Ultrasound changes following controlled mechanical stress in synovial tissue in the hands of healthy individuals

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Abstract

Objective: The physiological response of the synovium to acute mechanical stress has not been extensively studied. This response is interesting in terms of the morphological changes it can cause as any such changes should be taken into account during ultrasound examinations. The purpose of this study was to assess the extent of changes in ultrasound images of the synovial joint in the hands of healthy individuals after controlled mechanical stress.

Method: We included 110 healthy volunteers on whom we carried out two ultrasound examinations of the non-dominant hand: one at baseline and the other after controlled handgrip exercise at 70% of the maximum voluntary contraction.

Results: The synovitis scores at baseline and after exercise were 0.472±0.798 and 0.772±1.162 $t(109)=-3.791$, respectively; $p < 0.001$. We observed no tenosynovitis in 88.2% of the participants at baseline, while after exercise the percentage fell to 70.9%; x2 (1, N=110) =10.0851, $p = 0.0014$.

Conclusion: We conclude that synovitis and tenosynovitis are inducible by physical exercise and are detectable on ultrasound. This should be taken into account during ultrasound examinations for suspicion or follow-up of inflammatory rheumatism.

Keywords: Healthy subjects; Ultrasound; Synovitis; Tenosynovitis; Physical activity.

Introduction

Synovial tissue is found in the joint capsule and in tendon sheaths. Its functions include homeostasis of the synovial fluid and maintenance of the range of joint motion and tendon excursion[1,2]. Studies on blood biomarkers suggest that this tissue is capable of responding to mechanical stimuli depending on their intensity and frequency[3]. Locally, it has been demonstrated that the synovium responds to mechanical or inflammatory stimuli by producing synovial fluid, and developing, over time, hyperplasia or hyperaemia[4–7]. Furthermore, synovial tissue is the target of various immune-mediated diseases in which interactions with cell infiltrates and cytokines reproduce these effects[2].

Although it is well recognized that physical activity may be associated with synovial changes on ultrasound, there is a paucity of data on the effect of physical activity on the synovium in terms of ultrasound findings[8]. Given that ultrasound is a widely utilized and useful tool for the diagnosis and follow-up of patients with rheumatologic diseases with musculoskeletal manifestations[9], it is important to identify to what extent any synovial findings could be attributed to physiological changes rather than to the disease itself.

The purpose of this study was to determine the existence and magnitude of ultrasound-detectable synovial changes induced by controlled physical exercise.

METHODS

This was an interventional, single-blinded, analytic study utilizing a before-and-after design. The study population was comprised of healthy volunteers between 18 and 65 years of age, and included individuals who accompanied patients to rheumatology appointments, healthcare staff, university students and the general public, all of whom were invited to participate via posters displayed throughout our hospital. We excluded individuals with a personal or family (first-degree) history of rheumatoid arthritis, psoriatic arthritis, spondyloarthritis or any other connective tissue disease. We also excluded participants who had received corticosteroids during the last 14 days or non-steroidal anti-inflammatory drugs within the last 7 days for any reason. Recruitment was carried out from January to December 2019. The study was specifically approved by the ethics committee of the University Hospital of Getafe. The present study complies with the Declaration of Helsinki.

After candidates had given written informed consent to participate in the study, they were all interviewed to establish their eligibility. For those who met the criteria, measurements were taken of their weight and height, as well as their maximum non-dominant handgrip strength using a CAMRY Digital Hand Dynamometer (EH101). Next, we arranged two appointments for ultrasound examinations of both hands. The first appointment was the baseline measurement and the second occurred the day after the patient completed an exercise workout involving a finger flexion.

The ultrasound examination included scoring synovitis, based on grey scale and power Doppler power (PD) signal assessments, in accordance with the Outcome Measures in Rheumatology (OMERACT) recommendations,[9,10] for the dorsal aspect of the carpal bones, the 2nd, 3rd and 4th metacarpophalangeal (MCP) joints and the 2nd, 3rd and 4th proximal and distal interphalangeal (IP) joints. We also assessed whether there was tenosynovitis[9] in the tendons of these same fingers. Identification of tissue thickening or hypoechogenicity at the tendon insertion point of the deep and superficial flexors of the second to the fourth fingers, less than 2 mm from the cortical bone, together with a PD signal, was regarded as an indication of enthesitis.[11] Finally, peritenon extensor tendon inflammation (also known as paratenonitis) was defined as a hypoechoic (versus a compressible) area surrounding the extensor digitorum tendon.[12–14] Presence of paratenonitis was assessed at the dorsal aspect of the MCP joints.
A synovitis score was obtained by using the OMERACT grading of the grey-scale and PD signals in seven joints of the dominant hand; i.e., the carpal joint, MCPs and proximal IPs joints.

