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RESEARCH ARTICLE

# Is Bony Evidence of Enthesial Reaction Sufficient for Differential Diagnosis?

***Bruce Rothschild****

*Northeast Ohio Medical University, USA*

***Corresponding author:** *Bruce Rothschild, M.D., Northeast Ohio Medical University, Rootstown, Ohio 44272; Carnegie Museum, 4400 Forbes Ave, Pittsburgh, PA-15213, USA, Fax: 724-427-2707, E-mail: spondylair@gmail.com*

## Abstract

**Background:** Enthesial reaction, as a stress or disease marker, has been a generalized perspective, largely untested as to its veracity. Perhaps valid with soft tissue visualization by computerized tomography or magnetic resonance imaging, examination of standard radiographs reveals minimal evidence of enthesial reaction. The current study seeks to assess the disease-specificity of enthesial reaction by examining the primary evidence that of disease-related variation in its presence in defleshed skeletons.

**Methods:** Defleshed skeletons were evaluated macroscopically (in a manner blinded according to disease diagnosis) to assess presence of enthesial reaction. The skeletal sample included individuals diagnosed on the basis of clinical and previously validated non-enthesial reaction-based criteria as having spondyloarthropathy, Calcium pyrophosphate deposition disease (CPPD) and diffuse idiopathic skeletal hyperostosis. These diseases are classically considered predisposed to enthesial reaction. They were contrasted with those which are not (rheumatoid arthritis and healthy individuals). The latter cohort was developed by excluding individuals with diseases that could have an enthesial component (e.g., renal disease, hypertrophic osteoarthropathy). Sixty-six macroscopically examined sites were assessed (ANOVA) individually and also according to established scoring systems.

**Results:** Prevalence of enthesial reaction at individual sites was indistinguishable, with notable exception of posterior iliac spine, ischial tuberosity and lateral elbow largely spared in healthy individuals, greater trochanter was more commonly affected in spondyloarthropathy and CPPD and distal lateral femoral sparing occurred in rheumatoid arthritis. Limited scoring systems performed poorly.

**Conclusion:** Macroscopic bone manifestation of enthesitis has insufficient prevalence variation among diseases to be useful in distinguish among them. Absence of macroscopic evidence of significant enthesial reaction explains the inadequacy of plain radiographs in its recognition. Enthesitis appears to be predominantly a soft tissue phenomenon, analogous to dactylitis.

## Keywords

Enthesitis, Rheumatoid arthritis, Spondyloarthropathy, Calcium pyrophosphate deposition disease, Diffuse idiopathic skeletal hyperostosis, Anatomical study, Standard radiography

## Introduction

Alterations ofen theses (sites of ligament, tendon or capsule insertion) [1-3] have been suggested as markers of activity and pathology. Defined as bone reaction at sites of the insertions of tendons, ligaments and joint capsules [4,5], enthesial reaction has been variously considered to have a mechanical or inflammatory derivation [6-9]. Enthesitis was formerly been referred to as one of the musculoskeletal stress markers in assessment of skeletons from archeological sites because it was perceived as a marker of activity [10-13], although such attribution is controversial [14,15].

Clinical [16,17], ultrasound [17], MRI [18,19] and PET/CT [20] exposure of enthesial alterations have been shown to have documented value in distinguishing among several varieties of arthritis. The sensitivity of x-ray examination seems to be less established [16]. Is this related to the positioning of patients for x-rays, in which the orientation may not be sufficiently tangential to an enthesis to allow reaction to be observed? Is the reaction below the resolution (smaller than that) of x-ray techniques or is enthesitis predominantly a soft

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tissue phenomenon, with bone being altered less often?

Analysis of enthesial reactions has been subjected to a variety of approaches. Mariotti, et al. divided enthesial reaction into “osteophytic” and “osteolytic” [21]. Unfortunately, the former term causes confusion with osteophytes. A better term might be exostotic, although exostosis also has a different implication [4]. Djukic, et al. also suggested use of histologic scores, but this is a very destructive analysis that is not appropriate for reference collections such as the Hamman-Todd [22].

