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1 2 3	Topographical analysis of structural lesions between dominant and non-dominant hands in erosive osteoarthritis
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22	Clinical trial: NCT01068405
23	Keywords: erosive hand, osteoarthritis, topography, conventional radiography,
24	Key messages:
25	- No difference between both hands was observed for clinical and radiographical
26	presentations in EHOA patients.
27	- A bilateral and symmetrical relationship was found between hand joints.

28 Highlights:

• EHOA have symmetrical distribution and specific association in structural lesions.

30

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42 **Running title**

- 43 Topographical analysis of radiological structural lesions between dominant and non-dominant
- 44 hands in erosive osteoarthritis

45

- 47 Abstract
- 48

49 Objective: This study aims to analyse the preferential topographical distribution of clinical and
 50 structural lesions between the dominant and non-dominant hands in erosive hand osteoarthritis
 51 (EHOA) patients.

52

53 **Methods:** Both hands were assessed via radiography in EHOA patients. A comparative analysis 54 of the clinical features and structural lesions between the dominant and non-dominant hands 55 was performed. The structural lesions were assessed according to the anatomical radiographic 56 score of Verbruggen-Veys (VV). Next, a principal component analysis was performed to 57 describe and highlight the relationships observed between the joints.

Results: Sixty patients were included in this study: there were 57 women, and the mean age was 66.1 (±7.6) years. For the distal interphalangeal (DIP) joints, nodes were observed more frequently on the dominant hand (4 vs 3; p=0.005). No difference in structural lesions was observed between the two hands except for the 2nd proximal interphalangeal (PIP) (p=0.045). A principal component analysis with varimax rotation described relationships between the 2nd PIP, 3rd PIP, 4th PIP, 4th DIP and 5th DIP joints in both hands.

65 **Conclusion**: No significant differences between dominant and non-dominant hands were 66 observed for clinical and structural lesions in our sample of EHOA patients. A bilateral and 67 symmetrical injury was observed in most EHOA joints.

68 Introduction

Erosive hand osteoarthritis (EHOA) has a functional impact similar to rheumatoid arthritis.[1, 2] This chronic disease mainly affects older women, presents inflammatory flareups and evolves faster than non-erosive hand osteoarthritis (HOA).[3] The formal diagnosis of EHOA is based upon specific clinical and radiographic patterns. In practice, conventional radiography (CR) is the most relevant method used to evaluate structural lesions. [3]

74

In HOA, the topography of structural lesions between dominant and non-dominant hands is still debated. Some studies have found that HOA preferentially affects the dominant hand and DIP joints and assumes a mechanical origin, [4, 5] while others suggest that there are no radiographic or clinical differences between the dominant and non-dominant hands.[6] In particular, recent studies have shown a predisposition to bilateral involvement in EHOA.[7, 8] In fact, the pathophysiology of EHOA needs to be clarified .

81

If the mechanical hypothesis is commonly accepted for HOA, recent results also suggest a systemic component: structural lesions do not seem to be predominantly distributed in the dominant hand and the two hands may evolve in association.[7–9].For a systemic component, a specific topographical distribution can be observed: structural lesions are depicted on the same rank and/or on the same row for the dominant hand compared with the non-dominant hand.

87

This study aims to characterize the topographical distribution of clinical and structural lesions between the dominant and non-dominant hand in EHOA patients. The aim of this study is to evaluate two topographical distribution hypotheses. Hypothesis 1: joints affected by mechanical stress present more structural lesions compared with the non-dominant hand. Hypothesis 2: joints affected by a systemic component presented symmetrical involvement between dominant and non-dominant hands.

95 **METHODS**

This is an observational ancillary study which involved patients with symptomatic EHOA. The principal, monocentric randomized, double-blind, placebo-controlled study (NCT1968405) examined the effect of methotrexate on pain and structural progression in symptomatic EHOA.

100

101 Patients

Patients with EHOA were included in the ADEM cohort by the Department of Rheumatology of Nice (France). The inclusion criteria were as follows: patients 45-85 years old, suffering from EHOA in the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints for more than three months, according to the American College of Rheumatology (ACR) criteria for HOA. To be included in this study, patients had to present with at least one eroded joint from the PIP or DIP joints according to bilateral hand CR.

