–647.
13. Haugen IK and Hammer HB. Role of modern imaging techniques in hand osteoarthritis research and clinical practice. *Curr Rheumatol Rep* 2014; 16: 399.
14. Stummer U, Rintelen B and Leeb BF. The Short Form Score for the Assessment and Quantification of Chronic Rheumatic Affections of the Hands in daily clinical routines – its sensitivity to change and preliminary patient relevant variation values: a pilot study. *Front Med (Lausanne)* 2017; 4: 6–7.
15. Fries JF, Spitz P, Kraines R, *et al.* Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23: 137–145.
16. Dreiser RL, Maheu E, Guillou GB, *et al.* Validation of an algofunctional index for osteoarthritis of the hand. *Rev Rhum Engl Ed* 1995; 62(6 Suppl 1): 43S–53S.
17. Agostino MD, Terslev L, Aegerter P, *et al.* Scoring ultrasound synovitis in rheumatoid arthritis : a EULAR-OMERACT ultrasound taskforce – part 1: definition and development of a standardised, consensus-based scoring system. *RMD Open* 2017; 3: e000428.
18. Hammer HB, Iagnocco A, Mathiessen A, *et al.* Global ultrasound assessment of structural lesions in osteoarthritis: a reliability study by the OMERACT ultrasonography group on scoring cartilage and osteophytes in finger joints. *Ann Rheum Dis* 2016; 75: 402–407.

19. Mathiessen A, Haugen IK, Slatkowsky-Christensen B, *et al*. Ultrasonographic assessment of osteophytes in 127 patients with hand osteoarthritis: exploring reliability and associations with MRI, radiographs and clinical joint findings. *Ann Rheum Dis* 2013; 72: 51–56.
20. Berlin A, Simon D, Tascilar K, *et al*. The ageing joint-standard age- and sex-related values of bone erosions and osteophytes in the hand joints of healthy individuals. *Osteoarthritis Cartilage* 2019; 27: 1043–1047.
21. D'Ambrosia RD. Epidemiology of osteoarthritis. *Orthopedics* 2005; 28(2 Suppl): s201–s205.
22. Kortekaas MC, Kwok WY, Reijnierse M, *et al*. Osteophytes and joint space narrowing are independently associated with pain in finger joints in hand osteoarthritis. *Ann Rheum Dis* 2011; 70: 1835–1837.
23. Foltz V, Etchepare F, Rosenberg C, *et al*. Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. *Arthritis Rheum* 2012; 64: 67–76.
24. Minten MJM, Blom A, Snijders GF, *et al*. Exploring longitudinal associations of histologically assessed inflammation with symptoms and radiographic damage in knee osteoarthritis: combined results of three prospective cohort studies. *Osteoarthritis Cartilage* 2019; 27: 71–79.
25. Padovano I, Costantino F, Breban M, *et al*. Prevalence of ultrasound synovial inflammatory findings in healthy subjects. *Ann Rheum Dis* 2016; 75: 1819–1823.
26. Brown AK, Quinn MA, Karim Z, *et al*. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug – induced clinical remission evidence from an imaging study may explain structural progression. *Arthritis Rheum* 2006; 54: 3761–3773.
27. Millot F, Clavel G, Etchepare F, *et al*. Musculoskeletal ultrasonography in healthy subjects and ultrasound criteria for early arthritis (the ESPOIR cohort). *J Rheumatol* 2011; 38: 613–620.
28. Mancarella L, Addimanda O, Cavallari C, *et al*. Synovial inflammation drives structural damage in hand osteoarthritis: a narrative literature review. *Curr Rheumatol Rev* 2017; 13: 43–50.
29. Haugen IK, Bøyesen P, Slatkowsky-Christensen B, *et al*. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. *Ann Rheum Dis* 2012; 71: 899–904.
30. Keen HI, Wakefield RJ, Grainger AJ, *et al*. An ultrasonographic study of osteoarthritis of the hand: synovitis and its relationship to structural pathology and symptoms. *Arthritis Rheum* 2008; 59: 1756–1763.
31. Kortekaas MC, Kwok WY, Reijnierse M, *et al*. Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound. *Ann Rheum Dis* 2010; 69: 1367–1369.
32. McGrath PA. Psychological aspects of pain perception. *Arch Oral Biol* 1994; 39 Suppl: 55S–62S.
33. Jonsson H, Helgadottir GP, Aspelund T, *et al*. The use of digital photographs for the diagnosis of hand osteoarthritis: the AGES-Reykjavik study. *BMC Musculoskelet Disord* 2012; 13: 20.
34. Zayat AS, Ellegaard K, Conaghan PG, *et al*. The specificity of ultrasound-detected bone erosions for rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: 897–903.
35. Dejaco C, Stadlmayr A, Duftner C, *et al*. Ultrasound verified inflammation and structural damage in patients with hereditary haemochromatosis-related arthropathy. *Arthritis Res Ther* 2017; 19: 243.
36. Husic R, Finzel S, Stradner MH, *et al*. Ultrasound in osteoarthritis of the hand; a comparison to computed tomography and histology. *Rheumatology (Oxford)* 2021; 61: S173–S180.
37. Ross JM, Kowalchuk RM, Shaulinsky J, *et al*. Association of heterozygous hemochromatosis C282Y gene mutation with hand osteoarthritis. *J Rheumatol* 2003; 30: 121–125.
38. Kortekaas MC, Kwok WY, Reijnierse M, *et al*. Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound. *Ann Rheum Dis* 2010; 69: 1367–1369.
39. Iagnocco A and Naredo E. Ultrasound of the osteoarthritic joint. *Clin Exp Rheumatol* 2017; 35: 527–534.
40. von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies [published correction appears in *Ann Intern Med* 2008; 148(2): 168]. *Ann Intern Med* 2007; 147: 573–577.