One way of assessing this question is to examine the bones themselves. Therefore, macroscopic examination of defleshed bones was therefore pursued in Ddefined populations with disorders that are generally considered to be enthesial in nature. These include Diffuse idiopathic skeletal hyperostosis (DISH) [4,23], spondyloarthropathy [9,24-26] and calcium pyrophosphate deposition disease [4,9,27-29]. The findings in these conditions were contrasted with that of rheumatoid arthritis [20,30,31] and populations of healthy individuals [6,9,23]. Identifying the latter group required excluding individuals with disorders that also have enthesial components. The latter include hypertrophic osteoarthropathy, renal disease and less well studied syphilis.

Surveys for enthesitis (Table 1) have incorporated as many as 66 enthesis [32] or as few as four [33]. The Mander score incorporates 66 sites, including vertebral spinous processes, counting the number of enthesis affected [34]; the Spondyloarthritis Research Consortium of Canada (SPARCC) score, 18 sites [35,36]; the University of California, San Francisco Index, 17 sites [37]; the Maastricht AS Enthesitis Score (MASES), 13 sites [32]; the Berlin index, 12 sites [38]; the Leeds score, 6 sites [39]; and the IMPACT score, 4 sites [33].

## Materials and Methods

The enthesis listed in Table 1 were examined macroscopically for exophytic reaction. The term macroscopic examination entails physically examining all surfaces of the bones both by direct vision and by palpation for surface irregularities. The surface application of new bone at enthuses was interpreted as enthesial reac-

**Table 1:** Survey summaries utilized in comparison of enthesitis prevalence across population samples [29-32].

| Enthesis/Score*† | San Francisco | MASES | Berlin | SPARCC‡ | Impact | Leed | Major | Mander |
|---|---|---|---|---|---|---|---|---|
| Achilles R&L | + | + | + | + | + | + | + | + |
| Plantar R&L | + | | + | | + | | + | + |
| Lateral knee R&L | | | + | | | | + | + |
| Medial knee R&L | | | + | | | + | + | + |
| Patello-femoral R&L | | | | + | | | | |
| Patello-tibial R&L | | | | + | | | | |
| Medial distal tibia R&L | | | | | | | | |
| Greater trochanter R&L | + | | + | + | | | + | + |
| Ischial tuberosity R&L | + | | | | | | | + |
| Anterior superior iliac spine R&L | | + | | | | | | + |
| Iliac crest R&L | + | + | + | | | | + | + |
| Posterior superior iliac spine | | + | | | | | | + |
| Symphysis pubis | | | | | | | | |
| Lateral elbow R&L | | | | + | | + | | + |
| Medial elbow R&L | | | | + | | | | + |
| Greater tuberosity R&L | | | | + | | | | + |
| Lesser tuberosity R&L | | | | | | | | + |
| Nuchal crest R&L | | | | | | | | + |
| Cervical vertebra #1 | + | | | | | | | + |
| Cervical vertebra #2 | + | | | | | | | + |
| Cervical vertebra #1 or 2 | | | | | | | | |
| Cervical vertebra #3-7 | | | | | | | | + |
| Cervical vertebra #7 or Thoracic vertebra #1 | | | | | | | | |
| Thoracic vertebra #1-12 | | | | | | | | + |
| Thoracic vertebra #12 or Lumbar vertebra #1 | + | | | | | | | |
| Lumbar vertebra #1-5 | | | | | | | | + |
| Lumbar vertebra #5 | | | | | | | | |
| Costochondral #1 R&L | | + | | | | | | + |
| Costochondral #2-6 R&L | | | | | | | | + |
| Costochondral #7 R&L | | + | | | | | | + |

*Vertebra indicates spinous process involvement; ‡Spondyloarthritis Research Consortium of Canada Enthesitis Index.

tion. The skeletons to be examined were selected on the basis of established disease diagnoses [28,31,40] in the Hamann-Todd collection (Cleveland Museum of Natural History). The latter consists of 2906 human skeletons compiled in the early part of the 20th century (1912-1938) after autopsy and defleshing. The healthy individual sample was selected on the basis of order of incorporation (date of death) into the collection, contemporaneous to that of the examined individuals with documented rheumatoid arthritis, spondyloarthropathy, calcium pyrophosphate deposition disease, diffuse idiopathic and skeletal hyperostosis. Given the association of enthesial reaction with renal bone disease (hyperparathyroidism and osteomalacia) [41,42], hypertrophic osteoarthropathy [43], and syphilis [4,14,44], individuals with those diagnoses were excluded from the comparative sample designated as healthy. The health of the individuals studied was not distinguishable from that of contemporary living populations [31,45].

