"Up to a quarter of patients with certain chronic recalcitrant tendinopathies may have Central Sensitisation – a prospective cohort of more than 300 patients"

Background

Lower limb tendinopathy conditions are common causes of chronic musculoskeletal pain presenting to primary and secondary care. Whilst many of these will improve over twelve months, between 10-35% of patients can be left with ongoing symptoms that can have a significant impact on quality of life. [1-3] This project focuses on four specific common lower limb tendinopathy, and "tendinopathy-like", conditions and seeks to identify if any patients with chronic tendon pain may have central sensitisation as a component of their pain symptoms which may contribute to the chronicity of their symptoms, through the use of the Central Sensitisation Inventory (CSI) questionnaire. These include patients with Greater Trochanteric Pain Syndrome (GTPS), Patellar tendinopathy, Achilles tendinopathy (both insertional and non-insertional sub-types), and Plantar fasciitis, all if which are discussed below.

Although subject to clinical debate, the "Central Sensitisation Syndrome" is postulated as a condition in which the central nervous system has become hypersensitive to both noxious and non-noxious stimuli with dysfunction of both ascending and descending pathways.[4] This may be common in patients with chronic pain with a range of other diagnoses including chronic low back pain, osteoarthritis, and fibromyalgia, and which can potentially co-exist with those with structural pathology.[4-8] Identification of patients with this condition, could facilitate a more holistic pain management approach to their symptoms, potentially alongside other physical treatments. The Central Sensitisation Inventory (CSI) is a questionnaire with high reliability and validity in identifying patients thought to have this phenomenon; published work has shown that a score of more than 40 best distinguishes patients with/without Central Sensitisation. [7 9 10] Further work comparing this questionnaire against experienced clinical assessment demonstrated that the CSI has a sensitivity of 83% and a specificity of 55%, but

may have a high false positive rate in patients with complex pain and medical conditions, and the authors concluded that this questionnaire was found to be a useful and valid instrument in screening patients for the possibility of Central Sensitisation.[11]

Classical lower limb tendinopathies that were studied in this project include those of the Patella and the Achilles tendons. Two distinct anatomical locations of Achilles tendinopathy are described in the literature; the commoner site is in the mid-portion of the Achilles tendon with maximal pain and swelling occurring between 2 and 7 cm proximal to the calcaneal attachment, and is often called “non-insertional” (or mid-substance) tendinopathy.[12] A less common sub-type is the insertional tendinopathy which directly affects the insertion of the Achilles tendon into the posterior aspect of the calcaneus and is sometimes associated with an enlarged bursa.[13] Patellar tendinopathy is a similar degenerative tendinopathy affecting the patella tendon, which is the terminal portion of the knee extensor mechanism group.[14-16] The processes involved in the development of tendinopathy between these two, and other, sites, are thought to be very similar.[17 18] Other conditions studied here include Greater Trochanteric Pain Syndrome (GTPS) and Plantar Fasciitis, both of which have great similarities in pathology, biomechanical properties, and treatments to other classical tendinopathies.

Recent work in GTPS has looked beyond the trochanteric bursa being the primary source of pain and pathology and towards the insertion of the gluteal tendons, in particular gluteus medius and which behaves and is treated in a similar way to other insertional tendinopathies.[19-21] The plantar fascia, is anatomically not strictly a tendinopathy, but behaves in a very similar way to one and is treated in a similar way to one. The plantar fascia is a band of connective tissue in the sole of the foot originating at the medial process of the tuberosity of the calcaneus and inserting in slips to the proximal phalanxes which has roles both in supporting the longitudinal arch of the foot, and also in proprioception and

peripheral motor coordination.[22] The plantar fascia can develop a degenerative thickening process associated with pain similar to that seen in tendinopathies, called plantar fasciitis, with myxoid degeneration, associated with areas of proliferation of fibroblasts and increased vascularity.[23-26] Its insertion into bone is very similar to that of an insertional tendon, its degenerative processes are similar to those seen in an established tendinopathy, and the effective treatments used are very similar to those in tendinopathy management. Therefore, for the purposes of this review will be considered similar, if not the same, as a classical tendinopathy, although the challenges of this approach are recognised.