Volunteers were explicitly instructed not to comment on whether the ultrasound scan was performed before or after exercise. All ultrasound examinations were carried out on Friday evenings or Saturday mornings, except on two occasions. The number of ultrasound studies performed during a single scanning shift was never less than 10. Since the sonographer might recognise a given volunteer, he/she performed scans of both hands unaware of the hand dominance of said volunteer. The purpose of these measures was to reduce the bias of knowing whether the ultrasound performed was before or after the exercise.

Ultrasound examinations were carried out by a single specialist (CG) using a TOSHIBA Nemio XG (SSA-580A) ultrasound system equipped with an 8- to 12-MHz linear probe. For the ultrasound examination, volunteers were seated in front of the examiner with their hands resting on a hard surface and a thick layer of gel was used. Anonymised videos of 3-4 seconds were recorded for each examination. Three specialised rheumatologists assessed the videos independently and rated synovitis, tenosynovitis and enthesitis. In the case of synovitis and PD signals, we recorded the lowest score of the three observers. In contrast, for both tenosynovitis and enthesitis, we only considered those scores in which all three observers had provided the same score.

To assess flexor grip strength using the flexion, we calculated the mean of three measurements made with the non-dominant hand. Volunteers took a dynamometer home and were asked to perform specific exercises the day before the second ultrasound examination. The exercise routine consisted of 120 finger curl repetitions, throughout the day, at 70% of the mean maximum strength of the three baseline measurements. After the second ultrasound examination, volunteers were interviewed to determine whether they experienced pain in any of the joints evaluated, using a numerical pain rating scale from 0 to 10.

For the statistical analysis, subjects' baseline characteristics were described using measures of central tendency and dispersion. Before-and-after ultrasound scores were compared using the Wilcoxon signed-rank test for related samples. Kendall's Tau-B coefficients were calculated to assess the significance of the correlations between the gradients of change in the ultrasound findings and anthropometric variables. The statistical analysis was carried out using the IBM SPSS Statistics for Windows statistical package, Version 23.0 (IBM Corp., Armonk, NY).

The data set for present study has been electronically entered into the Synapse™ repository and is available for all subscribers at Synapse Storage (ID syn25955431, DOI 10.7303/syn25955431).

Results

We contacted 114 volunteers, all of whom met the inclusion criteria, although four did not complete the second ultrasound examination. Of the remaining 110 individuals, 58 were women (52.7%). The overall mean age and standard deviation were 40.7± 12.6 years (range 20 to 65 years). The mean body mass index was 25.9± 4.4 kg/m^2. The mean non-dominant handgrip strength with the flexion was 33.13 ± 11.17 kg. Table 1 summarises the anthropometric characteristics of the volunteers by sex.

In the baseline ultrasound examination, 38 individuals (34.5%) were found to have grey-scale synovitis in at least 1 of the 7 joints assessed. The synovitis score was 1 in 28 individuals (25.5%), 2 in 8 (7.3%), 3 in 1 (0.9%) and 5 in 1 other patient (0.9%). No PD signals, tenosynovitis, enthesitis or paratenonitis were found, respectively, in 108 (98.2%), 97 (88.2%), 110 (100%) and 92 (83.6%) of the subjects.

In the second ultrasound scan (after the controlled handgrip exercises), an additional 12 individuals (45.4%) had some degree of grey-scale synovitis. The increase in the percentage of patients with synovitis was not statistically significant; $x2(1, N = 110) = 2.7273$, $p = 0.0986$. At this stage, the synovitis score was 1 in 32 (29.1%) subjects, 2 in 10 (9.1%), 3 in 2 (1.8%), 4 in 3 (2.7%) and 5 in another 3 (2.7%). No PD signals, tenosynovitis, enthesitis or peritonitis were detected, respectively, in 103 (93.6%), 78 (70.9%), 110 (100%) and 92 (83.6%) subjects. The change in the percentage of individuals who had tenosynovitis was statistically significant ($x2$ (1, N=110) = 10.0851, $p = 0.0014$). The mean grey-scale synovitis score rose significantly, from 0.472± 0.798 at baseline to 0.772 ± 1.162 following exercise (p<0.001). Table 2 shows the before-and-after scores for all the domains assessed during the ultrasound examinations. The distribution of ultrasound findings before and after exertion is summarised in Figure 1.