The study samples of individuals with specific diseases of interest were derived from diagnostic cohorts previously validated as to diagnosis and general population representativeness (see Rothschild, 1997, 2005, 2007, 2015; Rothschild and Rothschild, 1996, 1998; Rothschild and Woods, 1990, 1991, 1992a,b; Rothschild, et al., 1990, 1992, 2002 in Rothschild and Martin, 2006). The diagnosis of rheumatoid arthritis was based on the presence of polyarticular, marginally distributed erosions, axial skeleton (atlanto-axial junction excepted) sparing and absent joint fusion [14,31]. A diagnosis of spondyloarthropathy was based on the presence of axial joint disease, joint fusion, or peripheral, predominantly subchondral erosions and reactive new bone formation [14,40]. The diagnosis of calcium pyrophosphate deposition disease diagnosis was based on recognition of a calcified sheet (reflecting onto the articular surface), radiocarpal articular surface indentation, or calcific concretions at the joint surface margins [14,28]. Diagnosis of Diffuse idiopathic skeletal hyperostosis (DISH) was based on ligamentous bridging of at least four contiguous thoracic vertebra in the absence of zygapophyseal joint erosions or fusion [4,46]. Diagnoses of renal disease and syphilis were based on the medical records component of the Hamman-Todd Collection [42,44]. Diagnosis of hypertrophic osteoarthritis was based on classic distal diaphyseal periosteal reaction in individu-

**Table 2:** Prevalence of entheseal reaction as a function of location and health status.

| Enthesis | Side | RA | Sp | CPPD | DISH | Healthy | Enthesis | Side | RA | Sp | CPPD | DISH | Healthy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Achilles | R | 9 | 9 | 10 | 10 | 11 | Vertebra C1* | | 0 | 1 | 1 | 0 | 0 |
| | L | 13 | 9 | 8 | 10 | 9 | C2 | | 0 | 2 | 2 | 0 | 0 |
| Plantar | R | 6 | 11 | 6 | 4 | 5 | C3 | | 0 | 2 | 2 | 0 | 0 |
| | L | 6 | 7 | 5 | 5 | 5 | C4 | | 0 | 2 | 1 | 0 | 0 |
| Lateral knee | R | 2 | 4 | 6 | 5 | 4 | C5 | | 0 | 2 | 2 | 0 | 0 |
| | L | 2 | 4 | 7 | 5 | 3 | C6 | | 0 | 2 | 2 | 0 | 0 |
| Medial knee | R | 4 | 5 | 5 | 5 | 3 | C7 | | 0 | 2 | 2 | 0 | 0 |
| | L | 4 | 5 | 6 | 6 | 4 | Vertebra T1 | | 0 | 2 | 2 | 5 | 1 |
| Patello-femoral | R | | | | | | T2 | | 0 | 2 | 2 | 5 | 1 |
| | L | | | | | | T3 | | 0 | 2 | 2 | 5 | 1 |
| Patello-tibial | R | | | | | | T4 | | 0 | 2 | 2 | 5 | 1 |
| | L | | | | | | T5 | | 0 | 2 | 2 | 5 | 1 |
| Greater trochanter | R | 7 | 8 | 9 | 5 | 4 | T6 | | 0 | 2 | 4 | 5 | 1 |
| | L | 7 | 8 | 9 | 6 | 3 | T7 | | 0 | 2 | 2 | 5 | 1 |
| Ischial tuberosity | R | 6 | 6 | 7 | 6 | 1 | T8 | | 0 | 2 | 2 | 5 | 1 |
| | L | 6 | 6 | 7 | 5 | 1 | T9 | | 0 | 2 | 2 | 5 | 1 |
| Anterior superior iliac spine | R | 0 | 0 | 1 | 0 | 0 | T10 | | 0 | 2 | 2 | 5 | 1 |
| | L | 0 | 0 | 1 | 0 | 0 | T11 | | 1 | 2 | 2 | 5 | 1 |
| Iliac crest | R | 2 | 1 | 3 | 0 | 1 | T12 | | 1 | 2 | 2 | 5 | 1 |
| | L | 2 | 1 | 3 | 0 | 1 | Vertebra L1* | | 0 | 7 | 7 | 4 | 4 |
| Posterior superior iliac spine | R | 5 | 6 | 6 | 6 | 0 | L2 | | 0 | 7 | 7 | 4 | 4 |
| | L | 6 | 6 | 6 | 6 | 0 | L3 | | 0 | 7 | 7 | 4 | 3 |
| Lateral elbow | R | 11 | 9 | 11 | 9 | 5 | L4 | | 1 | 7 | 7 | 4 | 3 |
| | L | 8 | 9 | 11 | 9 | 5 | L5 | | 1 | 7 | 7 | 4 | 3 |
| Medial elbow | R | 8 | 4 | 9 | 3 | 4 | Costochondral 1 | R | 0 | 0 | 0 | 0 | 0 |
| | L | 8 | 6 | 10 | 4 | 4 | | L | 0 | 0 | 1 | 0 | 0 |
| Greater tuberosity | R | 5 | 6 | 7 | 5 | 2 | 5 | R | 2 | 2 | 0 | 3 | 3 |
| | L | 2 | 6 | 7 | 4 | 4 | | L | 4 | 4 | 2 | 4 | 4 |
| Lesser tuberosity | R | | | | | | 6 | R | 1 | 1 | 4 | 1 | 1 |
| | L | | | | | | | L | 1 | 1 | 1 | 1 | 1 |
| Nuchal crest | R | 2 | 1 | 1 | 1 | 0 | 7 | R | 0 | 0 | 1 | 0 | 0 |
| | L | 2 | 1 | 2 | 4 | 4 | | L | 0 | 0 | 0 | 0 | 0 |

