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COMMENT & RESPONSE

Platelet-Rich Plasma Injection vs Sham Injection and Tendon Dysfunction in Patients With Chronic Midportion Achilles Tendinopathy

To the Editor The recent study[1] about injection of platelet-rich plasma (PRP) and tendon dysfunction in patients with chronic midportion Achilles tendinopathy confirmed findings of a recent meta-analysis.[2] However, we believe that this article[1] did not confirm or invalidate the effectiveness of PRP, which remains controversial. In addition to the lack of information about the exact composition of PRP used, the use of local anesthesia with lidocaine that may alter PRP effects,[3] and failure to perform ultrasound-guided injection of PRP, this study would have benefited from a precise description of tendinopathy subtypes (ie, nodular, fissuration, calcification, or neovascularization) in addition to knowledge about different medical and rehabilitation treatments undertaken by these patients. Also, therapies that may alter tendon metabolism, such as previous corticosteroid injections or fluoroquinolones, should have been reported.

In addition, the study participants may not have been representative of typical patients undergoing this treatment because they had a mean age of 52 years, had a mean body mass index greater than 30 (calculated as weight in kilograms divided by height in meters squared), had long-term symptoms (24 months), and may have undergone a variety of previous treatments. Indeed, tendinopathies should be first managed with a comprehensive framework for at least 3 months, including education about the condition, load monitoring, and specific exercises aimed at restoration of tendon function, based on knowledge of the different phases of tendon healing.[4] This program should also be performed after PRP injection, including standardized submaximal eccentric-based rehabilitation programs, as described for patellar tendinopathy after PRP injections.[5]

To conclude, we believe there is an urgent need for randomized clinical trials in this field that include precise lesion description, PRP characterization, ultrasound-guided injection, and an adapted concomitant rehabilitation program.

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To the Editor As clinical researchers in the area of orthobiologics, which includes the use of PRP in musculoskeletal conditions, we believe there were numerous methodological errors in the recent article[1] about PRP injection vs sham and tendon dysfunction in patients with chronic midportion Achilles tendinopathy.

The current literature on PRP for tendinopathy and other musculoskeletal conditions is flawed by the lack of appropriate quantification and definition of PRP used in the studies, resulting in conflicting results. These problems date back more than 5 years, with experts urging more appropriate and diligent quantification in publications on the efficacy of PRP.[2] A collaborative symposium published in the *Journal of the American Academy of Orthopedic Surgeons* specifically outlined "minimal reporting standards" for clinical studies evaluating PRP.[3] Unfortunately, the article by Dr Kearney and colleagues[1] contains no description of the PRP product that was injected and used a product called Glo PRP, which is not approved by the US Food and Drug Administration in the

United States. Thus, the authors failed to properly document that a true PRP product was injected and did not appropriately quantify what was injected.

Additional methodological flaws included the failure to use ultrasound guidance, which is currently believed to be standard in these procedures, to definitively place the injectate into the pathologic region of the tendon. Moreover, during the procedure, 5 mL of 2% lidocaine was injected, which is a much larger dose than necessary and can result in exposure of the tendon to lidocaine, which may have negative effects on tenocytes.[4]

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Conflict of Interest Disclosures: Dr Malanga reported being a founder and partner of DataBiologics LLC, a database registry, and past president and board member of the Interventional Orthobiologics Foundation. No other disclosures were reported.

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To the Editor The authors of a recent *JAMA* article[1] concluded that a single injection of intratendinous PRP was not superior to subcutaneous dry-needle insertion. Although this study provided valuable results, we believe some methodological concerns should be considered.

First, standardized ultrasound-guided injection should have been done to improve PRP efficacy. Studies have shown a higher degree of pain with intratendinous vascularity in pathologic tendons.[2] Additionally, the authors should have provided the exact anatomical locations of injections, such as midportion of Achilles tendon, peritendinous tissue, or Karger fat pad, because structural damage may cause different effects on pain and local sensitization.

Second, previous studies have shown that certain patients may have better outcomes after receiving PRP treatment.[3] Thus, it would be very useful if the article[1] provided subgroup analysis on baseline demographics, disease subtypes and severity, disease duration, and functional status. We believe further stratified analysis may identify certain beneficial subpopulations and strengthen clinical application of this study.

Third, as mentioned in the article, other studies have shown positive results with multiple PRP injections for chronic tendinopathy. We hope the authors could discuss possible explanations for these inconsistent results.