Regarding the categorical ultrasound finding of tenosynovitis, in the before-exercise scan, the ratings were discordant in two cases. Similarly, there were two cases of discordance in the post-exercise scan. All of these cases were considered negative for that attribute. There were no discordances in the other categorical variables.

In the correlation analysis of the gradients of change in the ultrasound findings, as reflected in both the before-and-after scores and anthropometric variables, the only significant correlation detected was between the PD signal score gradient and the grey-scale synovitis score gradient; two-tailed r (110) = 0.526, $p < 0.001$.

Out of the 110 volunteers, 24 (21.8%) recorded a pain rating scale score of at least 4 after the exercise for at least one of the joints assessed. No volunteers received 7/10 or higher scores, and only one rated the level of pain as 6/10. The mean age in this group (pain score ≥ 4) was 49.5 ± 5.6 years, significantly older than that of the remaining volunteers (46.4 ± 6.7 years), t (108) = 2.0718, p = 0.0407. We did not identify any other significant differences when comparing the percentage of women or the maximum grip strength and BMI between those with high pain ratings (≥ 4) and the other volunteers (data not shown).

Discussion

Although the effects of physical activity and inflammation on the synovium are well recognized, changes that are detectable by ultrasound, to our knowledge, this is the first study to demonstrate that such changes are also noticeable after controlled overexertion in healthy volunteers.

Our study has two significant limitations that were considered in its design. Both limitations are directly related to the instrument for measuring the primary outcome variable, namely, ultrasound scans. Specifically, ultrasound is operator dependent. For that reason, our study, like most robust studies, used a panel of experts to assess the images and videos obtained by a single sonographer using a single ultrasound machine. Furthermore, since our original hypothesis stated that exercise results in changes detectable by ultrasound, we arbitrarily assigned each case the lowest synovitis score among those given by the expert panel members. For this same reason, cases were only considered positive for categorical ultrasound changes (tenosynovitis and enthesitis) when all three members agreed.

The second limitation is that the sonographer could have recognized an individual at the second ultrasound scan, and hence be aware that this was a post-exercise scan. Although the ultrasound examination followed the same protocol on both occasions, the sonographer could possibly have made an exerted effort to look for certain findings knowing that this was the second scan.

The number of daily studies and the instruction to volunteers to avoid verbal comments were among those measures taken to minimize this potential bias.

In a study carried out in 2013, Guillen et al.[8] found an association between physical overexertion and ultrasound-detectable synovial changes - mainly joint effusion. In that study, unlike this one, the physical effort was not quantified.

Van Oudenaarde *et al.*[15] studied synovial reactions to knee trauma using magnetic resonance imaging. They found that 41% of patients had joint effusion following injury. Other studies assessing synovial response to mechanical stress in other joints, such as the ankle[16,17], have indicated a relationship between physical activity and some degree of adaptive synovial response. Similar conclusions can be drawn concerning the retrocalcaneal bursa. The immediate synovial response (<24 hours) at the level of the hand has not, however, been reported except in one previous study[8], although those authors did not control for exercise exposure.

Synovial responses to single events producing high-energy mechanical stress (low-frequency, high-intensity) have been documented in studies of patients with knee injuries who exhibited radiological signs of osteoarthritis[18]. On the other hand, synovial responses to high-frequency low-intensity mechanical stress (e.g., daily living activities, regular physical exercise) may involve homogeneous synovial proliferation. In such cases, the extent of synovial fluid overproduction may vary, an idea that has been indirectly supported by ultrasound findings in asymptomatic runners14 and biomechanical changes observed in women who often wear high heels[17,19]. We should note that none of these studies directly focused on the synovial tissue.

Finally, the synovial response to high-frequency moderate-intensity mechanical stress, such as that generated by our model of exercise, is manifested by a significant increase in synovitis scores and even the visualization of hyperaemia at sites where it has not previously been detected. These findings extend beyond the subclinical in a small proportion of individuals who report pain. These subjects tend to be older, which may be related to a stronger synovial response during the early stages of osteoarthritis. Finally, it might be that hyperaemia (PD signal) should be interpreted as a vasodilator effect in response to metabolic demand following exercise in a small proportion of participants, specifically those who were physically fit at the start of the study. The methodological design of our study did not allow us to confirm this suspicion.

Our results have various implications for clinical practice. In particular, given that rheumatologists use ultrasound for the diagnosis and follow-up of patients with immune-mediated diseases involving joint manifestations, we should take into account any physical exercise carried out prior to an ultrasound examination. In addition, we conclude that grade 1 synovitis may be regarded as a physiological phenomenon. Indeed, in some individuals, mild hyperaemia (a grade 1 PD signal) could also be attributed to a physiological process.

