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Original Research Article

Don't Assume the Control Group Is Normal—People with Asymptomatic Tendon Pathology Have Higher Pressure Pain Thresholds

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Abstract

Objective. Pain pressure thresholds (PPT) are used to study peripheral and central pain processing. In the tendon, pathological changes may exist without pain. This pilot study aimed to compare PPT between individuals with normal tendons and asymptomatic tendon pathology, and between individuals with and without a history of tendon pain. **Methods**. The patellar, Achilles, and supraspinatus tendons of 128 asymptomatic participants were examined with ultrasound. Global PPT average was determined using a digital algometer at the patellar tendon, quadriceps muscle, L3 spinous process, and deltoid muscle insertion. Participants were separated into three groups: (1) healthy control group (no pathology, no history of pain), (2) tendon pathology at any site without a history of pain, (3) history of tendon pain anywhere. **Results**. There were 92 controls, seven with asymptomatic pathology and 29 with a history of tendon pain. Asymptomatic tendon pathology at any site (without a history of pain) was associated with globally increased PPTs compared with controls ($P < 0.001$, pathology N = 7, N = 92 controls). Matched pair analysis remained significant ($P < 0.004$). A history of tendon pain was associated with globally increased PPTs compared with the control group ($P = 0.026$). Matched pair analysis was not significant ($P = 0.122$). **Conclusions**. Asymptomatic tendon pathology is associated with higher PPTs. These findings point toward central nervous system adaptations but in a novel way—central desensitization. This challenges the validity of conclusions drawn from PPT studies that do not verify normal structure in the control group; artificial inflation of control group data may incorrectly indicate decreased PPTs in the comparison group.

Key words: Musculoskeletal; Ultrasound; Central Sensitization; Pressure Pain Threshold; Asymptomatic Pathology; Tendon

Introduction

Tendinopathy is a painful musculoskeletal condition that can restrict participation in work [1], sports, and health-promoting physical activity [2,3]. The condition is often recalcitrant to treatment, which can place financial burden on the individual and local health care systems [4].

Tendon pathology is poorly linked with the experience of pain [5]. Tendon pain with normal imaging, while rare in nonathletes, is seen in up to 15% of elite volleyball players [6]. In contrast, pain may be absent even when people have gross tendon pathology [7,8]. This is most clearly demonstrated by the lack of any preceding pain or stiffness in 66% of pathological tendons that spontaneously rupture [9]. The disconnect between tendon pain and pathology seen on imaging is one of the current challenges for tendinopathy researchers and clinicians.

The simple explanation of pain associated with tendon injury is that primary nociceptors in the tendon are activated in response to tissue damage, or to prevent potential tissue damage [5,10]. However, the pain experience

is far more complex, and this simple explanation fails to account for many features of tendon pain observed in clinical practice [5]. Although the clinical presentation of localized nonspreading pain that is directly related to tendon loading likely indicates the presence of a nociceptive driver, tendon pain has other features of sensitization, such as reduced conditioned pain modulation [11]. However, it does appear that this is more so the case for upper limb compared with lower limb tendinopathy [12]. Sensitization refers to reduced sensation thresholds and may occur at the central or peripheral level, or indeed a combination [10]. In addition, cognitive and contextual factors are known to modulate the experience of pain. Initially reduced thresholds and increased sensitivity can be protective; however, this clinical feature can complicate management.

Pain pressure thresholds (PPTs) are often used as a surrogate measure of peripheral and central sensitization [10]. The PPT is measured by applying pressure to the skin at a standardized rate until the sensation of pressure changes to one of pain. When measured at the site of injury or pain, a decreased PPT indicates peripheral sensitization. When measured away from the injury site, a decrease is interpreted as evidence of central sensitization [13]. Although there are a number of studies on PPTs in individuals with musculoskeletal pain or healthy controls, there are currently no data on PPTs among people with asymptomatic tendon pathology. It is likely that many current studies (either describing reliability or case–control studies) that include healthy controls include people with asymptomatic pathology and/or a history of tendon pain. Therefore, this study aimed to establish whether asymptomatic tendon pathology at any site affects global PPTs and whether history of tendon pain affects global PPTs.

Methods

Participants in this study were healthy individuals aged 18–55 years and were recruited by placing posters in public locations and by snowball sampling. Participants in this study had no current tendon pain; they were excluded if they had experienced tendon pain within the previous three months. Other exclusion criteria were a history of tendon rupture or tendon surgery anywhere in the body and injuries requiring joint immobilization of three months' duration or longer within the previous two years. Postmenopausal women were excluded as menopause can impact tendon health [14]. La Trobe University and Deakin University Human Ethics Committee approved all procedures (EC 261-2006 and EC 06–61), and all participants gave written informed consent.

