TriNetX Analytics Network analyses of the USA population reveals bidirectional associations between Achilles tendinopathy and hypertension mediated by voltage-gated Ca^{2+} channel $Ca_V1.2$

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Introduction: Achilles tendon is highly prone to acute- and overuse-induced injuries that lead to chronic tendon degeneration called tendinopathy. Achilles tendinopathy is often associated with pain and disability. Current standard of care for Achilles tendinopathy does not result in effective long-term functional recover, although it provides short-term pain relief. The pathogenic mechanisms of Achilles tendinopathy are largely unknown, which prevents the development of new therapeutic strategies for tendinopathy. Using novel transgenic mouse models with $Ca_V1.2$ wildtype or a gain-of-function mutant channel, we observed potent regulatory effects of increased Ca^{2+} influx through $Ca_V1.2$ on Achilles tendinopathy development (data unpublished yet). Moreover, we found that $Ca_V1.2$ re-expression in Achilles tendon can be dramatically upregulated by inflammation upon acute Achilles tendon transection. Given the fact that $Ca_V1.2$ channel is the major pathway of Ca^{2+} influx to trigger smooth muscle contraction and dysregulation of $Ca_V1.2$ expression/activity has been implicated in hypertension (HT) development [1], we hypothesized that aberrant $Ca_V1.2$ function is a common pathological mechanism underlying both diseases. To test the hypothesis that $Ca_V1.2$ signaling is implicated in Achilles tendinopathy in patients, we performed a national database association study.

Methods: We used the TriNetX Analytics Network, a global healthcare network that captures de-identifiable data from electronic health records of over 111 million patients from 74 Healthcare Organizations, mostly in the USA. We first performed **a cross-sectional study** to investigate the prevalence of HT among Achilles tendinopathy patients and its potential association with Achilles tendinopathy. We identified patient disease conditions based on their ICD-10 codes. Student *t* test and Chi-squared test are used to compare continuous variable and categorical variable, respectively. Odds ratio (OR) and 95% confidence interval (CI) were used to quantify the correlation between these two diseases with maximally eliminated confounding factors (such as age, gender, and race) by population stratification and matching. To determine the sequence of events (a.k.a. cause-and-effect relationship between Achilles tendinopathy and HT), **two retrospective cohort studies** were carried out, with Cohort Study 1 having HT as the exposure factor and Achilles tendinopathy as the outcome to be followed up, while Cohort Study 2 having Achilles tendinopathy as the exposure and HT as the outcome. The exposure cohort included participants at entry diagnosed with the exposure condition but no outcome disease from 01/01/2011 to 12/31/2015, while the control cohort was matched with a 1:1 ratio using built-in propensity matching score who at entry had no diagnosis of the exposure and outcome conditions. Confounding factors were further eliminated by population stratification (age, gender, race, and BMI). A 7-year follow-up was performed for the outcome. To elucidate the role of $Ca_V1.2$ in the association of Achilles tendinopathy and HT, we performed **an additional cohort study on hypertensive patients** with the exposure cohort defined as all hypertensive subjects (from 01/01/2011 to 12/31/2015) having their first Ca^{2+} channel blocker (CCB) prescription but without previously diagnosed tendinopathy. The matched control hypertensive cohort was defined as the subjects on medication other than CCBs. A 7-year follow-up was performed for the outcome Achilles tendinopathy. Relative risk (RR), hazard ration (HR), and 95% CI were used to detect the association and the effect of CCBs on the reverse association between the two diseases. Kaplan-Meier analysis was done to estimate the incidence of outcome within the follow-up. Statistical significance was set at two-sided $p<0.05$.

