The association between radiographic progression, functional impairment, markers of dyslipidaemia and inflammation in patients with hand osteoarthritis: a five-year longitudinal study

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Abstract

Objective

This study aimed to investigate the associations between radiographic damage, serum biomarkers, and clinical assessments in Czech patients with hand osteoarthritis (HOA) over a five-year follow-up period.

Methods

The study cohort comprised 129 patients diagnosed with HOA, including 72 patients with an erosive subtype and 57 patients with a non-erosive subtype. Radiographs were evaluated using the Kallman scoring system by two independent readers. Blood samples were analysed for markers of dyslipidaemia, bone metabolism, and inflammation. Clinical assessments focused on symptom severity and functional impairment. We employed generalised additive modelling (GAM) to analyse the associations between the Kallman score, serum biomarkers and clinical outcomes.

Results

The Kallman score was consistently higher in the erosive subtype compared to the non-erosive subtype across all time points and demonstrated a positive correlation with age in both groups. We demonstrated significant positive associations between radiographic progression and erythrocyte sedimentation rate across both HOA subtypes. Additionally, positive associations with the number of swollen joints and health assessment questionnaire scores were observed in all HOA patients, particularly in those with non-erosive subtypes. In contrast, markers of dyslipidaemia (e.g. LDL-c or atherogenic index) were negatively associated with radiographic progression. No biomarker reliably differentiated between the erosive and non-erosive subtypes.

Conclusion

Our longitudinal study revealed a significant association between systemic/local inflammation, dyslipidaemia, functional impairment and structural progression in HOA. However, these findings warrant further validation through additional studies to confirm these associations.

Key words

osteoarthritis, biomarkers, dyslipidaemia, inflammation, longitudinal studies

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Introduction

Osteoarthritis (OA) is the most common chronic musculoskeletal disorder causing pain, swelling, and reduced mobility, primarily affecting the knees, hips, and hands (1). Hand osteoarthritis (HOA) is more common in women and increases with age (2). Indeed, it is a leading cause of disability and chronic pain in the elderly, with an estimated lifetime risk of 47.2% for women and 24.6% for men (3). Symptomatic HOA affects around 6–8% of all adults (4, 5) and can be further classified as either non-erosive HOA or erosive HOA subtypes, based on radiographic findings (6).

The erosive subtype involves a characteristic central erosion with collapse of the subchondral bone and a 'gull-wing' or 'saw-tooth' deformity of the hand joints (7) and is associated with severe symptoms than the non-erosive subtype, particularly manifesting as swollen joints, pain that worsens with use, and limited mobility (8). While most people with the primary disease remain asymptomatic until their 50s due to the slow progression of HOA, joint erosions can be detected via radiographs before the onset of symptoms. To standardise the evaluation, various scoring systems have been developed, including the Kellgren-Lawrence (KL) classification (9), Kallman scale (10), Kessler scale (11), the Osteoarthritis Research Society International (OARSI) scoring atlas (13), and the Verbruggen-Veys scoring system (14). While OARSI and KL scoring methods are widely used for different osteoarthritis types (15), the Kallman scale was developed specifically for HOA and better reflects radiographic changes in hand joints (16). Importantly, the Kallman scale has been validated for both cross-sectional and longitudinal studies of HOA, which offers improved assessment by independently evaluating clinical features of the 11 hand joints and assigns scores based on the presence and severity of features such as joint space narrowing, deformity, and osteophytes (10).

Despite the high prevalence of HOA, available treatments are limited to halt the progression on joint destruction and symptomatic relief (17, 18), given the poorly understood pathogenesis (19) and the absence of disease-modifying therapy for HOA (20). While a placebo-controlled trial demonstrated that denosumab reduced radiographic progression and prevented new erosive joints (21), early diagnosis and treatment, particularly for the erosive subtype, are still crucial to mitigate the disease progression (22). However, proactive clinical management faces challenges due to the lack of reliable biomarkers for disease progression as well as for the erosive subtype of HOA (review in Bean *et al*. ref. 17). Meanwhile, the limited availability of comprehensive and longitudinal data has been hindering the identification of potential biomarkers, representing a blind spot in our understanding of erosive HOA.

To better diagnose erosive progression, Ramonda *et al*. evaluated several soluble biomarkers, including CRP, myeloperoxidase, type II collagen-related neoepitope (C2C), and hyaluronic acid, which are correlated with disease activity, such as synovitis. However, none of these markers proved specific to erosions (23). Thus, this study aimed to fill this gap in knowledge and to evaluate the association of radiographic progression according to the Kallman scoring system with routine serum biomarkers and clinical assessment. For this purpose, we analysed these associations in 129 HOA patients, who underwent a series of routine biochemical and clinical examinations over 5 years.

Materials and methods

Patients

Of 154 subjects preselected from the outpatient department at the Institute of Rheumatology (Prague, CZ), 129 patients met the American College of Rheumatology (ACR) classification criteria for HOA (24) and their assessments were conducted at baseline and follow-ups after two and five years (Table I). Patients were consecutively recruited from the outpatient department at the Institute of Rheumatology in Prague between April 2012 and January 2021. Their serum samples were obtained after an overnight fast from each subject at baseline and follow-up visits for laboratory analyses. Among the 129 patients, 57 were diagnosed

with the non-erosive subtype, while 72 exhibited the erosive subtype of HOA. In this study, erosive HOA was defined as the presence of signs of central erosion on radiographs in at least one interphalangeal joint (2, 8).

We did not apply any sampling method to balance the sample size between non-erosive and erosive subtype groups. The exclusion criteria for HOA patients included the presence of rheumatic and autoimmune disorder, cancer or severe chronic infectious disease.

Prior to enrolment, written informed consent was obtained from each patient, and the study received approval from the local ethics committee at the Institute of Rheumatology in Prague, Czech Republic (approval no. 5675/2015). All study procedures were carried out in compliance with the laws and regulations governing the use of human subjects (Declaration of Helsinki) (25).

Kallman scale

The Kallman radiographic scale assesses 24 joints (all, but the metacarpophalangeal joints) for six radiographical features according to a seminumerical scale: osteophytes (0–3), JS narrowing (0–3), subchondral bone sclerosis (0–1), subchondral bone cysts (0–1), lateral bony deviation (>15°; 0–1) and bone erosion (0–1) (26). The score ranges from 0 to 208.