108

109 Demographic and clinical data

110 The patients underwent a specific physical examination of the hands for PIPs, DIPs, and 111 metacarpophalangeal joints (MCPs), for a total of 28 joints. The number of swollen nodes and 112 tender joints were counted (absent or present), and the visual analogue scale (VAS) was used 113 to score hand pain (0-100 mm); the VAS was implemented for physician global disease activity 114 and patient global disease activity. VAS was assessed in the last 48 hours preceding the 115 consultation. All patients were asked to fill out two questionnaires to measure the functional ability of the hand: the Functional Index for Hand Osteoarthritis (FIHOA) and the Cochin Hand 116 117 Functional Scale.

118

119 Conventional radiography

Hand X-rays were performed for all patients at baseline and 12-month follow-up. Blind
evaluation of the radiographs was performed by a senior and junior independent reader (SF and

122 RW). A comparison of the two readings was performed on erosive joints (VV scoring system).

123 The concordance between evaluators was 82%. Only the senior reading (RW) was considered

124 for the analysis. The anatomical VV score was determined for both hands.

126 Statistical analysis

- 127 Both descriptive and comparative analyses were conducted according to the nature and
- 128 distribution of the variables (normality assessed by Shapiro-Wilk test). Qualitative variables
- 129 are described as frequencies and percentages; quantitative variables are reported as the mean \pm
- 130 standard deviation (SD) or as the median with 25th and 75th percentiles.
- 131 The Wilcoxon signed-rank test was used for the analysis of clinical features and structural
- 132 lesions between the dominant and non-dominant hand (paired data).
- 133 To observe proximities between the structural lesions, we used a principal component analysis
- 134 (PCA). This analysis describes joints groups with the same characteristics (structural lesion135 stage).
- 136 To identify hand joints affected by mechanical stress (more structural lesions on dominant
- 137 hand); or joints affected by a systemic component (symmetric structural lesions were associated
- 138 between dominant and non-dominant hands) a PCA was performed.
- 139 A PCA with varimax rotation was performed to structure the results of all the relationships
- 140 between the radiographic structural lesions. Only the preferential projections (value of the
- 141 projection > 0.50) were retained on each of the first components, and the related variables were
- 142 then identified by component.
- 143 The p values <0.05 were considered statistically significant. We used IBM [™] SPSS Statistics
- 144 Software v23 for data analysis.
- 145

146 **Ethical considerations**

147

148 This study is registered with the Information Technology and Freedoms Commission for the

- 149 University Hospital of Nice (09-029 at 18/01/2010) and was designed in accordance with the
- 150 general ethical principles outlined in the Declaration of Helsinki. All patients gave their
- 151 informed consent for the use of their medical data during the time when they received medical
- 152 care at the University Hospital of Nice.

153 **RESULTS**

154

155 Demographic data and clinical characteristics

156 Among the 64 patients included in this cohort, 60 patients were involved in the systematic 157 examination of the hands by CR and were selected for this study according to the inclusion

- 158 criteria. The sample mostly comprised women (n=57), the mean age was 66.1 (+/-7.6) years,
- and most suffered from severe pain and dysfunction (table 1).
- 160

161 Clinical characteristics of the interphalangeal joints

The most painful joints were the DIP joints. They were more swollen and demonstrated more nodes than the PIP joints. Regarding pain and swelling, no significant difference was observed between the PIP and DIP joints in the dominant and contralateral hand. A significant difference was only found in the number of nodes in the DIP joints (p = 0.005), where the dominant hand

- 166 showed more lesions than the non-dominant hand (table 2).
- 167

168 Interphalangeal structural lesions in EHOA

According to the CR results, we observed more structural lesions in DIP than in PIP joints. Normal DIP and PIP joints were observed in 18.5% of the cases. No difference in the distribution of structural lesions was found between the dominant and non-dominant hands except for the 2nd PIP joint (p=0.045). On the 2nd PIP joint, the non-dominant hand demonstrated more erosive and remodelled lesions than the dominant hand. The DIP joints were generally more affected than the PIP joints, without a significant difference in terms of prevalence between both hands (table 3).

176

177 Structural lesions: relationship between dominant and non-dominant hands

178 For the principal component analysis, VV was used to score the joint stage. Eight components

- 179 were necessary to explain 81.7% of the total variation. Concerning the eight components, three
- 180 included symmetric hand joint involvement (1, 2 and 3), and four components (4, 5, 7, and 8)
- 181 included unilateral hand joint involvement

182 For component 6, hands were bilaterally involved with an asymmetric pattern. The joints

projected into at least one axis except for the 2nd DIP and the 5th PIP joints of the non-dominant

hand (table 4).