Results: In the cross-sectional study, we found that HT was significantly more prevalent among Achilles tendinopathy patients than in patients without tendinopathy (50.44% vs 15.09%, p<0.001). Further association analysis found that the incidence of Achilles tendinopathy was highly correlated with HT. Hypertensive subjects had about four times the odds of having Achilles tendinopathy compared to controls (OR: 4.05, 95%CI: 4.01 to 4.08, p<0.001). After stratification of age, race, BMI, and gender to minimize confounding factors, these two diseases remained significantly associated in all age groups, both genders, all races, and all BMI categories. Interestingly, this association was more prominent in aged, female and Africa American patients. In addition, we observed an increased association between HT and Achilles tendinopathy as the subjects' BMI increased. In the longitudinal retrospective cohort studies, we found that in patients over 30 years old without previous tendinopathy, a diagnosis of HT was associated with increased incidence of Achilles tendinopathy in the following 7 years. This association remained significantly strong after population stratification by gender, race, and BMI and more prominent in aged subjects. Likewise, we found that in patients without previous HT, a diagnosis of Achilles tendinopathy was associated with increased incidence of HT in all age groups (over 18 years old) in the following 7 years. Furthermore, in the longitudinal retrospective cohort study to evaluate the effect of CCB intervention, we found that hypertensive patients who were on CCBs to control their blood pressure had a 26% decreased risk of developing Achilles tendinopathy than hypertensive patients on other medications (HR:0.74, 95%CI: 0.62-0.88, p<0.001) (**Figure 1**). Interestingly, β-blockers (medication for hypertension, targeting β-adrenergic receptors which are known to regulate $Ca_V1.2$ activity in the fight-or-flight response) displayed similar effect as CCBs (HR:0.74, 95%CI: 0.66-0.84, p<0.001). In contrast, we didn't detect the decreased risk of Achilles tendinopathy in hypertensive patients who were on angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) or diuretics (these drugs don't directly affect $Ca_V1.2$ channel activity).

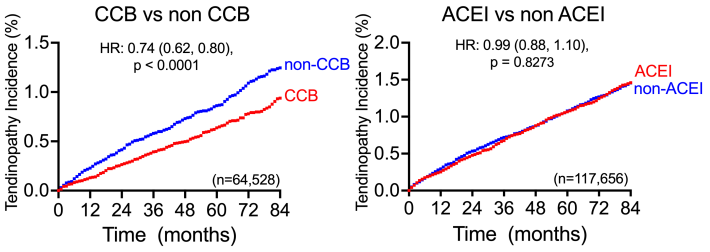

Figure 1. Calcium channel blocker (CCB) therapy, but not angiotensin-converting enzyme inhibitor (ACEI), is associated with the decreased incidence of Achilles tendinopathy in hypertensive patients in a retrospective cohort study using TriNetX network. HR: hazard ratio, 95%CI. p < 0.05 is considered significant.

Discussion: By analyzing the robust TriNetX database we identified a significant correlation between Achilles tendinopathy and HT in the US population. This association is bidirectional, suggesting that there is no cause-and-effect relationship between Achilles tendinopathy and HT, but shared pathological mechanism(s) may underlie both disease development. This is consistent with the hypovascular nature of tendon tissue, therefore, high blood pressure per se is unlikely capable of eliciting tendon pathogenesis directly. Furthermore, we found that pharmacological intervention with CCBs or β-blockers reduces the risk of Achilles tendinopathy in hypertensive patients, which provides clinical insights into the pathological mechanisms of Achilles tendinopathy and suggests that aberrant Cav1.2 expression/activity may be a predisposing factor for future Achilles tendinopathy. A limitation of this study is the lack of information on doses and duration of CCB therapy that hypertensive patients took, which may account for the relatively low effect of CCBs we observed to reduce the risk of Achilles tendinopathy. In addition, it is not known whether CCBs taken by hypertensive patients have reached their therapeutic doses in Achilles tendon to exert maximal inhibition on tendinopathy development given the fact of tendon hypovascularity. Ongoing evaluation of CCB efficacy to prevent Achilles tendinopathy in preclinical mouse models will further define the role of Ca^{2+} signaling via $Ca_V1.2$ in the pathogenesis of Achilles tendinopathy and provide a rationale for repurposing the use of FDA-approved generic CCBs to prevent or treat Achilles tendinopathy.

Clinical Significance: Our study provides clinical evidence, supporting that Ca^{2+} signaling through L-type $Ca_V1.2$ is implicated in Achilles tendinopathy. Our data provide a scientific rationale for repurposing the use of FDA-approved generic CCBs to mitigate Achilles tendinopathy development.

References: 1. Pratt PF, Bonnet S, Ludwig LM, Bonnet P, Rusch NJ. Upregulation of L-type Ca2+ channels in mesenteric and skeletal arteries of SHR. *Hypertension.* 2002;40(2):214-219.