Pain Pressure Threshold Assessment

Pain pressure threshold was measured with a digital algometer (Somedic Production AB, Sweden) using a probe size of 1 cm^2 at a rate of 40 kPa/sec. The standardized measurement protocol included bilateral PPT measurements from 1) the patellar tendon (at the proximal bone tendon interface); 2) the quadriceps muscle (10 cm above the superior pole of the patella); 3) the L3 spinous process; and 4) the deltoid muscle insertion. The PPT measures taken over the quadriceps muscle and patellar tendon were performed in supine position with the knee over a standard foam roll (diameter 15 cm) and the heel in a relaxed position just over the edge of the plinth. The measurement over the L3 spinous process was taken in prone. The PPT measure taken at the deltoid was performed in a sitting position. Assessors were blinded to whether participants had a history of tendon pain.

The locations were chosen to represent a lower limb (quadriceps) and upper limb (deltoid) site close to, but not directly over, a commonly injured tendon (i.e., patellar tendon and supraspinatus tendon). The patellar site was directly over the commonly injured site of the tendon. Initial pilot work demonstrated that it was not possible to obtain a reliable pressure pain threshold over the Achilles tendon, so this location was not included. The final location—the L3 spinous process—was included to provide a central location. Finally, the locations are anatomically reproducible through simple palpation, which maximizes study validity.

Participants had three familiarization trials for PPT over the right deltoid muscle. When the sensation first changed from pressure alone to pressure with discomfort, the participant pressed a button, which stored the instantaneous pressure reading in the algometer memory. Three recordings were taken, with a minimum 20-second interval between tests. The mean result of the three trials was considered the PPT for that area. The researchers assessing PPTs were blinded to the results of the tendon ultrasound imaging.

Ultrasound Imaging

An experienced musculoskeletal radiologist (ZSK) preformed bilateral ultrasound on the participant's left and right patellar, Achilles, and supraspinatus tendons. B-mode ultrasound was performed on an Acuson Aspen Advanced ultrasound system (Siemens AG, Munich, Germany) fitted with a 5–10-MHz linear array transducer. The tendons were examined longitudinally and transversely to assess their structure and determine tendon pathology. Care was taken to avoid anisotrophy, which can occur if imaging is not within the correct parallel fiber plane of the tendons [15]. Tendons were classified as either being normal or abnormal based on the ultrasound findings. An abnormal finding was made if any of the following were evident; 1) one or more focal hypoechoic lesions visible on both longitudinal and transverse imaging; 2) diffuse hypoechogenicity associated with bowing of the tendon border; 3) diffuse hypoechogenicity associated with diffuse thickening of the tendon.

Table 1. Demographic data of participants

	Controls (N = 92)	Asymptomatic Pathology (Path_No_Pain) (N = 7)	History of Tendon Pain Anywhere (Hx_PAIN) (N = 29)	Difference, *P* Value
Age, median (IQR), y	29 (8.75)	28.0 (19.0)	34.0 (15.5)	0.355
BMI, median (IQR), kg/m^2	23.05 (3.8)	25.0 (5.8)	23.6 (4.75)	0.231
Female sex, No. (%)	65 (70.7)	3 (42.9)	16 (55.2)	0.135

Nine participants in the Hx_PAIN group also exhibited pathology on tendons examined with ultrasound.
BMI = body mass index; IQR = interquartile range.

Participants were blinded to their ultrasound findings, and the radiologist was not provided with information regarding the participants' history of tendon pain or PPT results.

Data Analysis

Participants were separated into 3 groups;

1. CONTROL: no history of tendon pain and no tendon pathology on ultrasound (US);
2. PATH NO PAIN: no history of tendon pain but pathology on at least one tendon on US;
3. Hx PAIN: a history of tendon pain anywhere.

A priori decisions regarding data analysis were made based on study aims to reduce the number of statistical tests. The effect of asymptomatic tendon pathology with no history of pain on global PPTs (to indicate widespread hyperalgesia/central sensitization) was examined by comparing those with pathology and no pain (PATH_NO_PAIN) with those with normal tendons (CONTROL). The influence of a history of tendon pain on global PPTs (a proxy of central sensitization) was examined by analyzing those with a history of tendon pain (Hx_PAIN) against CONTROL. PPT has been used as an indicator of widespread hyperalgesia, and in turn central sensitization in a wide range of previous research [10,16]. A difference of more than 17.39 N/cm has been suggested to indicate true difference, in excess of measurement error [17].

