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Abstract

Background and aims: Achilles tendinopathy is common among runners, but the etiology remains unclear. High mechanical pain sensitivity may be a predictor of increased risk of developing Achilles tendinopathy in this group. The purpose of this study was to investigate whether local pain sensitivity could predict the development of Achilles tendinopathy in recreational male runners. The overall hypothesis was that high pain sensitivity would be related to a higher risk of developing Achilles tendinopathy among recreational male runners.
Methods: Ninety-nine recreational male runners were recruited and followed prospectively for 1 year. At baseline and after 500 km of running the pressure pain threshold (PPT) was assessed at the infraspinatus and at the Achilles tendon (AT-PPT). Based on the AT-PPT at baseline, a median split was used to divide the runners into two groups. The high pain sensitivity groups was defined as runners displaying a pain pressure threshold below 441 kPa on the Achilles tendon, while the low pain sensitivity group was defined as runners displaying a pain pressure threshold above 441 kPa on the Achilles tendon, respectively. Subsequently, the cumulative risk difference between the two groups was assessed by using the pseudo-observation method.
Results: High pain sensitivity runners sustained 5%-point (95% CI: −0.18 to 0.08) more Achilles tendinopathy episodes during the first 1,500 km. No significant group differences in risk were found at 100, 250, 500, 1,000 and 1,500 km of running.
Conclusions: No significant association was found between mechanical pain sensitivity in the Achilles tendon and the risk of developing Achilles tendinopathy. However, the risk difference indicated a association between a high mechanical pain sensitivity and an increased risk of developing Achilles tendinopathy. It is plausible that changes in pain sensitivity were masked by unmeasured covariates, such as the differences in progression/regression of training volume and running speed between the two groups. This study was limited in size, which limited the possibility to account for covariates, such as differences in progression/regression of running speed between runners. With the limitations in mind, future studies should control the training volume, speed and running shoes in the design or account for it in the analysis.
Implications: Pain sensitivity of the Achilles tendon seems not to be related to an increased risk of developing Achilles pain in relation to running.

Keywords: pain pressure threshold; runners; injury prevention; injury survival; epidemiology; achilles injury.

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1 Introduction

Runners sustain injuries with overall incidence rates from 7.2 to 17.2 injuries per 1,000 h of running [1].

Achilles tendinopathy constitutes approximately 7% of these injuries [2] but at the age of 45, one in every two have experienced symptoms from the Achilles tendon [3]. The condition, which is difficult to manage where the recovery period may be up to 400 days or more [2] can be precipitated by several factors such as gender (male) [4, 5], running in sand [6], muscle weakness [7], lower limb alignment [7], genetics [7, 8], poor capacity to regulate tendon temperature [7], previous tendon injury [7] and biomechanics [9]. In general, Achilles tendinopathy is related with excessive loading, causing a loss of tissue homeostasis [10], inflammation of the tendon [11, 12] or a combination of both [13] resulting in the rate of stress being greater than the rate of tissue repair [13–15].

Amongst athletes, the training volume seems less important with regard to the risk of injury as opposed to rapid progressions in workload within training sessions which seems to increase injury risk [16, 17]. Therefore, progression in training volume and intensity needs to account for the previous history of training as it determines the load the runner can tolerate [17–19]. This indicates that a mechanical overuse of somatic structures may lead to an injury, potentially explaining why unilateral Achilles tendinopathy increases the risk of sustaining another Achilles tendinopathy on the contralateral side at a later stage [20].

It is possible that the development of overuse injuries in running is related to changes in pain sensitivity [21]; a view that has gained favor in recent years. Emerging evidence suggests that regional and widespread sensitivity of pain mechanisms is increased in individuals suffering from pain from tendons of the lower limb [22] and pain in general [23]. Subjects with Achilles tendinopathy have demonstrated a significantly increased pain sensitivity over the Achilles tendon compared to controls [22]. Based on these findings, it is not possible to determine whether increased pain sensitivity was a cause or an effect of Achilles tendinopathy.