Fourth, 77 participants in this study[1] entered the primary analysis after seeking additional treatment, including injections of nonspecific medication, acupuncture, and even surgical interventions. We suggest that both intention-to-treat and per-protocol analyses should be conducted and presented.

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In Reply The entry criteria for our study[1] were broad to reflect real-world practice rather than narrowing to smaller subgroups. To further replicate real-world practice, participants were recruited from general foot and ankle clinics rather than social media and sports medicine clinics. To be referred, patients had generally not improved with noninvasive management (eg, physiotherapy; n = 207), which may account for the long symptom duration, increased age, and increased body mass index of our participants, as noted by Dr Gremeaux and colleagues. Their letter also speculates that prior treatment (eg, injections and fluoroquinolones) could have altered tendon metabolism. However, only 34 of 240 participants had received prior injections; we do not have further information on fluoroquinolone use. We agree with Gremeaux and colleagues that characteristics such as severity, disease duration, and baseline functional status may affect outcome. Our primary analysis model was therefore adjusted for age, sex, laterality, and baseline Victorian Institute of Sport Assessment-Achilles score. Two prespecified subgroup analyses were performed, for laterality and duration of symptoms, because patients with bilateral tendinopathy and those with longer symptom duration may have worse outcomes. However, our secondary analyses confirmed the primary results. Tendinopathy subtypes (eg, calcification) were not reported in our study because of a lack of standardized descriptors to define such

subtypes. After injection, study participants were not referred to physiotherapy for an eccentric loading program, as suggested by Gremeaux and colleagues. There is no consensus about concomitant interventions alongside PRP, and a previous randomized clinical trial about PRP published in *JAMA*[2] was challenged for including physiotherapy because the eccentric loading program may mask the potential effect of PRP.

Dr Malanga and colleagues express concern about the PRP product used in our study. In adherence to reporting standards for the evaluation of biologics, which provide a useful framework,[3] we provided additional description of the PRP product in our article's Supplement 3. The product was confirmed by an independent test laboratory, and there were quality assurance checks to assess adherence to the protocol. The choice of PRP product in our study was based on comparison with other commercially available PRP systems used in previous randomized clinical trials.[4,5] We also appreciate the concern expressed by Malanga and colleagues regarding the possible negative effects of lidocaine. However, our protocol, which reflected usual practice, was to inject this local anesthetic into the cutaneous tissues to reduce discomfort, as opposed to intratendinous injection.

We agree that ultrasound-guided injections are most accurate for tendons situated deep within the body. However, the Achilles tendon is located directly below the skin, and the symptomatic area is easily identified through palpation, so ultrasound localization is not required. Drs Tung and Wei suggest that multiple injections may have different results, which is possible, although unproven. Our protocol reflected real-world practice, in which 1 injection is typically administered and the result is assessed before considering further injections. Although we asked study participants not to undergo any additional treatments during their 6-month follow up, Tung and Wei are correct that 77 participants did seek additional treatment. However, our secondary per-protocol analysis confirmed the result of our primary intention-to-treat analysis.

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Disclaimer: The views expressed are those of the authors and not necessarily those of Versus Arthritis.

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A Review of the Diagnosis and Treatment of Alcohol-Associated Liver Disease

To the Editor In the recent Review of alcohol-associated liver disease,[1] we believe that the pattern of fibrosis in alcohol-associated liver disease was mischaracterized in the legend of the article's Figure 1. Despite a history compatible with alcohol use disorder, periportal and portal fibrosis strongly suggests another etiology of liver disease. In alcohol-associated liver disease, fibrosis begins in zone 3 with fibrous strands surrounding the central vein of the liver lobule with pericellular fibrosis in zone 3 as well.[2] Non–alcohol-associated liver disease in patients with alcohol use disorder is a well-recognized phenomenon.[3] Liver biopsy is unnecessary in most patients with alcohol-associated liver disease, but when performed, it does offer valuable diagnostic clues.

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Conflict of Interest Disclosures: None reported.

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In Reply We do not agree with the claim by Drs Conteh and Levin that the legend in Figure 1 in our recent Review[1] was mischaracterized. We and others have shown that portal fibrosis is frequently observed in patients with alcohol-associated liver disease.[2,3] Furthermore, unlike centrilobular fibrosis, portal fibrosis is highly correlated with fibrosis progression.[1,2] The METAVIR staging system is one of the recommended histological scales to evaluate fibrosis extent in patients with alcohol-associated liver disease.