Greater Trochanteric Pain Syndrome, Achilles Tendinopathy, and Plantar Fasciitis are all common conditions; both GTPS and Achilles tendinopathy have an incidence of about 1.8-2.3/1000 adults, and there may be a lifetime risk of 10% of developing Plantar Fasciitis [2 26 27] These conditions most commonly affect people between 40 and 60, affect women slightly more than men, and have a wide range of risk factors including activity, or lack thereof, obesity, impaired lower limb flexibility, and multiple genetic factors.[19 28-30] Patellar tendinopathy is less common in sedentary populations than other tendon conditions, and is associated most with individuals particularly involved in sports with sprinting or jumping/landing components, and has been previously known as “jumpers knee”.[15 31] Patellar tendinopathy more commonly affects younger populations than some other tendon conditions, with athletes in one study having a mean onset of patellar tendinopathy symptoms at age 23.8 years (range 16-47).[32]

The underlying pathology of tendinopathies have been extensively studied over many years, with hypotheses moving away from a primarily inflammatory-driven pathology (aka “tendinitis) to a degenerative / mechanical “failed-healing” model,[18 33 34] however recent work has shown inflammatory processes remain involved within the entity of “tendinopathy”, particularly in the early stages.[35 36] A wide-range of treatment options are available to treat

these conditions, which conceptually address nociceptive pain as well as functional impairment. Depending on the tendon location, these may include Tension Night Splints (TNS) [37-40], guided injections - including High-Volume Image-Guided Injections (HVIGI)[41 42] or Autologous Blood Injections (ABI)[43-45], Extra-Corporeal Shockwave Therapy (ESWT)[46-48], or surgery in recalcitrant cases.[49-51]

It is believed that neuronal regulation has a vital role in tendon homeostasis, and the presence of neuropathic pain in chronic tendinopathies has been proposed.[52 53] Vasculo-neural ingrowth into chronic tendinopathy is recognised as has been proposed as a cause of pain, with tendinopathy associated with a local increase in a range of neurotransmitters including glutamate, as well as an increase in substance-P positive nerve fibres, however mixed results have been found and no consistent answer is yet identified. [54-57] Previous clinical work has suggested that more than a quarter of patients with chronic, recalcitrant lower limb tendinopathies scored highly on the painDETECT questionnaire which rates the likelihood of neuropathic pain.[58] Whilst this is not truly diagnostic of neuropathic pain, there is a consideration that many patients with chronic pain from a range of sources, including possibly tendinopathy, have pain that is not simply nociceptive in origin.

This project therefore seeks to identify if patients with chronic tendon pain may have central sensitisation as a component of their pain symptoms, through the use of the Central Sensitisation Inventory (CSI) questionnaire.

Methods

Procedure logs were examined from a single UK hospital outpatient clinic, which has a regional reputation for the management of patients with chronic tendinopathy. Patients that had been referred with a chronic lower limb tendinopathy / tendon-like condition, including

Greater Trochanteric Pain Syndrome, Patella tendinopathy, Achilles tendinopathy (both insertional and non-insertional sub-types), and Plantar fasciitis were identified. The treatments that these patients were to undertake included Tension Night Splint (TNS) devices, Extra-corporeal Shockwave Therapy (ESWT), High-Volume Image-Guided Injections (HVIGI), or Autologous Blood injections (ABI). The diagnosis of the condition was made by a single NHS Consultant, who specialises in musculoskeletal conditions and whose patient case mix is heavily slanted towards patients with pain from chronic tendinopathy, on the basis of clinical assessment, the exclusion of other differential diagnoses, and the use of investigation modalities. All patients had symptoms that had failed to settle with simple conservative therapies, including a structured home rehabilitation programme.

Prior to the treatments and as a part of their routine care, patients completed baseline questionnaires about their pain and level of functioning, including a 0-10 self-rated value of their “average pain”, their “worst pain” and their “average stiffness”. In addition, specific validated questionnaires including the Central Sensitisation Inventory (CSI) questionnaire [9-11] to examine possible central sensitisation, and also the EQ-5D-5L questionnaire [59 60] as a marker of global health and functioning, were also completed by the patient. Data were available for the period from 25th November 2015 to 13th November 2017, these were identified and transcribed by the author for analysis in this project.