It is well known that exercise can reduce pain by engaging the supraspinal areas involved in endogenous pain inhibition [24, 25] with aerobic exercise showing a moderately acute hypoalgesic response in pain-free populations [26]. It is less known whether high local pain sensitivity can increase the risk of mechanical injury.

The aim of this study was to investigate whether mechanical pain sensitivity in the Achilles tendon can predict the development of Achilles tendinopathy in recreational male runners. The overall hypothesis was that runners with the highest pain sensitivity were more prone to develop Achilles tendinopathy.

2 Materials and methods

2.1 Study design

The RUNning TECHnique study (RUNTECH) was designed as an epidemiological observational prospective cohort study with a 1-year follow-up. Reporting follows the STROBE statement [27]. Ethical approval of the study was granted by The North Denmark Region Committee on Health Research Ethics (N-20130074). The study was approved by the Danish Data Protection Agency. The participants gave informed consent in writing according to the declaration of Helsinki.

Between February and June 2014 99 male runners were recruited in the northern part of Denmark. A flowchart of the study setup has been reported elsewhere [28]. The runners were recruited from local sports clubs, by word of mouth in large companies, hospitals and in a university population. During the 5-month recruitment period, a total of 207 persons volunteered for the study. For inclusion in the study, runners had to: (1) be male between 18 and 60 years, (2) run at least twice a week, and (3) have a minimum of 2 years' running experience. (4) Runners had not sustained injuries within the 3 months prior to completing the baseline questionnaire, and (5) they had to be familiar with treadmill running. Volunteers were not included in the study if they: (1) had no e-mail address or no access to the internet, (2) participated in other sports for more than 4 h a week, (3) were using custom-made insoles while running, or (4) had a previous history of a serious disease, e.g. stroke, heart disease, or chest pain when exercising. Further, volunteers were not included if they were unwilling (5) to run in a neutral pair of running shoes or (6) to use a global position system (GPS) watch or smartphone to quantify the running characteristics.

Following the inclusion, the smartphone or GPS watch of each runner was screened for compatibility with a web-based database (www.mit-loebeprogram.dk), which was used to collect training distance and injury status of the runners. A recruitment questionnaire provided self reported information on the runners BMI and previous injuries.

The runner was equipped with a pair of conventional neutral running shoes (Asics Gel-pulse5; designed with a heel raise, medial arch support and a 12 mm heel to toe drop) and an armband suitable for a smartphone. During the first 500 km, runners were required to run at least twice a week and minimum 10 km each week wearing the running shoes as per above. Apart from this, no restrictions were made with regard to the type of running or pace.

2.2 Pressure-pain thresholds (PPT)

Pressure-pain thresholds (PPT) were determined bilaterally on the Achilles tendon and infraspinatus muscle. For the assessment, a handheld pressure algometer (Algometer®, Somedic, Sweden) with a 1 cm^2 probe (covered by a disposable latex sheath) was used. The pressure was increased gradually (30 kPa/s) until the PPT was reached, which the runner indicated by pressing a button. The PPT was defined to the runner as the very first instance the pressure became painful. The test sites at (1) the midportion of the Achilles tendon (approximately 2–3 cm proximal to the insertion) and (2) the infraspinatus (midpoint between spinae scapulae and margo medialis) were located by manual palpation and marked before starting the measurements. At baseline and follow-up, the measurements were performed three times at all sites and the average value was used for the data analysis.

Based on the assessment of PPT measured at baseline, the right and the left foot of each runner were categorized into one of two Achilles tendon pressure threshold groups, separated by the median into low pain sensitivity PPT group and high pain sensitivity PPT group, respectively.

2.3 Outcome

The outcome of interest was the first Achilles tendinopathy during follow-up. All other injuries were considered competing risk injuries [29]. An injury was defined as absence from running for minimum one week due to a musculoskeletal complaint in the lower extremity or the spine caused by running. Runners received a weekly email containing a link to a web-based questionnaire for reporting of injury status. If runners reported an injury during the follow-up period, they attended a clinical examination performed by a sports physiotherapist or sports physician. If necessary, equipment such as ultrasound and color Doppler was available to verify the injury type [30, 31].