Postero-anterior plain radiographs of both hands were independently scored by two trained readers (J.G., a radiologist, and O.S., a rheumatologist) according to the Kallman score (10). The inter-rater reliability was assessed using weighted Cohen's Kappa for the two raters (27). Given the high level of agreement between the raters, we used the mean scores of their readings for subsequent analyses, which is a standard procedure in the evaluation of the radiographic progression using the Kallman scale (10).

Laboratory assessment

ESR levels were measured on a BD-15™ instrument (BD, New Jersey, USA). The concentrations of serum alkaline phosphatase, beta-carboxy-terminal type I collagen crosslinks (β-CTX), procollagen 1 N-terminal propeptide (P1NP), and osteocalcin were determined using the Beckman Coulter AU 680 (Beckman Coulter, USA), Roche cobas e601 (Roche, Switzerland), and Liaison XL (Diasorin, Italy) analytical systems. The CRP level and serum lipid levels such as total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG), were assessed by the Beckman Coulter AU analyzer (Beckman Coulter, Inc., Brea, CA, USA). The atherogenic index was calculated as the logarithmically transformed ratio of TG over HDL.

Clinical assessment

Qualified rheumatologists conducted clinical examinations, documenting the number of clinically tender and swollen joints. Pain, stiffness, and functional impairment were assessed by the Australian/Canadian (AUSCAN) Hand Osteoarthritis Index (28). Hand disability was quantified based on the algofunctional index (12). The visual analogue scale for pain (VAS-pain) and the health assessment questionnaire (HAQ) were used to evaluate pain and function/disability (29).

Data analysis

Serum biomarkers and clinical assessment parameters were subjected to exploratory data analyses (Table I). Parameters with the normal distribution are presented as the mean with standard deviation, and the association was assessed by a t-test. Parameters deviated distribution are presented as the median with interquartile range, and the associations were evaluated by Mann-Whitney U-test. The gender and erosive subtype were assessed by the χ^2 test. We employed Kendall rank correlation to estimate the correlation or dependency between Kallman scale and clinical features or biomarkers. The effect of statins on the presence of erosive disease was evaluated using logistic regression.

We employed generalised additive models (GAM) (30), chosen based on the Akaike information criterion (AIC) and distribution of residuals in the model, which outperformed (generalised) linear mixed-effect models. GAM is an extension of the generalised linear model, allowing one or more predictors to be specified using a smooth function. As a non-parametric model, GAM provides flexibility for modelling non-linear relationships without specifying the non-linear functional form. Given its flexibility compared to traditional parametric modelling tools, GAM is optimised for non-parametric regression (31). Additionally, GAM included the random effect (patients). In our study, we adjusted GAM for gender, age, and erosive subtype to explore the shape of the association of the Kallman score with serum biomarkers and clinical assessment parameters in this longitudinal study. The associations derived from GAM were plotted with 95% confidence intervals. All analyses were performed using R version 4.1. (32) and its extended packages (33, 34).

Results

Patients' characteristics

The demographic and clinical characteristics of evaluated patients are summarised in Table I. Our study included 129 subjects who underwent all specified examinations of this five-year study. Among these patients, 72 were initially diagnosed with the erosive subtype, while 57 presented with the non-erosive subtype at baseline. The medians of HOA duration at baseline were comparable between patients with the erosive and non-erosive forms: 11.0 years (IQR: 6.0–15.0) and 8.0 years (IQR: 2.0–13.0), respectively (p=0.06). At baseline, although patients with erosive HOA were older than those with non-erosive (t=1.615, p=0.109), this difference was not statistically significant. However, three patients initially diagnosed with non-erosive HOA progressed into the erosive subtype after two years, which caused minor differences in the age at the follow-ups after two (t=2.366, p=0.020) and five years (t=2.376, p=0.019). The majority of our cohort included female subjects (χ^2=77.52, p<0.001; 89%), reflecting the gender distribution in the general HOA population, but the test of gender proportion did not indicate any significant difference between groups at baseline (χ^2=0.032, p=0.858) and after two

Table I. Demographic and clinical characteristics. Demographic and clinical characteristics of patients with erosive and non-erosive hand osteoarthritis (HOA). Unless stated otherwise, data are presented as median (IQR) or mean (SD). *p*-values below 0.05 are highlighted in bold.