Statistical Analysis

Mann-Whitney *U* tests were used to compare groups, because of the difference in group size. In each analysis, two independent groups were compared for the continuous variable of PPT algometry. PPT data from each location were pooled and averaged, before comparing between groups for analysis. Effect sizes were also computed based on Mann-Whitney *Z* values, as well as Common Language Effect Size (CLES), to determine the strength of any differences found. CLES is the probability that a person randomly selected from one group has a higher value than a person randomly selected from the other and may be used for comparisons with low or heterogeneous sample sizes [18]. To validate the findings, a secondary analysis was conducted using matched pairs. For each individual in the case group (e.g., PATH_NO_PAIN), one control individual with matched sex, age ± 2

years, and body mass index (BMI) ± 2 kg/m^2 was randomly selected from the pool of suitable controls. A researcher blinded to PPT data selected the matches. The alpha level was set at 0.05, and no Bonferroni adjustments were made. All statistical analysis was conducted using SPSS software (v21.0.0, SPSS Inc, Chicago, IL, USA).

Results

PPT data were collected from a convenience sample of 130 participants. Two people were excluded from analysis for reporting a history of musculoskeletal pain other than tendon pain. The median age of the participants (interquartile range [IQR]) was 29 (10.75) years, and the median BMI (IQR) was 23.6 (4.58) kg/m^2. These people without current tendon pain were allocated to the control group (N = 92), asymptomatic pathology (N = 7), history of tendon pain anywhere (N = 29). Nine of the participants demonstrated tendon pathology in this group. Tendons can transition from reactive pathology (that can be painful) back to normal structure [6,19]. There were no differences between groups in these variables that have been reported to influence PPTs (all $P > 0.05$) (Table 1).

Asymptomatic tendon pathology at any site without a history of pain was associated with increased global PPTs compared with controls ($P < 0.001$, ES $r = 0.36$, CLES = 0.91, PATH_NO_PAIN N = 7, N = 92 CONTROL) (Figure 1). The analysis repeated with matched pairs remained significant ($P < 0.004$, ES $r = 0.73$, CLES = 0.94, N = 7 each group) (Figure 1).

A history of tendon pain (Hx_PAIN) was associated with increased global PPTs compared with the CONTROL group ($P = 0.026$, ES $r = 0.31$, CLES = 0.63) (Figure 2). The analysis repeated with matched pairs was not significant ($P = 0.122$, N = 29 in each group) (Figure 2), though effect sizes were similar (ES $r = 0.20$, CLES= 0.61).

Discussion

This study compared PPT in people with ultrasound-determined tendon pathology with those without, and those with a history of tendon pain with those without. To our

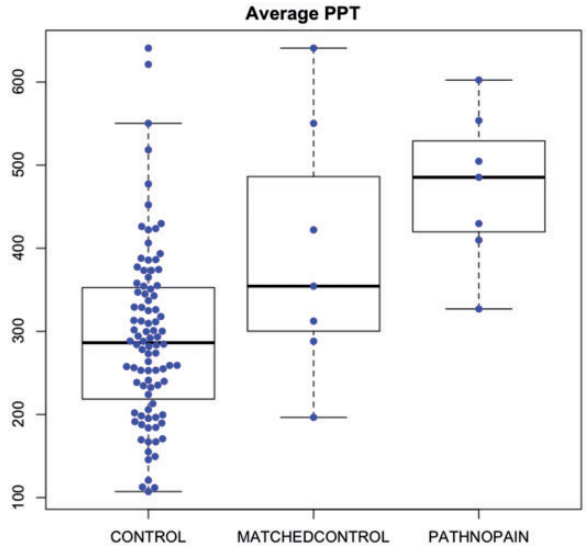

Figure 1. Comparison of pressure pain thresholds (kPa) between people with asymptomatic tendon pathology (PATHNOPAIN) and controls. PPT = pressure pain threshold.