*Spinous process.

als with disorders known to cause the disease: pneumonia, tuberculosis, intrathoracic pathology, endocarditis, cirrhosis [4,43].

The necessary sample size for this study, calculated to assure a Beta error of less than 10% revealing the requirement for at least 11 patients in each group. Therefore, skeletons from twenty randomly selected synchronic individuals from each group were examined. The releence of enthesial reaction at individual sites and the indexes in Table 1 was subjected to Chi square, t-test and ANOVA statistics to assess differential occurrence among individuals with rheumatoid arthritis, spondyloarthropathy, calcium pyrophosphate deposition disease, DISH and otherwise healthy individuals without evidence of those diseases or of hypertrophic osteoarthropathy, renal disease or syphilis.

## Results

While males predominated in the current study, age and gender distribution were indistinguishable among the study groups. Enthesial reaction was predominantly localized to the Achilles and plantar tendon insertions into the calcanei, greater femoral trochanter and to the medial and lateral surfaces of the elbow (Table 2). The next most commonly involved sites were the medial and lateral knee regions, ischial tuberosity, posterior superior iliac spine, greater humeral tuberosity and lumbar spinous processes. Prevalence at individual enthesial sites was virtually indistinguishable, with statistical significance noted only with the following subgroups. The posterior iliac spine, ischial tuberosity and lateral elbow insertion sites were less commonly involved in the healthy group (Chi square 11.06, 11.09, and 6.86 respectively, $p < 0.01$). Medial elbow insertion enthesitis was less common (Chi square 7.08, $p < 0.01$) in individuals without inflammatory arthritis (DISH and healthy groups). The greater trochanter was more commonly affected in the spondyloarthropathy and CPPD groups than in healthy individuals (Chi square 4.94, $p < 0.05$ and 7.04, $p < 0.004$, respectively). Plantar insertion involvement was more common in CPPD than in DISH and healthy individuals (Chi square 4.53, $p < 0.04$), medial elbow, in healthy individuals (Chi square 3.96, $p < 0.05$), and lateral knee, and was rare in those with rheumatoid arthritis RA (Chi square 6.76, $p < 0.01$). Evaluation of a further 21 individuals with rheumatoid arthritis confirmed its infrequency.