		Baseline			2 years			5 years		
Characteristics	Parameter	Erosive HOA	Non-erosive HOA	*p*-value	Erosive HOA	Non-erosive HOA	*p*-value	Erosive HOA	Non-erosive HOA	*p*-value
Kallman score	Median (IQR)	55.2 (42.9 - 76.6)	19.0 (8.0 - 27.0)	**<0.001**	61.5 (43.2 - 79.0)	19.5 (8.0 - 27.4)	**<0.001**	63.5 (44.8 - 83.5)	22.0 (9.2 - 29.2)	**<0.001**
Age [years]	Mean (SD)	66.2 (8.0)	63.9 (7.7)	0.11	68.6 (8.3)	65.3 (7.1)	**0.023**	71.5 (8.3)	68.3 (7.1)	**0.022**
Gender	Female (%)	65 (90.3)	50 (87.7)	0.858	68 (90.7)	47 (87.0)	0.714	68 (90.7)	47 (87.0)	0.714
BMI [kg/m^2]	Mean (SD)	28.0 (4.3)	26.9 (3.6)	0.124	28.0 (4.8)	27.0 (4.4)	0.234	27.8 (4.5)	27.5 (4.6)	0.709
Smoking	Non-smoker n (%) Smoker n (%) Former smoker n (%)	24 (33.3) 1 (1.4) 47 (65.3)	22 (38.6) 4 (7.0) 31 (54.4)	0.176	25 (33.3) 1 (1.3) 49 (65.3)	22 (40.7) 4 (7.4) 28 (51.9)	0.11	24 (32.4) 1 (1.4) 49 (66.2)	22 (40.7) 4 (7.4) 28 (51.9)	0.1
CRP [mg/L]	Median (IQR)	1.9 (0.9 - 3.1)	1.6 (1.0 - 3.6)	0.833	1.9 (1.1 - 3.1)	1.5 (1.0 - 2.8)	0.347	1.9 (1.1 - 3.1)	1.6 (0.9 - 3.1)	0.434
ESR [mm/hour]	Median (IQR)	10.0 (6.0 - 16.0)	10.0 (6.0 - 15.0)	0.921	10.0 (7.0 - 16.0)	8.5 (6.0 - 14.0)	0.355	10.0 (6.0 - 16.0)	8.0 (6.0 - 12.5)	0.122
Total cholesterol [mmol/L]	Median (IQR)	6.0 (5.3 - 6.7)	5.9 (5.3 - 6.5)	0.427	5.6 (5.0 - 6.4)	5.6 (5.0 - 6.3)	0.735	5.7 (4.8 - 6.1)	5.6 (4.8 - 6.3)	0.819
Triglycerides [mmol/L]	Median (IQR)	1.3 (1.0 - 1.9)	1.4 (1.0 - 1.8)	0.824	1.3 (1.1 - 1.7)	1.3 (1.0 - 1.8)	0.664	1.3 (1.0 - 1.6)	1.4 (1.0 - 1.8)	0.518
HDL-c [mmol/L]	Mean (SD)	1.7 (0.5)	1.7 (0.5)	0.832	1.7 (0.4)	1.6 (0.4)	0.642	1.7 (0.4)	1.7 (0.4)	0.679
LDL-c [mmol/L]	Mean (SD)	3.7 (0.9)	3.7 (1.2)	0.86	3.4 (1.0)	3.4 (1.0)	0.976	3.2 (0.9)	3.2 (1.1)	0.804
Atherogenic index	Median (IQR)	2.6 (2.1 - 3.2)	2.7 (1.9 - 3.5)	0.996	2.5 (2.0 - 3.0)	2.4 (1.8 - 3.2)	0.924	2.4 (1.8 - 2.8)	2.0 (1.8 - 2.9)	0.795
Ratio of total to HDL cholesterols	Median (IQR)	3.5 (3.0 - 4.1)	3.7 (3.0 - 4.5)	0.627	3.5 (3.0 - 4.0)	3.4 (2.8 - 4.2)	0.924	3.4 (2.8 - 3.8)	3.0 (2.8 - 3.9)	0.795
Alkaline phosphatase [µkat/L]	Median (IQR)	1.4 (1.1 - 1.6)	1.4 (1.1 - 1.6)	0.42				1.3 (1.1 - 1.5)	1.3 (1.1 - 1.5)	0.642
Vitamin D [nmol/L]	Median (IQR)	54.2 (39.5 - 67.5)	51.4 (38.6 - 68.2)	0.904	65.9 (45.2 - 75.3)	59.7 (49.7 - 75.8)	0.664	61.7 (49.9 - 76.8)	60.1 (46.9 - 70.0)	0.62
β-CTX [µg/L]	Median (IQR)	0.5 (0.3 - 0.6)	0.5 (0.3 - 0.6)	0.604	0.4 (0.3 - 0.6)	0.4 (0.3 - 0.5)	0.726	0.5 (0.3 - 0.6)	0.4 (0.3 - 0.5)	0.435
P1NP [µg/L]	Median (IQR)	48.6 (39.5 - 62.7)	46.4 (35.2 - 57.8)	0.639	44.6 (33.3 - 61.8)	44.2 (39.6 - 54.5)	0.88	47.9 (35.2 - 65.1)	52.3 (39.9 - 60.1)	0.747
Osteocalcin [µg/L]	Median (IQR)	19.7 (14.6 - 23.7)	21.5 (14.9 - 25.6)	0.438	21.9 (19.4 - 25.4)	21.0 (19.1 - 25.9)	0.752	23.1 (19.6 - 27.1)	22.9 (20.1 - 25.9)	0.821
HAQ	Median (IQR)	0.8 (0.2 - 1.1)	0.8 (0.2 - 1.1)	0.597	0.9 (0.4 - 1.4)	0.8 (0.4 - 1.2)	0.41	1.0 (0.6 - 1.5)	0.8 (0.5 - 1.4)	0.248
Algofunctional index	Median (IQR)	18.0 (13.8 - 22.0)	16.0 (14.0 - 20.0)	0.12	18.0 (14.0 - 22.5)	15.0 (13.0 - 20.0)	**0.019**	19.0 (15.0 - 24.0)	17.5 (13.0 - 21.8)	0.055
DAS28-ESR	Mean (SD)	4.0 (1.1)	4.6 (5.5)	0.316	4.1 (1.0)	3.7 (1.2)	**0.029**	4.4 (1.1)	4.0 (2.5)	0.305
AUSCAN total	Median (IQR)	21.5 (15.0 - 29.0)	19.0 (13.0 - 28.0)	0.352	22.0 (15.0 - 29.0)	18.5 (12.0 - 27.0)	**0.04**	24.0 (16.5 - 32.0)	20.5 (11.5 - 28.8)	**0.044**
AUSCAN pain	Median (IQR)	8.0 (5.0 - 11.0)	8.0 (5.0 - 10.0)	0.742	9.0 (5.0 - 12.0)	6.0 (5.0 - 9.0)	**0.02**	9.0 (6.0 - 11.0)	7.5 (5.0 - 10.0)	0.054
AUSCAN stiffness	Median (IQR)	2.0 (1.0 - 2.0)	2.0 (1.0 - 3.0)	0.582	2.0 (1.0 - 2.0)	1.5 (1.0 - 2.0)	0.079	2.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	0.100
AUSCAN function	Median (IQR)	11.0 (7.8 - 16.2)	9.0 (6.0 - 15.0)	0.137	11.0 (7.0 - 16.0)	9.5 (5.2 - 15.0)	0.131	14.0 (9.0 - 18.0)	11.0 (6.0 - 17.0)	0.080
Tender joint count	Median (IQR)	7.5 (3.8 - 11.0)	8.0 (4.0 - 12.0)	0.700	8.0 (3.0 - 12.0)	5.0 (2.0 - 11.0)	0.134	8.0 (4.0 - 13.0)	5.5 (3.2 - 12.0)	0.1850
Swollen joint count	Median (IQR)	1.0 (0.0 - 3.0)	0.0 (0.0 - 2.0)	0.200	2.0 (0.0 - 4.0)	1.0 (0.0 - 2.8)	**0.027**	3.0 (1.0 - 7.0)	0.0 (0.0 - 1.0)	**<0.001**
VAS-pain [mm]	Mean (SD)	44.5 (20.4)	41.6 (20.9)	0.432	49.3 (18.8)	43.3 (20.1)	0.085	49.5 (21.5)	41.7 (18.9)	**0.035**
Diabetes mellitus	Yes n (%)	4 (5.6)	6 (10.5)	0.473	4 (8.5)	0 (0.0)	0.391			
Metabolic disease	Yes n (%)	36 (50.0)	26 (45.6)	0.751	28 (56.0)	7 (29.2)	0.055			
Hypertension	Yes n (%)	37 (51.4)	25 (43.9)	0.501	26 (55.3)	8 (36.4)	0.227			
Chronic kidney disease	Yes n (%)	9 (12.5)	4 (7.0)	0.464	7 (14.9)	3 (13.6)	1.000			