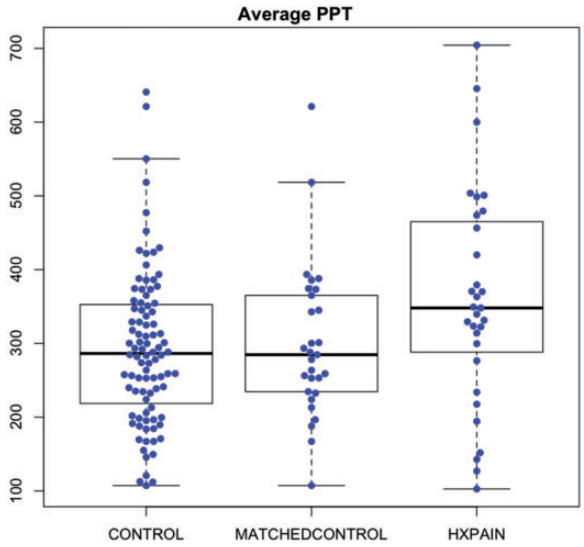

Figure 2. Comparison of pressure pain thresholds (kPa) between those with a history of tendon pain (HxPAIN) and control group. PPT = pressure pain threshold.

knowledge, this study demonstrates for the first time unique pain processing in those with asymptomatic tendon pathology in a community sample. Asymptomatic pathology was associated with increased PPT—that is, they were less sensitive. Further, there was no hypersensitivity in those with a history of tendon pain, and in one but not both analyses, there was a decrease in sensitivity. Although primary hyperalgesia at the patellar tendon has been observed in symptomatic patellar tendon pain [12,20,21], there were insufficient numbers in this group to examine whether there was evidence of persistent primary hyperalgesia (peripheral sensitization) in those reporting a history of patellar tendon pain.

Without ultrasound imaging, this entire cohort could be considered a "healthy" control group in a study measuring PPTs, as they were all asymptomatic, yet there were differences in their PPTs associated with tendon pathology. There are a number of clinical and research implications of this finding. First and foremost, this observation may necessitate a re-examination of the validity of conclusions drawn from prior studies on PPT in tendinopathy where normal tendon structure was not verified by ultrasound in the control group. The data here show that if people with asymptomatic tendon pathology are included in the control group, the control PPT will be artificially inflated, which may lead to the incorrect conclusion that the comparison group has decreased PPTs. This may also be important in other research not exclusively investigating tendon pain, as asymptomatic tendon pathology may confound PPT findings in other conditions.

Palpation is commonly used in the clinical diagnosis of tendon pain. However, patellar tendon sensitivity is not specific to patellar tendon pain [16,22], and therefore algometry should not be used diagnostically. It is known that pathology on imaging is a risk factor for the development of pain [23], yet it is not known why some people experience pain while others remain asymptomatic. This study demonstrates changes in sensory processing and pressure thresholds associated with pathology, which reinforces the lack of specificity around tenderness on palpation.

Fernández-Carnero and colleagues found decreased bilateral PPT of the common extensor tendon in 26 individuals with unilateral lateral epicondylalgia [24]. The authors concluded that segmental sensory sensitization might exist in people with unilateral lateral epicondylalgia, which would explain the bilateral PPT changes observed. Sustained unilateral nociceptive afferent input results in the dorsal horn neurons becoming "hyperactive" at the specific spinal segment [16]. This segmental hyperactivity may cause unilateral pain to spread contralaterally [25] due to common bilateral myotomal and dermatomal distributions supplied by that spinal segment. This is consistent with evidence of contralateral tendon pathology after unilateral overload–induced tendon pathology [26] and human tendinopathy [27].

A number of factors could be contributing to alterations to sensory processing. Synaptic plasticity is characterized by permanent, long-term memory and long-term potentiation (LTP) changes of synapses that may strengthen or weaken over time through activation [28]. Previously active synaptic pathways, such as nociceptive pathways from a tendon to the dorsal horn of the spinal cord, may be strengthened due to the history of increased nociceptive afferents [29], or conversely LTP may be avoided if the frequency of nociceptive input is low. For example, patellar tendon pain is predominantly observed in young male jumping athletes [30] and aggravated mainly during jumping and fast change of direction. If

these athletes are playing and training several times a week, the rest days create space between nociceptive barrages, which may limit LTP.

Tendon nociceptive afferents most likely follow a particular synaptic chain. Facilitation or strengthening of the synapses within this chain through increased activation is called heterosynaptic plasticity [28]. Van Wilgen and colleagues found an altered somatosensory profile, namely decreased mechanical pain thresholds, in the patellar tendon in individuals with patellar tendinopathy [31]. Conversely, the Achilles and patellar tendon appeared to have local, not widespread, pain and lacked features of central sensitization [12]. The current study supports those data for the patellar tendon and extends our understanding— history of tendon pain was not associated with sensitization.