An injury was classified as either Achilles tendinopathy, running-related injury, an injury from other sports or an acute injury. Only diagnoses sustained from running, in combination with running or influencing the running exposure were included in the analysis.

2.4 Assessment of running distance

Duration scale was running distance. Runners were to upload the running distances collected by their smartphones or GPS watches to a personal running diary at www.mit-loebeprogram.dk. In case of missing GPS data, runners were to recall the time spent running and the distance covered and upload this information manually [32].

2.5 Statistics

Differences in PPT values between runners reporting no running-related injuries (no RRI), running-related injuries (RRI) and those sustaining Achilles tendinopathy from baseline to post-test period were estimated using a two-tailed pairwise *t*-test analysis. Changes in PPTs were used to describe the effect of RRI on the specific injured area compared with a reference area. Kilometer to first injury was analyzed using the cumulative running distance as duration scale. The Nelson-Aalen cumulative hazard curve was used to visualize the injury proportion as a function of running distance. Runners were right-censored in case of disease, lack of motivation, non- running-related injury causing a permanent stop of running or end of follow-up after 1 year. Generalized linear regressions using the pseudo-observation method were used to assess the cumulative risk difference (absolute difference) in Achilles tendinopathy across the PPT groups [33]. Here, the cumulated risk difference was the difference in incidence rate at a given time point between the high and low pain sensitive runners [34]. Right censoring accounted for the runner leaving the study without Achilles tendinopathy, by including their running distance in the analysis. In case they sustained another type of an injury, a model on cause-specific hazards of two endpoints (Achilles tendinopathy and another injury) was calculated as competing risks [29]. The pseudo-observation method also allows correction for a possible dependency between the two legs by clustering the individual runner as one cluster with two legs [33]. When one leg sustained an injury, the contralateral leg was still monitored until the end of follow-up, censoring or injury. In case of too few injuries occurring in the cohort, sensitivity analyses were performed using a bootstrap with 50 replications of the data to confirm the confidence intervals range [35, 36]. All statistical analyses were performed using Stata Version 14 (StataCorp LP, College Station, TX, USA). A p-value < 0.05 was considered statistically significant.

3 Results

Out of the 207 runners volunteering for the study, 99 were included. One runner was excluded prior to analysis

because the PPT data were lost, leaving a sample of 98 runners available for the data analysis. The runners were separated by the median giving low sensitivity runners displaying a pain pressure threshold above 441 kPa on the Achilles tendon, while the high sensitivity runners were below this median. Demographics of runners can be seen in Table 1. Table 1 reveals that age (p-value: 0.001) and the average amount of kilometers run per week in the previous 3 months (p-value: 0.04) were higher in the low pain sensitivity group. BMI and previous injuries were not significantly different between the two groups although previous injuries trended towards being more frequent in the low pain sensitivity group (p-value: 0.084). The 99 runners ran in total 72.076 km until injury or censoring. On average, runners with high mechanical pain sensitivity and low mechanical pain sensitivity ran 750 km (95% CI: 627–872) and 1,050 km (95% CI: 867–1234), respectively, over the 1-year period. Thirty-two runners reported a running-related injury at the 1-year follow-up. After 1,500 km, 10 runners had sustained AT injuries, of which two were bilateral, resulting in a total of 12 Achilles tendinopathy.

3.1 Pressure pain threshold characteristics and risk of injury

Table 2 shows the mechanical pain sensitivity at baseline and after 500 km of running at the infraspinatus and the Achilles tendon. A two-tailed pairwise t-test analysis demonstrated that runners sustaining Achilles tendinopathy during the follow-up exhibited a significant increase in the PPT value of the Achilles tendon (198 kPa; 95% CI: 1–397 kPa). No significant changes were found for infraspinatus (Table 2). Survival analyses for the two groups performed at 100, 250, 500, 1,000, and 1,500 km, respectively, showed no significant risk differences between groups (See Fig. 1 and Table 3). After 1,500 km of running, seven injuries were sustained in the high pain sensitivity group and four incidences occurred in the low pain sensitivity group. Hign pain sensitivity runners sustained 5%-point (p-value: 0.47; 95% CI: −0.08 to 0.18) more Achilles tendinopathy during the first 1,500 km. The differences in risk between the two groups at 100, 250, 500, 1,000 and 1,500 km of running were non-significant. The bootstrap sensitivity analyses confirmed the confidence interval and did not change the risk differences.