		Baseline			2 years			5 years		
Characteristics	Parameter	Erosive HOA	Non-erosive HOA	*p*-value	Erosive HOA	Non-erosive HOA	*p*-value	Erosive HOA	Non-erosive HOA	*p*-value
Coronary artery disease	Yes n (%)	9 (12.5)	4 (7.0)	0.464	11 (14.7)	4 (7.4)	0.322	11 (14.7)	4 (7.4)	0.322
SYSADOA	Yes n (%)	52 (72.2)	41 (71.9)	1.000	65 (86.7)	43 (79.6)	0.409	64 (87.7)	48 (88.9)	1.000
Dyslipidaemia Treatment	Yes n (%)	22 (30.6)	18 (31.6)	1.000	22 (29.7)	18 (33.3)	0.809	28 (42.4)	20 (42.6)	1.000
Paracetamol (last three months)	No n (%) Occasionally n (%) Daily n (%) Multiple times a day n (%)	54 (75.0) 18 (25.0) 0 (0.0) 0 (0.0)	40 (70.2) 17 (29.8) 0 (0.0) 0 (0.0)	0.680	51 (68.0) 22 (29.3) 1 (1.3) 1 (1.3)	42 (77.8) 11 (20.4) 1 (1.9) 0 (0.0)	0.537	55 (74.3) 15 (20.3) 2 (2.7) 2 (2.7)	46 (85.2) 7 (13.0) 1 (1.9) 0 (0.0)	0.393
NSAIDs (last three months)	No n (%) Occasionally n (%) Daily n (%) Multiple times a day n (%)	31 (43.1) 35 (48.6) 5 (6.9) 1 (1.4)	28 (49.1) 24 (42.1) 5 (8.8) 0 (0.0)	0.687	35 (46.7) 33 (44.0) 5 (6.7) 2 (2.7)	27 (50.0) 25 (46.3) 0 (0.0) 2 (3.7)	0.282	40 (54.1) 29 (39.2) 5 (6.8)	27 (50.0) 27 (50.0) 0 (0.0)	0.101
Other analgesics (last three months)	No n (% Occasionally n (%) Dail n (%) Multiple times a day n (%)	60 (83.3) 9 (12.5) 3 (4.2) 1 (1.3)	51 (89.5) 6 (10.5) 0 (0.0) 0 (0.0)	0.270	63 (84.0) 8 (10.7) 3 (4.0)	48 (88.9) 5 (9.3) 1 (1.9)	0.721	63 (85.1) 11 (14.9)	51 (94.4) 3 (5.6)	0.168)

β-CTX: β-isomerised C-terminal telopeptides; AUSCAN: Australian/Canadian Osteoarthritis Hand Index; DAS28: Disease Activity Scores 28-joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HOA: hand OA; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; NSAIDs: non-steroidal anti-inflammatory drugs; OA: osteoarthritis; P1NP: procollagen 1 intact N-terminal propeptide; SYSADOA: symptomatic slow-acting drugs in osteoarthritis; VAS: visual analogue scale [0-100mm].

and five years (χ^2=0.135, *p*=0.714). Additionally, 13 patients with HOA were diagnosed with osteoporosis, including ten with the erosive subtype and three with the non-erosive subtype. Of these, 11 received bisphosphonates (nine with the erosive and two with the non-erosive subtype). No patients received treatment with denosumab.

At baseline, 87.4% of the patients were taking symptomatic slow-acting drugs for osteoarthritis (SYSADOA) and nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesics on demand. This medication usage remained consistent after two years (92.3%) and five years (93.2%).

Clinical assessment parameters, including hand pain defined by AUSCAN pain (t=0.470, *p*=0.642), hand stiffness defined by AUSCAN stiffness (W=1945.5, *p*=0.582), functional limitation defined by AUSCAN function (t=1.616, *p*=0.114), and the sum of AUSCAN indexes defined by the AUSCAN total (t=1.099, *p*=0.281), showed no significant differences between patients with erosive and non-erosive HOA at baseline. However, significant differences emerged in AUSCAN pain and AUSCAN total after two (t=2.153, *p*=0.036; t= 2.560, *p*=0.014) and five (t=2.143, *p*=0.035; t=2.099, *p*=0.037) years between erosive and non-erosive HOA. Clinically swollen joints were comparable between non-erosive and erosive subtypes at baseline (W= 2307.0, *p*=0.200), but the difference became noticeable after two (W=2472.0, *p*=0.027) and five (W=2947.0, *p*<0.001)