- 186 Approximately half of the dispersion was explained by the first three components (56.8%)
- 187 corresponding to a symmetric joint involvement. Component 1 was related to the 2nd PIP; the
- 188 3rd PIP and the 4th PIP joints; component 2 was related to the 5th DIP joints and component 3
- 189 to the 4th DIP joints (figure 1).

- 190 **DISCUSSION**
- 191

Our study failed to demonstrate any predominance of clinical and structural lesions in the dominant hand; no independence or preferential relationship of joint lesions was found in either hand. More precisely, there seems to exist a specific association between the two 2nd PIP joints, the two 3rds PIP joints, the two 4ths PIP joints, the two 5ths DIP joints, and the two 4ths DIP joints.

197

In fact, the proximity existing here between the two 2nd PIP joints, the two 3rds PIP joints, the two 4th PIP joints (first component), the two 5th PIP joints (second component) and the two

200 4th PIP joints (third component) represents a substantial contribution to all components,

201 explaining more than half of the dispersion.

Among the clinical features and structural lesions, no difference was found between the two hands, except for the second PIP joint and for Heberden's nodes.

204

In the Framingham Community cohort, the authors observed a female predominance of prevalent and incident EHOA with more structural lesions for DIP than for PIP. [10] Marshall *et al.* included 80 patients with EHOA. [7] The study of Nakamura *et al.* highlighted a difference in the incidence of Heberden's nodes in women with HOA depending on occupation: a 19.2% incidence among cooks and 5.9% among municipal administrative officers. [4]

210 In our work, with a similar cohort including predominantly women and being representative of

EHOA, we found more structural lesions in the DIP joints than in the PIP joints. There was also a predominance of Heberden's nodes on the dominant hand. The lack of difference in pain sensation between the dominant and non-dominant hand described in our study has also been observed in the literature. [6]

215

Egger and colleagues showed that the presence of DIP structural lesions in HOA increased the risk of developing or observing PIP lesions (OR 3.1, [95% CI 1.4-6.8]), another DIP lesion (OR

218 10.0, [95% CI 7.3-13.7]) or symmetric bilateral DIP lesions (OR 38.8 [95% CI 14.5-103.5]).

219 [11] In EHOA, they noticed similar results: greater risk of developing a structural lesion in the

same joint in the opposite hand (OR 6.5, [95% CI 3.0-14.1]) but not in the same row or ray of

the ipsilateral hand. [7] In this study, it has been shown that the EHOA structural lesions rank

222 was the same in HOA for joints assessed as grade 4 according to the Kellgren & Lawrence

scoring system: first DIP2, second DIP3 and third DIP5.

224

The main component analysis of our study allowed us to observe the bilateral and symmetrical proximity between the 3rd, 4th, and 5th joints, which had little mechanical stress compared to the 1st and 2nd joints. The most commonly affected joints (DIP 2-3) were included in the component, but the bilateral joints were not in the same component. We suppose an independent evolution for these joints.

230

231 These results suggest the presence of miscellaneous pathophysiological factors responsible for 232 EHOA in addition to mechanical constraints. First, the female predominance in EHOA may 233 suggest hormonal involvement. The consequences of obesity and, more particularly, adipokines 234 have been reported in EHOA development. [7, 8, 12] Our results also support inflammatory 235 mechanisms, as suggested in the literature. Hussain *et al.* compared inflammatory and structural 236 ultrasound lesions in HOA and rheumatoid arthritis. Unexpectedly, no significant difference 237 between the two pathologies was demonstrated in the prevalence of grade 2 and 3 synovial 238 hypertrophies assessed by B-mode or synovitis assessed by power Doppler modes. [13]

Prospective studies have characterized synovitis at baseline as a major factor of central erosion
involvement during follow-up. [14–16] Biological markers have been studied, with one study
conducted in 2016 on 18 patients with HOA reporting a relationship between interleukin 1

242 levels and structural erosive lesions (r=0.70) as well as loss of function (r=0.73). [17]

243

Finally, a neurogenic component has also been suggested: no ipsilateral hand lesions were found on the injured side following a stroke hemiparesis or poliomyelitis in the framework of HOA. [18] Such a systematization of the distribution of EHOA may involve additional mechanisms to local causes.