The only distribution difference of enthesial reaction prevalence between spondyloarthropathy and rheumatoid arthritis was at the spinous process of the third lumbar vertebra and was less prevalent in the latter (Fisher exact test $p = 0.0092$). However, Tukey test correction for multiple comparisons erases the statistical significance, except for sparing of the third lumbar vertebra in rheumatoid arthritis.

The number of involved sites was obviously dependent on the scoring system. However, only the most inclusive scoring system (Mander) demonstrated statistical differences among the groups, and that was only when the rheumatoid and healthy groups were secondarily combined (Table 3).

## Discussion

Macroscopic examination of skeletons provides insights into the dichotomy between the clinical and radiological recognition of enthesitis. If there is no evidence of enthesial reaction on macroscopic examination of potentially afflicted sites, one would not that anticipate x-rays would reveal pathology at those sites. The prevalence of enthesial reaction noted on macroscopic examination of skeletons in the Hamann-Todd collection is indistinguishable from that reported in recent healthy individuals [6,9,23], further documenting its representativeness.

The distribution of macroscopic evidence of enthesial reaction was similar to that noted on clinical examination [47], although with lower prevalence than observed clinically [24,26]. Secundini, et al. noted that only one-third of clinically identified Achilles or plantar insertion tenderness had radiologic evidence of enthesitis [16]. Gladman, et al. reported the average number of enthesial sites in ankylosing spondylitis as four (range 1-21) and in axial psoriatic arthritis (a form of spondyloarthropthy), as 1.8 (range 1-11), confirming the low sensitivity of the plain radiographic approach for enthesitis-based recognition of disease [48]. One concludes that limited enthesitis indexes are of little applicability to radiologic and macroscopic evaluation, and it is unclear if more extensive surveys would be productive.

**Table 3:** Efficacy of the survey approach to distinguishing entheseal reaction disease specificity.

| Status | Age | San Francisco | Mases | Berlin | SPARCC‡ | Impact | Leed | Major | Mander |
|---|---|---|---|---|---|---|---|---|---|
| Rheumatoid | 57.18 | 1.53 | 0.24 | 1.88 | 4.94 | 1.35 | 1.24 | 2.88 | 7.41 |
| Spondyloarthropathy | 58.12 | 1.53 | 0.24 | 1.88 | 4.82 | 1.38 | 1.24 | 3.59 | 11.35 |
| CPPD | 59.38 | 1.57 | 0.48 | 1.96 | 5.43 | 1.29 | 1.48 | 3.57 | 13.00 |
| DISH | 64.25 | 1.50 | 0.13 | 1.75 | 4.19 | 1.38 | 1.25 | 3.06 | 10.31 |
| Healthy* | 61.06 | 1.50 | 0.13 | 1.75 | 3.63 | 1.38 | 1.25 | 2.50 | 5.75 |
| ANOVA | NS† | NS | NS | NS | NS | NS | NS | NS | P = 0.068 |
| RA+healthy vs. others | | | | | | | | | P = 0.038 |

*Absence of disorders in which enthesial reaction is suspected, including hypertrophic osteoarthropathy, renal disease, syphilis; †Not significant; ‡Spondyloarthritis Research Consortium of Canada Enthesitis Index.

## Conclusion

The prevalence of macroscopic skeletal involvement seems significantly less than would be anticipated for some disorders (e.g., DISH), but is similar to that found radiologically. Perhaps enthesitis is similar to dactylitis in that the clinical findings are not matched by what is seen on x-ray [16]. MRI similarly reveals significantly less evidence of enthesitis than clinical examination, finding less than half the sites identified by the latter [47,49]. Intriguingly, enthesial sites were previously noted not to overlap when MRI and clinical localization were compared [50]. The differential diagnostic value of enthesitis thus may be more dependent on soft tissue findings than on actual osseous alterations. An additional consideration is the possibility that there may have once been enthesial reaction at other sites some time during the individual's life but that it had diminished prior to death. D'Agostino and Oliveri [51] suggested that enthesial reaction diminishes over a period of several years.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## Ethical Approval

"All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards".

This article does not contain current patient data and the Hamann-Todd skeletal collection and its study were approved by Case Western Reserve University.

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