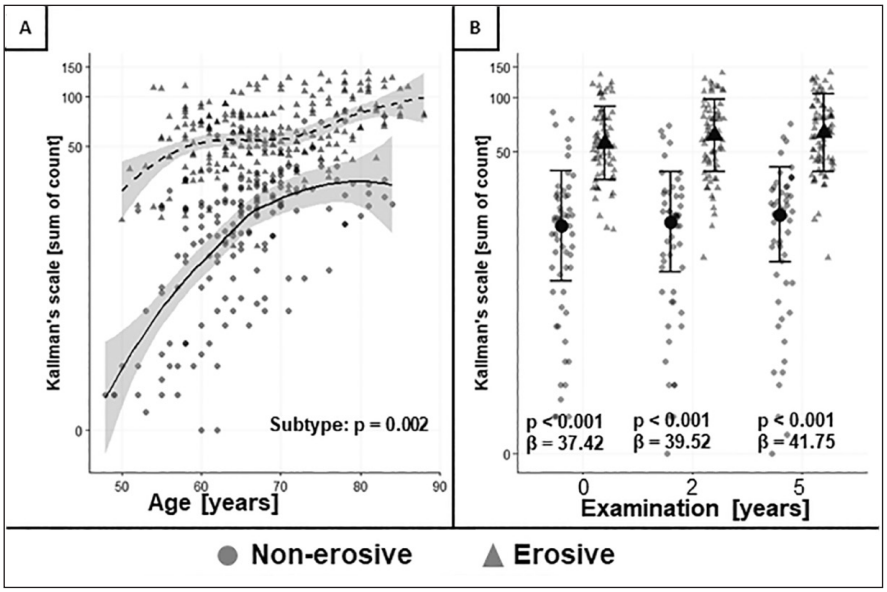

Fig. 1. The correlation between the Kallman score and age (A) and the median of the score at each time point (B). In both figures, each dot represents a patient with erosive (triangles) or non-erosive (circles) hand osteoarthritis (HOA). Figure A includes the trendline for each HOA subtype (erosive: dashed line; non-erosive: solid line) computed using local polynomial regression (LOESS). The P-value (in black) in the bottom-right corner indicates the significant association between Kallman scale and HOA subtypes over 5 years, adjusted for age and gender. In Figure B, the filled circles or triangles represent medians of the Kallman score for each subset at each time point and error bars represent the median absolute deviations. The figure includes the significance (p-value) and estimated difference (β) in Kallman scores between the HOA subtypes at each time point.
Data is detailed in Supplementary Table I.

years. The VAS-pain score was different between subtypes after five years (t=2.176, p=0.035). Algofunctional index and DAS28-ESR were different between subtypes only after two years (t=2.668, p=0.009; t=2.159, p=0.029).

Inter-rater reliability

The inter-rater reliability between the two readers was computed using weighted Cohen's Kappa. To gauge reliability, we preferred to include all subparameters (*e.g.* joint space narrowing, osteophytes, and deformity) measured in each joint of both hands, instead of relying on the overall Kallman score. The observed similarity was 98.77% (kappa = 0.978, p<0.001). However, when we compared the overall Kallman scores between readers, we found a similarity of 57.25% (kappa = 0.916, p<0.001). It is crucial to note that the Kallman score is the sum of six subparameters in 11 hand joints of each hand, meaning that a difference in one subparameter can alter the overall Kallman score. To summarise, both computations revealed high similarity between the readers.

Given the satisfactory agreement between both raters, we employed the average Kallman scores in the follow-up analyses to enhance statistical parsimony.

Kallman score association with erosive disease and age

Initially, we investigated the relationship between the Kallman score and erosive disease in each examination. Our findings revealed significantly increased Kallman scores among patients with erosive HOA compared to non-erosive HOA at all examinations throughout the five years of this study (Supplementary Table S1, Fig. 1). Additionally, we discovered a significant association of age with the scores in all examinations, illustrating a positive correlation between the scores and age in both subtypes. Finally, we demonstrated that the association between the Kallman score and HOA subtypes remained significant even after adjusting for age and gender over five years; therefore, the subtype was included in the statistical model.

Table II. Selected results from the adjusted generalised additive model (GAM) on the assessment of serum biomarkers and clinical assessment parameters and their significant associations (p<0.05 in bold) with the Kallman score in all HOA patients, erosive, and non-erosive HOA subtypes. The table contains effective degrees of freedom (EDF), p-value, and the percentage of deviance explained by the model.

		Patients' group	EDF	p-value	Deviance explained (%)
Serum biomarkers	Atherogenic index	all HOA patients	1	**0.028**	99.28
		erosive patients	1	0.141	99.30
		non-erosive patients	3.1	**0.031**	99.30
	ESR [mm/hour]	all HOA patients	1.9	**0.014**	99.27
		erosive patients	1	**0.017**	99.30
		non-erosive patients	4.3	**0.020**	99.30
	LDL-c [mmol/L]	all HOA patients	2.6	0.300	99.28
		erosive patients	1.9	0.454	99.29
		non-erosive patients	2.9	**0.045**	99.29
	Ratio of total to HDL-c cholesterols	all HOA patients	1	**0.024**	99.28
		erosive patients	1	0.098	99.30
		non-erosive patients	3.4	**0.019**	99.30
	Total cholesterol [mmol/L]	all HOA patients	1	0.193	99.27
		erosive patients	1	0.917	99.27
		non-erosive patients	1	**0.047**	99.27
Clinical parameters	Swollen joint count	all HOA patients	1	**0.041**	99.26
		erosive patients	1.8	0.469	99.29
		non-erosive patients	4	**0.046**	99.29
	Algofunctional index	all HOA patients	1.9	**0.020**	99.29
		erosive patients	2.3	0.090	99.31
		non-erosive patients	2.6	0.080	99.31
	HAQ	all HOA patients	2.5	**0.016**	99.31
		erosive patients	2.5	0.210	99.31
		non-erosive patients	1.7	**0.027**	99.31

EDF: effective degree of freedom; ESR, erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HOA: hand OA; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; OA: osteoarthritis.

Kendall rank correlation analyses

Kendall rank coefficients were computed to explore the potential correlation of the Kallman score with serum biomarkers and clinical assessments parameters. We analysed these correlations for all HOA patients and subsequently for both the erosive and non-erosive subtypes. The results are shown in Supplementary Table S2 and Supplementary Figure S1.