- **Statistical analysis**

Anonymised data from the procedural logs were inputted into a bespoke Excel spreadsheet (MS Excel for Mac 2011 – current version 15.39) by the author. All data was anonymised prior to analysis and held/used in accordance to hospital Trust procedures. From this, group values (including means, standard deviations, medians, and ranges) were calculated for the patient group as a whole, and also for different conditions as sub-groups. The majority of data collected (age, numerical rating scales, and CSI) were scale data. This information was

analysed through SPSS (v22) and the Shapiro-Wilk test was performed to assess normality. The majority of the data were found not to be normally distributed, therefore non-parametric testing was used, typically independent samples Mann-Whitney U, Kruskal-Wallis, or Pearson Chi-Square tests as appropriate, with Spearman's correlation used to assess relationships between variables. Statistical significance was set at $p<0.05$

- **Ethical approvals**

This project utilised anonymised data from questionnaires that patients who attended this outpatient department completed as a part of their routine clinical care. Patients were advised that these questions were designed to better understand their pain and the impact that their symptoms had on their quality of life and they were free to choose not to complete the questionnaires if they so wished. This specific project, which compares anonymised data across different conditions is a part of a wider ongoing body of work examining different aspects of chronic tendinopathy which is fully registered with the hospital Trust and authorities. This specific project does not fulfil the criteria of research as stipulated by HRA and specific formalised ethics approvals were not required for this project.

Results

Results were available for a total of 312 consecutive patients who attended this hospital clinic for specialised treatments for their lower limb tendinopathy / tendon-like conditions and who had completed the CSI questionnaire. All data collected was from November 2015 to November 2017. All patients had their diagnosis confirmed on imaging, typically ultrasound or MRI. Results were available for 109 patients with Greater Trochanteric Pain Syndrome (GTPS), 12 patients with patella tendinopathy, a total of 81 patients with Achilles tendinopathy (of which 33 had non-insertional and 48 had insertional tendinopathy and are listed separately hereafter), and 110 patients with plantar fasciitis.

The age range for the patients was between 23.7 years and 88.6 years; 66% of patients were female and 34% male. The duration of pre-existing symptoms ranged from 2 months to 30 years, and all patients had previously undertaken a rehabilitation programme of exercises. The patient demographics for each condition are displayed in table 1; as data is not normally distributed, the median values and inter-quartile ranges (IQR) are displayed.

As highlighted in table 1, these demographic variables differed significantly between the different conditions studied: age ($p<0.001$), gender ($p<0.001$), and duration of symptoms ($p=0.003$), which was predominately explained by the differences seen from the group seen with patellar tendinopathy, compared to the remainder of the conditions studied. There was a weak, but statistically significant correlation between the CSI score and the duration of symptoms ($r_s=0.217$, $p<0.001$), but not patient age ($p=0.137$).

- **Self-reported pain and function scores**

There was a median (IQR) overall self-reported “average pain” of 7.0/10 (IQR: 5.0-10.0), a “worst pain” score of 8.0/10 (IQR: 7.0-10.0), and a self-reported “average stiffness” rating of 5.0/10 (IQR: 3.0-10.0). There was a median value of 71% (IQR: 60-100%) scored on the EQ-5D global health percentage scale, and a median CSI score of 25% (IQR: 14-78%) for the patients studied. As data was not normally distributed the median values (and inter-quartile ranges) for each of these measures are displayed in table 2, with significance of differences in variables between groups indicated.

The self-reported rating for “average stiffness” and the EQ-5D %health score did not differ significantly between the different conditions ($p=0.126$ and $p=0.901$ respectively), but there were significant differences between the conditions for the other parameter studied including the values for “average pain” ($p=0.003$), and worst pain ($p=0.005$). The median value for CSI

in patients with patellar tendinopathy was 17%, compared to that in patients with GTPS of 29%, and those with plantar fasciitis of 27%. These differences between groups in the CSI score was statistically significant (p=0.002. These values are displayed in Table 2.

There were no gender differences found between any of the variables studied except for the CSI value, which had a median (IQR) of 20% (IQR:13-78%) for the 106 male patients studied, and 28% (IQR:19-28%) for the 206 female patients studied (p<0.001). However, this may have been influenced by the different proportion of male/female patients with different conditions, as when sub-groups were analysed this difference was found to be non-significant and appears to be at least partially confounded by different proportions of male/female patients with the different conditions studied.