248

Our study presented some limitations, including the small sample size (n=60) and the lack of data on professional and leisure activities. The lack of power explains the large inertia of the results in the main component analysis (8 components). Furthermore, this cross-sectional study did not confirm the robustness of this topography over time. In addition, since structural lesions reflect prolonged impairment, they are not informative about either the early mechanisms responsible for these lesions or about inflammatory lesions (bone marrow lesions, synovitis, tenosynovitis).

257 This study, however, presents an original design, where the first 3 components underline a 258 symmetrical distribution. Despite the small sample size, the completeness of the clinical and 259 CR data of 1080 joints reinforces the relevance of the results. The use of a suitable radiographic 260 score and the realization of double-blind reading of the imaging with very good concordance 261 also reinforces the relevance of our conclusions. To confirm these findings, a longitudinal 262 analysis of structural and inflammatory lesions would be relevant to assess the constancy in 263 time of this topographic pattern, while clarifying the links between these lesions and their 264 mechanisms.

265

In conclusion, there is no significant difference between the two hands regarding clinical and structural lesions. This study observed a symmetrical association of EHOA structural lesions. Systemic mechanisms or central inflammatory mechanisms are strongly suspected. These results raise the hypothesis of a continuum between inflammatory rheumatism and EHOA. Further studies are needed to examine the effects of conventional or biological diseasemodifying antirheumatic drugs in EHOA.

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Tables/figures

Table 1. Baseline demographic and clin	nical characteristics (n=60)
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Women	57 (95.0%)
Age, years	66.1 (7,6)
Body mass index, kg/m2	24.0 (3,8)
Dominant hand (right-handed)	57 (95.0)
Visual analogue scale for pain [0-100] (mm)	64.9 (15.9)
Evaluator's global disease activity (mm)	61.7 (15.5)
Patient global disease activity (mm)	63.5 (14.1)
Joints with pain (DIP, PIP, and MCP joints of both hands [0-28])	10 [7 – 13]
Joints with nodes (DIP, PIP, and MCP joints of both hands [0-28])	8 [6-12.5]
Joints with swelling (DIP, PIP, and MCP joints of the dominant hand [0-28])	4 [2-6]
Cochin Hand Functional Scale [0 - 90]	25 [11.5-43.5]
Functional index for hand osteoarthritis (FIHOA) [0 – 30]	13 [8-17]

Data are presented as n (%) for dichotomous variables, mean (SD) for continuous demographic variables with normal distribution and median $[25^{th} - 75^{th} \text{ percentiles}]$ with non-normal distribution.

	Total (n=120)	Dominant hand (n=60)	Non-dominant hand (n=60)	*P value
DIP with pain	5 (3-6)	2.5(1-4)	2 (1 – 3)	0.172
PIP with pain	4 (2-5)	2(1-3)	2 (1 – 3)	0.961
DIP with node	6 (4-8)	4(2-4)	3 (1.25 - 4)	0.005
PIP with node	2 (0-5)	1(0-3)	1 (0 – 3)	0.547
DIP with swelling	2.5 (1-4)	1 (0 - 2)	1 (0.25-2)	0.141
PIP with swelling	1 (0-2)	0 (0 - 1)	0 (0 - 1)	0.291

Table 2. The clinical features of the interphalangeal joints of the 1st-5th fingers

Data are presented as n (%) for dichotomous variables, mean (SD) for continuous demographic variables with normal distribution and median $[25^{th} - 75^{th} \text{ percentiles}]$ with non-normal distribution.

* We use the Wilcoxon signed-rank

Table 3. Verbruggen-Veys radiographic scores in the interphalangeal joints of the 1st-5th fingers