Data availability statement

The data set for the present study has been electronically entered into the Synapse™ repository and is available for all subscribers at Synapse Storage (ID syn25955431, DOI 10.7303/syn25955431).

Figures and Tables

Figure 1 - Distribution of ultrasound findings before and after exercise. All numbers are absolute values. Synovitis and power Doppler scoring are not represented. S: Number of any grade of synovitis; PD: Number of any degree of power Doppler signal; T: Number of tenosynovitis detected.

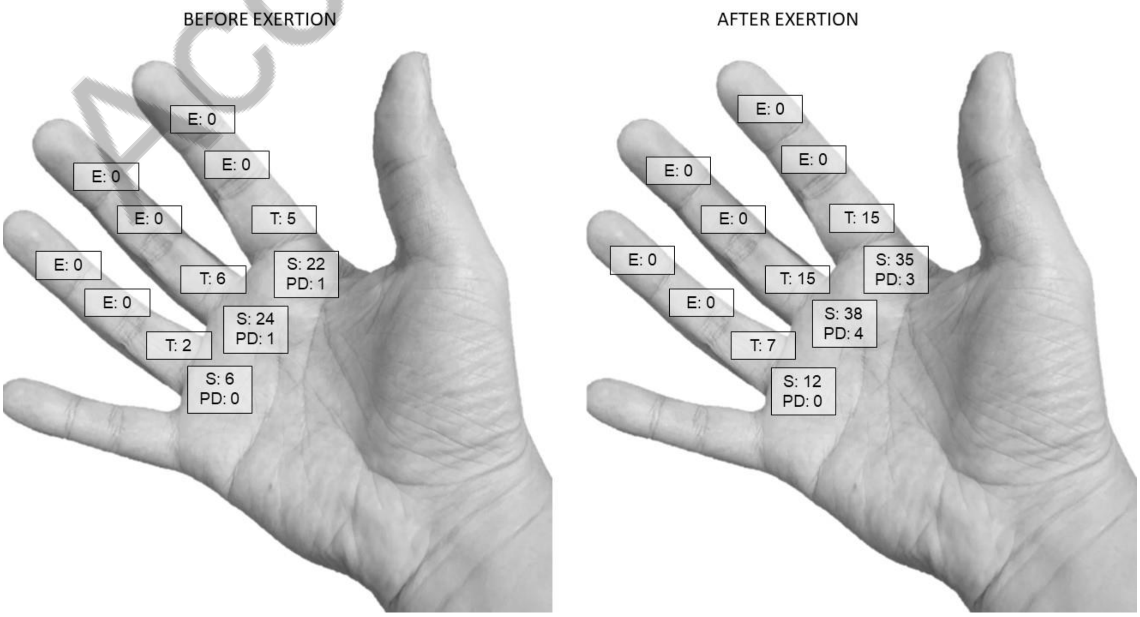

Table I. Characteristics of participants segregated by sex. SD: Standard deviation.

Variable	Women	Men	P value
Age, years ± SD	40.58 ± 12.73	40.82 ± 12.7	0.921
Body mass index, kg/m^2 ± SD	26.12 ± 4.75	25.76 ± 4.18	0.673
Grip strength, kg ± SD	24.41 ± 2.74	42.86 ± 8.68	<0.001

Table II. Results of comparing ultrasound assessments before and after the exercise. In the case of cumulative frequencies for enthesitis and peritenon enlargement, we were unable to estimate T, as the standard error of the difference was 0. PD: Power Doppler; SD: Standard deviation.

Ultrasound assessment	**Before exertion**		**After exertion**		**Wilcoxon signed-rank test, P-value**
	Mean ± SD	Median ± variance	Mean ± SD	Median ± variance	
Synovitis score (greyscale)	0.472 ± 0.798	0 ± 1.352	0.772 ± 1.162	0 ± 0.637	<0.001
Women	0.586 ± 0.955	0 ± 0.913	0.982 ± 1.395	0 ± 1.947	0.003
Men	0.346 ± 0.556	0 ± 0.309	0.538 ± 0.778	0 ± 0.606	0.032
PD signal score	0.018 ± 0.134	0 ± 0.06	0.063 ± 0.245	0 ± 0.018	0.025
Women	0.034 ± 0.184	0 ± 0.034	0.103 ± 0.307	0 ± 0.094	0.044
Men	0 ± 0	0 ± 0	0.019 ± 0.138	0 ± 0.019	NA.
Tenosynovitis recount	0.118 ± 0.324	0 ± 0.105	0.336 ± 0.563	0 ± 0.317	<0.001
Women	0.189 ± 0.395	0 ± 0.156	0.396 ± 0.590	0 ± 0.349	0.001
Men	0.038 ± 0.194	0 ± 0.038	0.269 ± 0.528	0 ± 0.279	0.073