Specifically, we discovered a positive correlation between the Kallman score and the number of clinically swollen joints in all HOA patients across all examinations. Moreover, we observed a difference in the number of swollen joints between the two HOA subtypes. Notably, a positive correlation of the algofunctional index was significant (p<0.05) at two and five years after the initial assessment. Additionally, we found a positive correlation of the Kallman score with the treatment of hyperlipidaemia only in patients with non-erosive HOA. Interestingly, we observed a negative, but statistically not significant, correlation of the Kallman score with several lipid parameters (LDL-c, total cholesterol, atherogenic index, and the ratio of total to HDL cholesterols) in all HOA patients, erosive, and non-erosive patients.

Next, we focused on the erosive subtype of HOA and its correlation with serum biomarkers and clinical assessments (Suppl. Table S2, Suppl. Fig. S1). No correlation was observed between the erosive subtype and the levels of studied biomarkers. A significant association between the erosive subtype and clinical assessments was found in the algofunctional index and the number of clinically swollen joints. We also evaluated the effect of statin treatment on the presence of the erosive subtype, but no significant association was observed (OR=0.9[0.04–19.22], p=0.948).

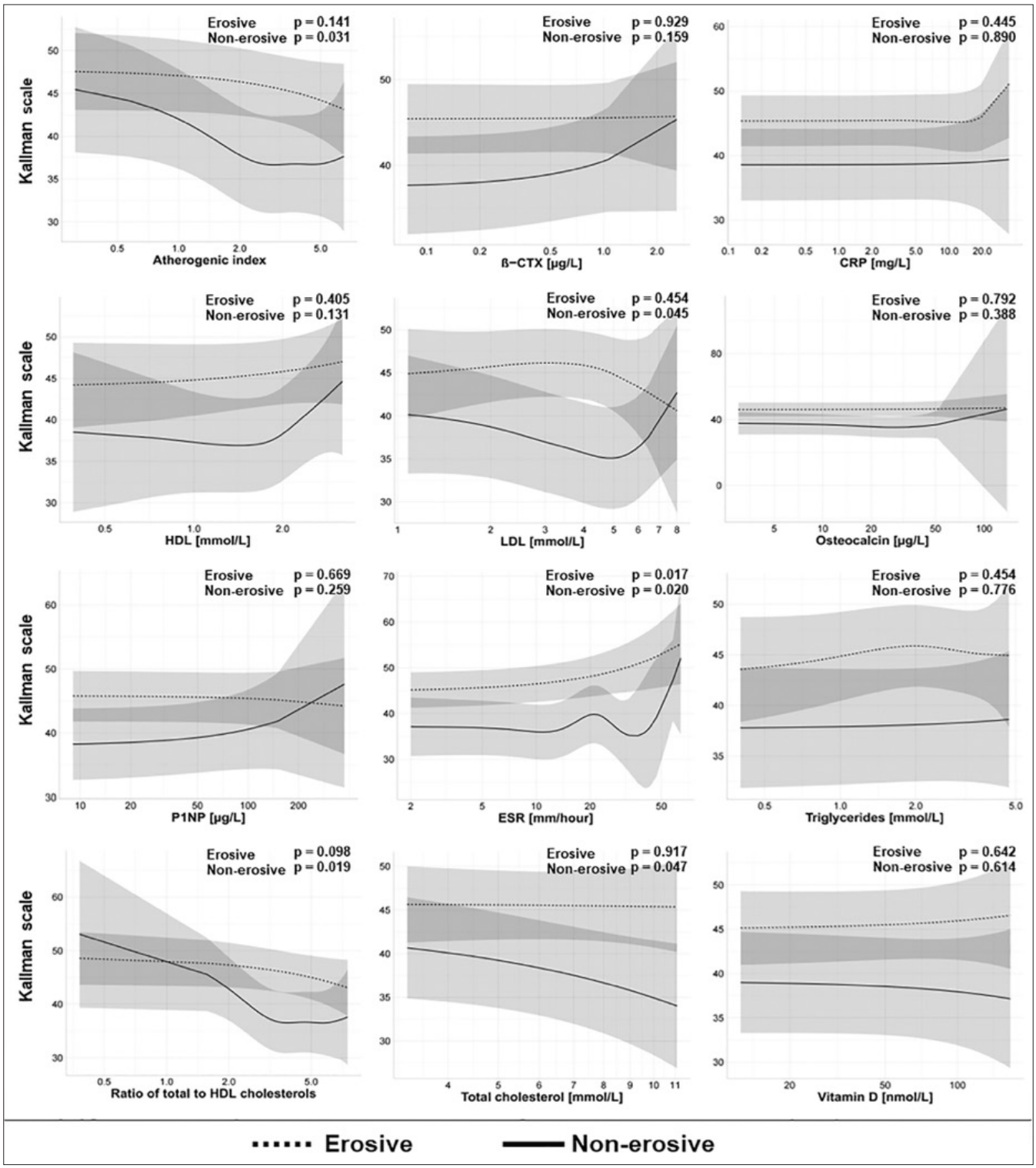

Fig. 2. The shape of associations estimated by the adjusted generalised additive model (GAM) between serum biomarkers and the Kallman score in patients with erosive (dashed line) and non-erosive (solid line) subtypes. Each shape is defined by 95% confidence interval (CI). The horizontal trend line suggests no discernible association between the Kallman scale and serum biomarkers within the subtype; in contrast, an increasingly positive or negative slope implies a growing association. The overlapping signifies no difference between erosive and non-erosive subtypes. *p*-values for both subsets of erosive and non-erosive patients are shown in upper right corners. Data is detailed in Supplementary Table 3A.

