Elevated Levels of Inflammatory Cytokines, Matrix Metalloproteases, and Pain Neuromediators in Pathologic Posterior Tibial Tendons of Patients with Posterior Tibial Tendon Dysfunction

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Introduction: The posterior tibial tendon (PTT) is critical for normal ambulatory function. It provides foot inversion and plantar flexion as well as arch stability. When the PTT elongates, through repetitive microtears, it results in a syndrome of significant pain, disability, and progressive deformity, called posterior tibial tendon dysfunction (PTTDD). In addition to loss of function, pain is the predominant symptom of PTTDD yet the pathophysiology of the pain is not well understood in this degenerative disease, as tendons are relatively avascular and aneural. Inflammatory cytokines, matrix metalloproteases (MMPs) and pain neurotransmitters (glutamate, substance P, CGRP) have been shown to play a role in Achilles and patellar tendinopathy and as such we expect it to play a role in PTTDD. Furthermore, the involvement of the PTT insertion has never been explored and this is important as many surgeons use the PTT insertion as an anchorage point for tendon transfers during operative treatment for PTTDD. The purpose of this study was to characterize the inflammatory cytokine, MMP, and pain neurotransmitter profiles in the diseased PTT as well as the PTT insertion.

Methods: To-be-discarded PTT and flexor digitorum longus (FDL) samples were collected from twenty-one patients undergoing FDL tendon transfer surgery for stage II PTTDD that failed conservative management. Samples were grouped as PTT insertion (I), diseased PTT (D) or healthy (H) FDL tendon and trimmed to make them approximately the same size per patient. The tissue was washed twice in PBS, weighed and then cultured in 3 mL of DMEM without serum for 48 hours to allow for substance diffusion. After 48 hours, the spent media was frozen at -80°C until use. Inflammatory cytokine and MMP concentrations were determined by multiplex electrochemiluminescence (Meso Scale Discovery, Gaithersburg, MD). Glutamate was detected using a colorimetric assay kit. All measurements were adjusted for mass and analyzed by Friedman’s test and Wilcoxon-signed-rank post-hoc tests with Bonferroni corrected α = 0.0167. Tendon samples were frozen sectioned for immunohistochemistry.

Results: The samples were obtained from 15 females and 6 males with a mean age of 64 years (range, 53 to 76 years). Diseased PTT and PTT insertion groups were significantly elevated compared to healthy FDL for inflammatory cytokines IL-1β, IL-6, IL-8, IL-10, TNF-α and MMPs MMP-1, MMP-2, and MMP-3. Differences in glutamate concentrations were also significant, but only the diseased PTT group was significantly elevated compared to the healthy FDL tendons. Figure 1 shows a selection of this data. Discussion: The etiology of debilitating pain in PTTDD is not well understood. This study demonstrates elevated levels of inflammatory cytokines and MMPs in diseased PTT and PTT insertion compared to healthy FDL tendon from the same individual. This marked increase in inflammatory cytokines and MMPs suggest that both the diseased tendon and the tendon insertion are involved in the degenerative process. Glutamate may contribute to pain in the diseased portion of the tendon through binding with NMDA receptors within the tendon or the surrounding tissues. Characterizing the local production of pain-generating, excitatory neurotransmitters potentially improves our understanding of the pathophysiology of pain and may yield better surgical and non-surgical treatment options.

Significance: Pathologic PTTs do not heal. These data provide insight into the inflammatory and tissue degradation mechanisms that can prevent the PTT from healing as well as targets for therapeutic intervention.

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Figure 1—A selection of statistically significant cytokines NP, TNF and pannexin transcripts.

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