There were statistically significant, although weak-level, correlations found between the CSI score and the other variables studied, including the self-reported “average pain” score (r_s=0.161, p=0.004), “worst pain” (r_s=0.216, p<0.001), “average stiffness” (r_s=0.266, p<0.001), and the %health score of EQ-5D (r_s=-0.386, p<0.001).

- **Possible presence of central sensitisation**

A CSI score above 40% has been suggested from the published literature to best identify those who are most likely to have central sensitisation, however a high false positive is noted giving a noted limitation to this approach.[7 9-11] In this prospective study, a total of 19.6% of all subjects met this threshold, with variability apparent between different conditions. The condition with the highest proportion of scores above this threshold was GTPS with 25.9% subjects identified, next was plantar fasciitis with 23.6%, however none of the subjects with patella tendinopathy scored above this threshold in this series. The proportion of those scoring over the 40% threshold on the CSI questionnaire is displayed in table 3.

“Classical” tendinopathies (such as non-insertional Achilles tendinopathy and Patella tendinopathy) had lower prevalence levels than other studied conditions (GTPS and plantar fasciitis) using this cut-off value. This difference reached statistical significance (p=0.011), and the clinical significance of this remains uncertain.

There was no statistical difference found when directly comparing only those with non-insertional and insertional Achilles tendinopathy (p=0.493), nor when comparing those with insertional Achilles tendinopathy (attaching to the posterior of the calcaneus) with those with plantar fasciitis (attachment on the under-surface of the calcaneus) (p=0.054).

Discussion

This is a pragmatic project which investigated the possible prevalence of central sensitisation in patients presenting with a range of recalcitrant lower-limb tendinopathy and similar conditions to this single outpatient department for further treatment. This project has shown that in some conditions a quarter of patients score highly enough on the CSI questionnaire to raise the possibility of Central Sensitisation. There were statistically significant differences found in this prevalence between different conditions; however, the reasons for this, and any clinical significance of this, remain unknown at this time. The study had limited numbers in some sub-population groups (notably patella tendinopathy) and this is a noted limitation of this data set.

The CSI questionnaire has been shown to be a useful and valid instrument in screening patients for the possibility of Central Sensitisation in hospital outpatient departments. [7 9-11] However, the high false-positive rate means that the information presented here must be treated with some reservations and may have given an artificially high prevalence figure, although there remains no alternative validated PROM to assess this concept. Irrespective

of this, the statistically significant difference in point prevalence rates between different conditions of those scoring more than 40% on the CSI, which has been used as a threshold to determine those most likely to have a component of central sensitisation, is of interest and would be worthy of further study. In addition, as there were only weak correlations identified between the CSI and the other markers studied, it is suggestive that these may be measuring different aspects of function, and the CSI may be useful in the global assessment of patients, without too great an overlap with other aspects presented here.

It is important to highlight that the clinical population studied here was not necessarily typical of the general population suffering from lower-limb tendinopathy, and instead was a population that was often resistant to previous treatments with the majority having symptoms for at least two years duration. It is unclear from this data whether the patients may have been resistant to other treatments due to the presence of a possible central sensitisation (as recorded by the CSI score), or whether this may have developed due to the chronicity of the symptoms, or if the two are unrelated. There was only a weak correlation found between the CSI and duration of symptoms, but this did reach statistical significance. Therefore, this domain should be considered in future research, with a longitudinal study from early onset of symptoms being best placed to examine this.

Lastly, the clinical significance of those scoring highly on the CSI questionnaire remains unclear. There was only a weak statistical correlation between the CSI and the patient's self-reported "average" or "worst" levels of pain, indicating that this did not just identify patients with the most problematic symptoms. Instead, this may have identified those patients in which factors other than purely nociceptive pain may be involved. If this is the case, then further work could examine whether the CSI is of value as a prognostic factor in the response to treatments, and if so could be of value in determining an individualised pathway of care.

In summary, the CSI is a patient-rated questionnaire that may have some application in the management of patients with recalcitrant lower-limb tendinopathies. This study suggests that a up to a quarter of patients with some lower-limb conditions score highly enough to be suggestive of central sensitisation being present, based on an identified threshold score from previously published work. There was found to be a weak correlation between the CSI score and the duration of symptoms, and also weak correlations between the CSI and other markers of patient pain/function. However, the clinical implications of these CSI scores in this clinical population remain unclear at this time, and is in need of further research.

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