Association between the Kallman scale and serum biomarkers

The association of the Kallman scale with clinical characteristics or serum biomarkers was analysed in HOA patients over five years using GAM, which was commonly used in non-linear time-series studies, especially allowing for serial correlations (35). Since the erosive subtype and age revealed a significant association with Kallman score and gender is a known confound-

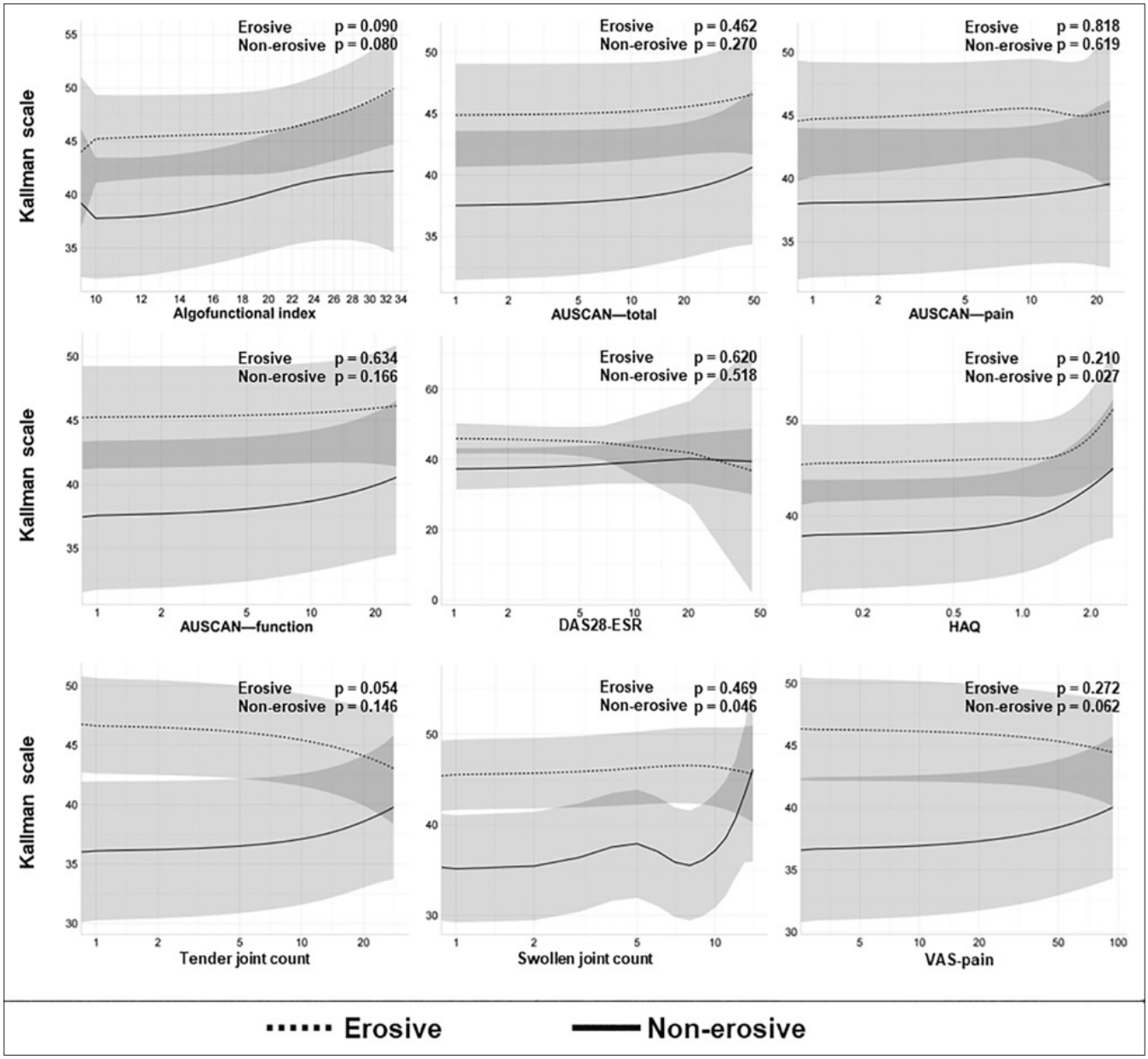

Fig. 3. The shape of associations estimated by the adjusted generalised additive model (GAM) between clinical assessment features and the Kallman score in patients with erosive (dashed line) and non-erosive (solid line) subtypes. Each shape is defined by 95% confidence interval (CI). The horizontal trend line suggests no discernible association between the Kallman scale and clinical assessment features within the subtype; in contrast, an increasingly positive or negative slope implies a growing association. The overlapping ribbons signifies no difference between erosive and non-erosive subtypes. *p*-values for both subsets of erosive and non-erosive patients are shown in upper right corners. Data is detailed in Supplementary Table 3B.

er in HOA disease, we adjusted our GAM analyses for these variables.

The association between the Kallman score and serum biomarkers is presented in Table II and Supplementary Table S3A and is illustrated in Figure 2. An effective degree of freedom (EDF) of 1 in GAM analyses denotes linear association, whereas EDF>1 indicates a non-linear association, and EDF of 0 shows no effect of the covariate on the outcome (31). After adjusting for gender, age, and the erosive subtype, we discovered that ESR was significantly associated with the Kallman score in all HOA patients (EDF=1.9, p=0.014), patients with erosive (EDF=1, p=0.017) and non-erosive (EDF=4.3, p=0.02) HOA. The Kallman score was also associated with the atherogenic index and ratio of total to HDL cholesterol in all HOA patients (EDF=1, p=0.028; EDF=1, p=0.028) and patients of the non-erosive subtype (EDF=3.1, p=0.031; EDF=3.4, p=0.019). In the non-erosive subtype of HOA patients, LDL-c and total cholesterol were also associated with the Kallman score (EDF=2.9, p=0.045; EDF=1, p=0.047). Our models of the association between the Kallman score and biomarkers could explain over 98% of the variance.

The analyses included examining the association between radiographic progression in the hand and bone metabolism biomarkers (*e.g.* osteocalcin, β-CTX, alkaline phosphatase, and P1NP). However, no link was observed between the progression and these biomarkers.

Association between the Kallman score and clinical assessments

To find an association of the Kallman score with selected clinical assessments, we employed GAM and selected assessments with known relevance to HOA.

The association between the Kallman score and clinical assessments is presented in Table II and Supplementary Table S3B and is depicted in Figure 3. After adjusting for gender, age, and erosive subtype, the GAM analysis revealed an association of the Kallman score with HAQ in all patients (EDF=2.5, p=0.016) and in patients with non-erosive HOA (EDF=1.7, p=0.027). The association of the Kallman score was found with the number of clinically swollen joints in all HOA patients (EDF=1, p=0.041) and patients with non-erosive HOA (EDF=4, p=0.046). Algofunctional index (EDF=1.9, p=0.02) was associated with the Kallman score in all patients with HOA. Our models of the association between the Kallman score and relevant clinical assessments could explain over 98% of the variance.