References

1. Manzo A, Bugatti S, Caporali R, et al. Histopathology of the synovial tissue: perspectives for biomarker development in chronic inflammatory arthritides. *Reumatismo* 2018; 70: 121–132.

2. Najm A, Le Goff B, Orr C, et al. Standardisation of synovial biopsy analyses in rheumatic diseases: a consensus of the EULAR Synovitis and OMERACT Synovial Tissue Biopsy Groups. *Arthritis Res Ther* 2018; 20: 265.

3. Roberts HM, Law R-J, Thom JM. The time course and mechanisms of change in biomarkers of joint metabolism in response to acute exercise and chronic training in physiologic and pathological conditions. *Eur J Appl Physiol* 2019; 119: 2401–2420.

4. Noh K-C, Park S-H, Yang CJ, et al. Involvement of synovial matrix degradation and angiogenesis in oxidative stress-exposed degenerative rotator cuff tears with osteoarthritis. *J Shoulder Elbow Surg* 2018; 27: 141–150.

5. Gaigneux E, Cormier G, Varin S, et al. Ultrasound abnormalities in septic arthritis are associated with functional outcomes. *Joint Bone Spine* 2017; 84: 599–604.

6. Canoso JJ, Liu N, Traill MR, et al. Physiology of the retrocalcaneal bursa. *Ann Rheum Dis* 1988; 47: 910–912.

7. Schett G, Tohidast-Akrad M, Steiner G, et al. The stressed synovium. *Arthritis Res* 2001; 3: 80–86.

8. Guillén Astete CA, Boteanu A, Zea Mendoza A. Comparison of prevalence of synovitis by ultrasound assessment in subjects exposed or not to self-reported physical overexertion: the Monday's synovitis. *ScientificWorldJournal* 2014; 2014: 563981.

9. Wakefield RJ, Balint PV, Szkudlarek M, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32: 2485–2487.

10. D'Agostino M-A, Terslev L, Aegerter P, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 1: definition and development of a standardised, consensus-based scoring system. *RMD Open* 2017; 3: e000428.

11. Bruyn GA, Iagnocco A, Naredo E, et al. OMERACT Definitions for Ultrasonographic Pathologies and Elementary Lesions of Rheumatic Disorders 15 Years On. *J Rheumatol* 2019; 46: 1388–1393.

12. Gutierrez M, Filippucci E, Salaffi F, et al. Differential diagnosis between rheumatoid arthritis and psoriatic arthritis: the value of ultrasound findings at metacarpophalangeal joints level. *Ann Rheum Dis* 2011; 70: 1111–1114.

13. Zabotti A, Salvin S, Quartuccio L, et al. Differentiation between early rheumatoid and early psoriatic arthritis by the ultrasonographic study of the synovio-entheseal complex of the small joints of the hands. *Clin Exp Rheumatol* 2016; 34: 459–465.

14. Husic R, Gretler J, Felber A, et al. Disparity between ultrasound and clinical findings in psoriatic arthritis. *Ann Rheum Dis* 2014; 73: 1529–1536.

15. van Oudenaarde K, Swart NM, Bloem JL, et al. Post-traumatic knee MRI findings and associations with patient, trauma, and clinical characteristics: a subgroup analysis in primary care in the Netherlands. *Br J Gen Pract* 2017; 67: e851–e858.

16. Revak A, Diers K, Kernozek TW, et al. Achilles Tendon Loading During Heel-Raising and -Lowering Exercises. *J Athl Train* 2017; 52: 89–96.

17. Wang M, Gu Y, Baker JS. Analysis of foot kinematics wearing high heels using the Oxford foot model. *Technol Health Care* 2018; 26: 815–823.

18. Kijowski R, Roemer F, Englund M, et al. Imaging following acute knee trauma. *Osteoarthr Cartil* 2014; 22: 1429–1443.

19. Zöllner AM, Pok JM, McWalter EJ, et al. On high heels and short muscles: a multiscale model for sarcomere loss in the gastrocnemius muscle. *J Theor Biol* 2015; 365: 301–310.