Descending facilitation or inhibition from the cerebral cortex appears to influence PPT in individuals with pathology. Descending facilitation occurs from the rostroventromedial medulla (RVM) [29]. The balance of descending inhibition and facilitation is dynamic and is influenced by many emotional, behavioural, and pathological states at a cortical level [31,32]. Anxiety of testing may influence the enhancement of descending facilitation [33]. "Off-cells" and "on-cells," located in the RVM, exert and reduce cortical descending facilitation, respectively [34]. Individuals with long-term pathological changes, such as tendinopathy, may be susceptible to an increase of activity from on-cells or off-cells; thus facilitation or inhibition of nociceptive mechanisms may occur at the spinal dorsal horn [35]. The persistence of peripheral afferents [29] that affects these mechanisms may be different depending upon the individual and frequency of input.

This study also tested PPT at multiple locations. The findings might reflect increased descending inhibition from the RVM. It has been suggested that long-term noxious stimuli can stimulate descending inhibition pathways [33]. Ren and Dubner stated that descending inhibition increases gradually, with changes being notable after three days, which is theorized to counteract potential noxious afferents [36]. In animal studies, enhancement of descending inhibition is marked when noxious stimuli are continuous and persistent [36]. Descending inhibition can be transient and is modified according to the internal and external environment of the individual, although there is limited evidence underpinning these theories in humans due to ethical considerations [34].

Increased PPT associated with pathology has been observed in patients with radiographic osteoarthritis. A significant inverse association between PPT and self-reported pain symptoms has been shown in this population [37]. Higher PPTs were recorded in individuals with asymptomatic knee and hip osteoarthritis compared with individuals with minimal radiographic changes and higher perceived pain [37]. Furthermore, another study revealed that individuals with higher grades of radiographic osteoarthritis had increased PPTs compared with those who had lower grades of radiographic osteoarthritis [38]. This suggests that descending inhibition may be involved in these people who have joint pathology but do not experience pain. The degree of sensitization appeared to be correlated with reported pain but not radiographic findings [10], reflecting the complexity of the pain experience and the lack of association with tissue damage.

Limitations

This study has several limitations that should be acknowledged. First, due to the small number of individuals with asymptomatic pathology, or a history of tendon pain, a type 1 statistical error may have occurred. Second, the data were not normally distributed, which did not allow covariant analysis. To account for heterogeneous sample sizes between groups, two different effect sizes were calculated, and matched pairs analysis was completed to ensure strength of statistical findings. Third, women may have a lower PPT then men [24], and there was an imbalance in the gender proportion. This difference, however, was not statistically significant, and thus may not have impacted the findings enough to change the outcomes. Fourth, there was no screening for potential confounders such as depression or mood disorders. Psychosocial disorders have been shown to have a powerful effect on the perception of pain [39] and could therefore influence PPT measurements [24].

Clinical Implications

This is the first study to separate the presence of tendon pathology and a history of tendon pain in terms of their potentially unique effects on sensory stimulus processing. Evidence suggests that those with abnormal tendon imaging without pain are at increased risk of developing pain in the future [6,23,40]. This study points toward changes in central processing, however, possibly not in the expected direction; people with asymptomatic tendon pathology appear to demonstrate lower levels of central sensitization (evidenced by higher PPT). Therefore, it is possible that while pathology is a known risk factor for developing symptoms, there may be people with pathology who are less sensitive and, in fact, protected from symptoms. This cross-sectional study established an association but not causation, and the features that make someone more or less vulnerable to symptoms are unknown. Tendinopathies are complex and require comprehensive clinical reasoning for musculoskeletal, neural, local nociceptive, and central contributors [5]. This study has highlighted the potential central mechanisms associated with tissue pathology. Surprisingly, it was equivocal whether central processing changes remained after the experience of pain had resolved, and there is potential for variability within this group (HxPAIN) that warrants

further exploration to identify those who may experience recurrence.

Conclusion

Central processing adaptation (or maladaptation) is complex, and we are far from understanding it in the presence of pain in people recovered from pain, or the presence of pathology. In a community sample of 128 people (who could reasonably be recruited for studies in PPT as healthy controls), we found that asymptomatic pathology independently affected PPTs. Therefore, pathology appears to be relevant in screening. We acknowledge that this presents a huge challenge but must be considered in terms of factors that may affect data and conclusions. Further research in the asymptomatic population may help elucidate the central pain processes at play in tendinopathy.

Authors' Contributions

EKR contributed to data interpretation, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. RFE, JMH, VRF, and MAG contributed to data analysis, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. ZSK contributed to study design, data collection, and critical revision of the manuscript for important intellectual content. JLC and JEG contributed to study design, data collection, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors have read and approved the final version.

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