Discussion

In this longitudinal study spanning five years, we examined the relationship between radiographic progression in HOA and various clinical and serum biomarkers. Our cohort included 57 patients diagnosed with the non-erosive form of HOA, of which only three patients progressed to the erosive form. This finding underscores that HOA is a slow-progressing disorder[2]. Our follow-up analysis utilised GAM, providing robust trend estimation and statistical inference over time. We demonstrated significant associations between HOA radiographic progression and factors such as dyslipidaemia, systemic as well as local inflammation, and algofunctional impairment. There is a substantial number of experimental and epidemiological evidence that dyslipidaemia may contribute to the radiographic progression of OA, particularly of HOA (36). It has been suggested that lipid deposition in the cartilage might trigger the onset and exacerbation of OA (37), likely mediated by dysregulated lipid metabolism (38) and low-grade inflammation (39). Additionally, differences in lipid profile partially accounted for varying degrees of HOA severity in a two-year prospective study (40). While prior experimental and epidemiological research suggested a role for lipid metabolism in OA progression, particularly of HOA (36), our study introduces another perspective. We found an unexpected negative trend of total cholesterol and LDL-c levels with radiographic progression in non-erosive HOA, both at baseline and during follow-ups over a five-year period. In contrast, patients with the erosive subtype of HOA demonstrated a positive trend between the Kallman score and total to HDL cholesterol ratio, as well as the atherogenic index, beginning at two years and continuing onwards. We are currently unable to fully explain the observed negative significant associations between radiographic progression and both LDL-c and total cholesterol levels in patients with non-erosive HOA, but similar findings have been reported in large Swedish and British cohorts, where elevated LDL-c levels were causally associated with a lower risk of OA (36). The authors speculated on the effect of cholesterol-lowering drugs, such as statins. However, previous observational studies have provided conflicting results regarding the impact of statins on OA outcomes (41), including one study by Burkard *et al*. which found no association between statin use and HOA (42). Our findings observe no link between statin treatment and the erosive subtype of HOA.

Of note, several studies have indicated the positive association of OA with BMI, which is closely related to lipid profile, as a risk factor for OA progression (43, 44), particularly in weight-bearing joints such as the knee (45). However, more recent research and our findings suggest that BMI is involved in the development of the knee and hip OA, but do not support the same conclusion for HOA (39, 46).

The onset and radiographic progression of erosive OA have been previously associated with chondrocyte apoptosis and extracellular matrix degradation. These mechanisms may be influenced by the inhibition of autophagy mediated through vitamin D levels and the AMPK/mTOR signalling pathway, leading to low-grade inflammation (7, 47). Therefore, markers of systemic immune mediators have been investigated as non-invasive biomarkers correlating with disease activity (48) or as potential therapeutic targets. For example, tumour necrosis factor (TNF) inhibitors have been shown to reduce the number of swollen joints and levels of inflammatory markers such as CRP, but they have not consistently improved outcomes in terms of pain, stiffness, and function (49). Indeed, the degree of inflammatory response does not always correspond to the severity of clinical symptoms in OA (50). Although our results revealed no association between CRP levels and the Kallman score, we observed an association between the Kallman score and ESR in all HOA patients, including both the erosive and non-erosive HOA subtypes. These findings underscore the complex and often contentious role of inflammation in the pathogenesis of erosive HOA and highlight the need for further research.

While radiography and grading systems are the gold standards for objective assessment of HOA, they do not always correlate with the severity of HOA symptoms (51, 52). Therefore, we also included patient-reported outcomes and findings from physical examination, particularly regarding pain and function, in our analysis. We observed positive associations of the Kallman score with HAQ and the number of clinically swollen joints in the non-erosive subset as well as across all HOA patients. In contrast, Perrotta *et al*. (22) found no correlation between clinical findings and the Kallman score, and their analyses did not differentiate between the erosive and non-erosive subtypes. Furthermore, we found significant associations between the Kallman score and the algofunctional index in all HOA patients, consistent with previous reports linking the algofunctional index and KL scores of HOA (53). However, the reliability of the algofunctional index, which is based on subjective evaluation, in distinguishing between both subsets remains questionable due to

conflicting results in prior studies (39, 53, 54).

Although biomarkers of bone metabolism have previously been associated with the assessment of bone resorption and degradation (reviewed in Lennerova *et al*.) (55), our results do not indicate any connection between these biomarkers and radiographic progression. This lack of correlation may be attributed to the fact that hand osteoarthritis primarily affects small joints, whereas other large joints such as the knee or hip may influence more the levels of these biomarkers.

The main strength of our study lies in its extensive five-year follow-up period. Moreover, we incorporated multiple assessment modalities for HOA, including serum biomarkers and patient-reported outcomes, to obtain more comprehensive insights into the contributing factors. However, several limitations of this study must be acknowledged. First, the relatively small size of our cohort could have limited the statistical power of our analyses and made it challenging to account for all confounding factors. Moreover, the erosive subtype was determined by the KL and Kallman scoring systems; other scoring systems might categorise patients differently (56, 57). Furthermore, although concomitant OA at other sites might influence serum biomarker levels and patient-reported outcomes, we did not adjust for other types of OA, as the prevalence of hip and knee OA was consistent across both erosive and non-erosive subtypes in this cohort. For ethical reasons, we did not perform additional radiographs, *e.g*. spine. Given the descriptive nature of this study, we cannot draw causal conclusions. It is therefore crucial to validate these findings and thoroughly evaluate the risk factors associated with the radiographic progression of HOA, especially of the erosive subtype.

Conclusion

Our study demonstrates that erosive HOA is associated with higher Kallman scores, indicating more severe radiographic progression, which worsens with age across both erosive and non-erosive subtypes of HOA. Although we did not identify any reliable biomarkers for radiographic progression in HOA, the Kallman score showed a surprising negative association with LDL-c and total cholesterol in the non-erosive subtype. Additionally, the Kallman score was positively associated with the number of clinically swollen joints as well as with the algofunctional index and HAQ, highlighting its relevance to patient-reported outcomes. Due to the small sample size, further research in larger cohorts is needed to validate our findings and enhance understanding of HOA progression.

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