	Dominant hand (n=60)					Non-dominant hand (n=60)					*p-value
	Ν	S	J	E	R	Ν	S	J	Е	R	-
2 nd DIP	6 (10)	20 (33.3)	1 (1.7)	19 (31.7)	14 (23.3)	8 (13.3)	14 (23.3)	2 (3.3)	24 (40)	12 (20)	0.682
3 rd DIP	7 (11.7)	16 (26.7)	1 (1.7)	20 (33.3)	16 (26.7)	8 (13.3)	15 (25)	1 (1.7)	22 (36.7)	14 (23.3)	0.773
4 th DIP	8 (13.3)	23 (38.3)	4 (6.7)	19 (31.7)	6 (10)	8 (13.3)	24 (40)	5 (8.3)	19 (31.7)	4 (6.7)	0.498
5 th DIP	7 (11.7)	20 (33.3)	4 (6.7)	21 (35)	8 (13.3)	8 (13.3)	15 (25)	7 (11.7)	25 (41.7)	5 (8.3)	0.890
1 st PIP	8 (13.3)	30 (50)	8 (13.3)	1 (1.7)	13 (21.7)	9 (15)	32 (53.3)	8 (13.3)	2 (3.3)	9 (15)	0.333
2 nd PIP	20 (33.3)	26 (43.3)	1 (1.7)	8 (13.3)	5 (8.3)	16 (26.7)	24 (40)	1 (1.7)	9 (16.7)	10 (16.7)	0.045
3 rd PIP	15 (25)	27 (45)	1 (1.7)	10 (16.7)	7 (11.7)	19 (31.7)	24 (40)	2 (3.3)	8 (13.3)	7 (11.7)	0.567
4 th PIP	16 (26.7)	30 (50)	2 (3.3)	6 (10)	6 (10)	12 (40)	29 (48.3)	4 (6.7)	12 (20)	3 (5)	0.260
5 th PIP	13 (21.7)	28 (46.7)	2 (3.3)	10 (16.7)	7 (11.7)	12 (40)	31 (51.7)	1 (1.7)	7 (11.7)	9 (15)	0.989
Total	100 (18.5)	220 (40.7)	24 (4.4)	114 (21.1)	82 (15.2)	100 (18.5)	208 (38.5)	31 (5.7)	128 (23.7)	73 (13.5)	

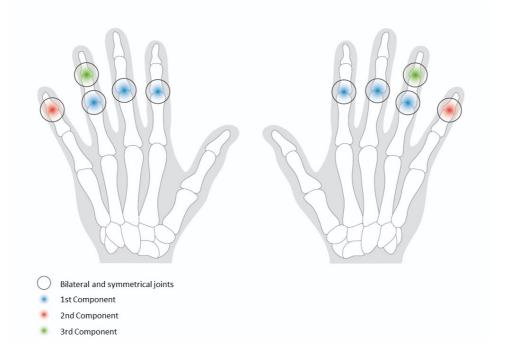
* We use the Wilcoxon signed-rank The number (%) of affected joints is presented For VV score: N –Normal joint; S – Stationary phase, J - Joint space phase, E – Erosive phase R – Remodelling phase

Table 4. Principal component analysis after varimax rotation: Projections of the interphalangeal joints from Verbruggen-Veys radiographic score assessment on the eight retained components (n=60 patients).

	Components							
	1	2	3	4	5	6	7	8
2 nd DIP – Non-dominant hand								
3 rd DIP – Non-dominant hand						0.523		
4 th DIP – Non-dominant hand			0.882					
5 th DIP – Non-dominant hand		0.794						
1 st PIP – Non-dominant hand								0.909
2 nd PIP – Non-dominant hand	0.867							
3 rd PIP – Non-dominant hand	0.808							
4 th PIP – Non-dominant hand	0.753							
5 th PIP – Non-dominant hand								
2 nd DIP – Dominant hand							0.899	
3 rd DIP – Dominant hand					0.892			
4 th DIP – Dominant hand			0.714					
5 th DIP – Dominant hand		0.808						
1 st PIP – Dominant hand						0.905		
2 nd PIP – Dominant hand	0.532							
3 rd PIP – Dominant hand	0.677							
4 th PIP – Dominant hand	0.593							
5 th PIP – Dominant hand				0.822				
Variance (%)	37.2	11.8	7.8	6.3	5.4	5.1	4.5	3.5
Cumulative variance (%)	37.2	49.0	56.8	63.1	68.6	73.7	78.1	81.7

These results illustrate the relationship between variables with the components of the principal component analysis. Only projections with a value greater than 0.50 on a component are presented.

Figure 1. Projections of the interphalangeal joints from Verbruggen-Veys radiographic score assessment on the first three components on the eight retained components (n=60 patients)



Legend: These results illustrate the relationship between variables with the first three components of the principal component analysis after varimax rotation. Only projections with a value greater than 0.50 on a component are presented. We use the same colour by component (blue for first, red for second and green for third). We use circles to identify bilateral and symmetrical joints in the same component.