4 Discussion

In this study, we hypothesized that runners with the highest pain sensitivity were more prone to develop Achilles tendinopathy. Our hypothesis was not confirmed, although the risk difference indicated the high mechanical pain sensitivity runners were at increased risk (non-significant) of developing Achilles tendinopathy as hypothesized. Moreover, an exploratory analysis identified runners developing Achilles tendinopathy to increase their pain sensitivity after being recovered from the injury.

4.1 Pain sensitivity as a predictor for running-induced Achilles tendinopathy

In the current study, no relationship was found between the mechanical pressure pain sensitivity and injury incidence when comparing groups with low and high pain sensitivity assessed from the Achilles tendon.

Widespread sensory deficits have been described in patients with unilateral tendon pain and disability [23], implicating central changes in the processing of nociceptive afferent signals. It is worth considering that compared with controls individuals with chronic Achilles tendinopathy have been shown to have less active conditioned pain modulation [22]; a brainstem-mediated mechanism [37]

Table 1: Characteristics of the participants in each of the two PPT groups measured at baseline.

	High pain sensitivity (99 legs)	Low pain sensitivity (97 legs)	p-Value
Age (years; mean ± sd)	35 ± 11	40 ± 9.8	0.001[a]
BMI (kg/m^2; mean ± sd)	24 ± 2.8	24 ± 2.3	0.86
Km per week (mean ± sd)	27 ± 23	32 ± 16	0.04[a]
Previous injuries (y/n/?)	52/46/1	63/31/3	0.084
Achilles Tendon pre (kPa; mean ± sd)	331 ± 68	635 ± 152	0.000[a]

Km per week is defined as kilometers ran per week averaged across the 3 months prior to the follow-up. Previous injuries are defined as musculoskeletal complaints related to running. The median cut-point separating the groups were 441 kPa. The p-values represent the statistical significance level of each test; in case of continuous data, a t-test was used and a χ^2 (R × C) tests were used in categorical data.
[a]Significant results.

Table 2: Development in PPT between groups from pre to post.

Injury	Mean PPT (kPa) pre	Mean PPT (kPa) post	Pain sensitivity difference (AT-PPT (kPa))	95% Confidence interval	*P*>|z|
Within stratum: Achilles tendon (kPa)					
No injury (*n* = 114 legs)	501	493	−7	−60 to 45	0.79
Other lower limb injuries (*n* = 21 legs)	525	544	20	−103 to 143	0.75
Achilles tendinopathy (*n* = 8 legs)	375	572	198	1–397	0.05[a]
Within stratum: Infraspinatus (kPa)					
No injury (*n* = 114 legs)	559	539	−20	−22 to 61	0.99
Other lower limb injuries (*n* = 21 legs)	574	570	−4	−142 to 150	0.99
Achilles tendinopathy (*n* = 8 legs)	480	540	60	−371 to 251	0.99

The mechanical pain sensitivity at baseline (pre) and after 500 km of running (post) in infraspinatus and Achilles tendon between runners reporting no running-related injuries (no RRI), running-related injuries (RRI) and those sustaining Achilles tendinopathy during follow-up. Only injuries developed before the 500 km examination was included. The mean difference in PPT from pre to post was estimated using a two-tailed pairwise *t*-test. *p*-Value was considered significant below 0.05. [a]Significant results.

