

Letter

Biomechanical Factors May Be the Main Contributor to Enteseal Changes in Normal Adults

To the Editor:

We compliment Bakirci, *et al* for their article¹ on the prevalence of ultrasound (US) elementary lesions at mainly lower extremity entheses sites in 80 (50 female, 30 male) healthy adults (20–80+ yrs) and their analyses of contributory factors. We also compliment the accompanying editorial by Hánová, *et al*.² The core set of US enthesitis elementary lesions defined by the Outcomes in Rheumatology (OMERACT) group³ were analyzed in the following categories: (1) inflammation (hypoechoogenicity and/or increased thickening of the tendon insertion, and power Doppler activity); (2) damage (enthesophytes, calcification, and erosions); and (3) total US scores, all within a 2-mm distance of the bone cortex¹. The Bakirci, *et al* article¹ followed a similar US study by Guldberg-Møller, *et al*⁴ of 64 (32 female, 32 male) healthy adults (20–59 yrs) that did not analyze the total US score or its damage and inflammation components. The Bakirci, *et al* article¹ concluded, “These results support the effect of biomechanical forces on the entheses, not necessarily reflecting a pathology leading to any symptoms.” The accompanying editorial by Hánová, *et al*² states, “The innate immune system has been implicated as the main driver of enthesitis...” They² also raised the consideration that the entheses may be “hybridly responding to stimuli in health or to mechano-inflammatory stimuli in various diseases.”




In Figure 1¹, the relation of age (X-axis) to enthesitis scores (Y-axis) is a visual example of a segmental linear regression for inflammation and total US scores with an increase in slope at 50- to 54-year age group. The Bakirci, *et al* article¹ indicated, “The total US scores correlated with age ($r = 0.561$, $P < 0.001$; Figure 1)” and that “Supplementary Table 6 [is] available from the authors on request.” Supplementary Table 6 indicates that age significantly correlated with all US categorical lesions at each entheses site, except for the proximal and distal patellar tendon origin and insertion. Supplementary Table 5 was also requested and showed highly significant differences ($P < 0.001$) in inflammation, damage, and total scores between the younger (20–39 and 40–59 yrs) and older (60+ yrs) age groups. Assuming that a linear regression was used for age in their multivariate regression (Table 2¹), the results are likely to be incorrect for age and other analyzed variables.

To confirm our visual interpretation, 5-year interval datapoints were derived from the magnification of Figure 1¹. Separate linear slopes (95% CI) over 5-year age groups were documented to significantly differ for inflammation in the younger (20–49 yrs; 0.046, 95% CI –0.188 to 0.280) versus older (50–80+ yrs; 1.964, 95% CI 0.910–3.019) groups, as well as total US scores in the younger (0.480, 95% CI –0.012 to 0.972) versus older (3.686; 95% CI 1.953–5.148) age groups. Statistical consultation with an expert in the ADAPTIVEREG procedure for multiple adaptive regression spline (MARS) in SAS could resolve the nonlinear age regression and complex interactions with other variables in Table 2¹.

Our other observation in the Bakirci, *et al* study¹ is the similarity of inflammation and damage scores in the 5-year age groups (Figure 1) and their similar correlations with other variables (Table 2). Visual examination of Figure 1 shows intertwining inflammation and damage scores over the 13 age groups. In Table 2, negative intercepts are specified for inflammation (–13.2), damage (–12.0), and total (–25.3) scores. Such data are impressive for their additive result, but such a large negative intercept (Y-axis) at zero age (X-axis) is not expected¹. The B values in Table 2 for the 5 predictor variables of inflammation, damage, and total scores range from –0.14 to 5.05. The higher B values for sex and physical activity, rather than the usual –1.0 to 1.0 range, may reflect nonlinearity of age and intercorrelation of variables.

The Bakirci, *et al*¹ study raises fundamental questions as to the relative contributions from inflammation vs adaptive (or maladaptive) biomechanical responses to physical stress in causing enthesal changes. Given biomechanical interconnections between multiple adjacent structural tissues, it may be useful to compare pathology in enthesitis to changes in chronic overuse tendon disease/tendinopathy. In tendinopathy—where tendon thickening and localized bone growth are common—biomechanical factors play a significant role in molecular, structural, and functional pathophysiologic contributions and therapy^{5,6,7,8}. Further, while immune cell infiltrate is considered important for early tendon remodeling, impaired homeostasis between anabolic and catabolic cellular repair processes defines chronic tendinopathy pathology in response to repeated mechanical overloading (as opposed to persistent inflammation)⁹.

Similar to the increase in slope at age 50–54 (Figure 1) in the regression of age with inflammatory and total enthesal scores, the survey prevalence of osteoarthritis (OA) rises sharply after age 50 years⁹. While the ability of the joint to compensate to stress is preserved in youth, impaired resilience of aged tissues is a hallmark of OA and is connected to cellular senescence and changes in extracellular matrix mechanical properties⁹.

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REFERENCES

1. Bakirci S, Solmaz D, Stephenson W, Eder L, Roth J, Aydin SZ. Enteseal changes in response to age, body mass index, and physical activity: an ultrasound study in healthy people. *J Rheumatol* 2020;47:968-72.
2. Hánová P, Faith N, Bruyn GA. Enthesitis: myth or reality? *J Rheumatol* 2020;47:945-6.
3. Balint PV, Terslev L, Aegerter P, Bruyn GA, Chary-Valckenaere I, Gandjbakhch F, et al; OMERACT Ultrasound Task Force members. Reliability of a consensus-based ultrasound definition and scoring for enthesitis in spondyloarthritis and psoriatic arthritis: an OMERACT US initiative. *Ann Rheum Dis* 2018;77:1730-5.
4. Guldberg-Møller J, Terslev L, Nielsen SM, König MJ, Torp-Pedersen ST, Torp-Pedersen A, et al. Ultrasound pathology of the entheses in an age and gender stratified sample of healthy adult subjects: a prospective cross-sectional frequency study. *Clin Exp Rheumatol* 2019;37:408-13.
5. Tran PH, Malmgaard-Clausen NM, Puggaard RS, Svensson RB, Nybing JD, Hansen P, et al. Early development of tendinopathy in humans: sequence of pathological changes in structure and tissue turnover signaling. *FASEB J* 2020;34:776-88.
6. Finnamore E, Waugh C, Solomons L, Ryan M, West C, Scott A. Transverse tendon stiffness is reduced in people with Achilles tendinopathy: a cross-sectional study. *PLoS One* 2019;14:e0211863.
7. Coombes BK, Tucker K, Vicenzino B, Vuvan V, Mellor R, Heales L, et al. Achilles and patellar tendinopathy display opposite changes in elastic properties: a shear wave elastography study. *Scand J Med Sci Sports* 2018;28:1201-8.

8. Sancho I, Malliaras P, Barton C, Willy RW, Morrissey D. Biomechanical alterations in individuals with Achilles tendinopathy during running and hopping: a systematic review with meta-analysis. *Gait Posture* 2019;73:189-201.
9. Shane Anderson A, Loeser RF. Why is osteoarthritis an age-related disease? *Best Pract Res Clin Rheumatol* 2010;24:15-26.