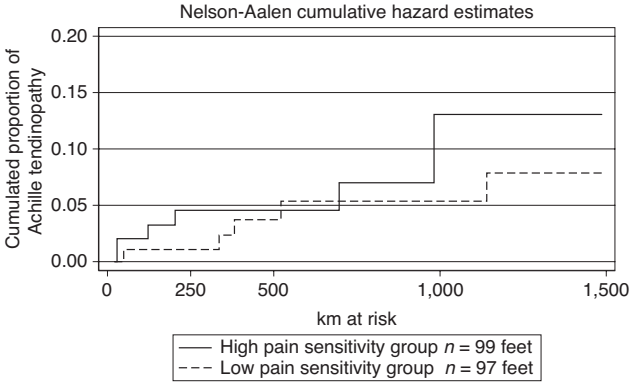

Fig. 1: The figure illustrates differences in the development of Achilles tendinopathy between the low and high pain sensitivity group during the follow-up period. On the y-axis the cumulated proportion of Achilles tendinopathy is illustrated, while the running distance in kilometers are on the x-axis. High pain sensitivity group: runners displaying a pain pressure threshold below 441 kPa on the Achilles tendon; Low pain sensitivity group: runners displaying a pain pressure threshold above 441 kPa on the Achilles tendon.

responsible for the endogenous modulation of peripherally driven nociceptive signals. Along these lines, similarities in pain modulation have been found when comparing exercise-induced hypoalgesia with conditioned pain modulation [38]; a mechanism also related to the endogenous opioid and non-opioid systems [39]. It is interesting that a chronic training load as in the current study, did not affect the pain sensitivity similar to what is seen when acute exercises are induced [40]. In this study, an Achilles tendinopathy reduced the mechanical pain sensitivity in the Achilles tendon continuing after the runners had recovered from the Achilles tendinopathy (Table 2). The reason for this is unclear but it may relate to an adaptive response where the pain sensitivity is reduced, as part of the recovery process; a change that may slowly regress towards the baseline pain sensitivity [41].

High pain sensitivity was not identified to be related to the development of Achilles tendinopathy, indicating that Achilles tendinopathy may occur regardless of the

Table 3: Cumulative risk differences (RD) for Achilles tendinopathy according to PPT values at the Achilles tendon.

Analysis time	PPT	Number of feet remaining	Number of Achilles tendinopathy	Risk difference (%-point)	95% Confidence interval	*P*>|z|
100 km	High pain sensitivity	99	2	0.001	−0.035 to 0.05	0.675
Ref	Low pain sensitivity	97	1			
250 km	High pain sensitivity	86	4	0.03	−0.02 to 0.09	0.807
Ref	Low pain sensitivity	89	1			
500 km	High pain sensitivity	58	4	0.008	−0.06 to 0.07	0.807
Ref	Low pain sensitivity	63	3			
1,000 km	High pain sensitivity	31	7	0.07	−0.05 to 0.19	0.248
Ref	Low pain sensitivity	43	4			
1,500 km	High pain sensitivity	14	7	0.05	−0.08 to 0.18	0.467
Ref	Low pain sensitivity	25	5			

The risk differences between the two groups are reported at 100, 250, 500, 1,000 and 1,500 km, respectively. Risk difference is a measure of the absolute difference in risk (%-point) between the High pain sensitivity and Low pain sensitivity groups.

sensitivity of pain mechanisms. However, it is important to note that pain does not equate to tissue damage as the perception of pain is thought to occur secondary to a sense of threat to the person, determined via multiple interacting domains including biological, psychological and social factors [42, 43]. In the context of this current study, it is therefore possible that runners with high mechanical pain sensitivity may have reported an injury at the slightest perception of pain whereas runners with low mechanical pain sensitivity may have continued their running beyond the point where they perceived pain; a behavior which may be related to the competitive nature of the individual runner [44]. It is therefore reasonable to posit that pain from a noxious input could be secondary to a tissue overload with or without hypersensitivity of the Achilles tendon [45] but an appropriately designed study would be needed to determine whether this was the case in this cohort.

4.2 Load management during running

Managing the load during running is important to prevent an injury [16, 46] and requires a delicate balance between how much load is prescribed and how much load each structure can withstand before failure [17, 46, 47]. The load management may be affected by the mechanical pain sensitivity in each structure by changing the capacity to withstand the load applied to the structure. For example, low mechanical pain sensitivity in the Achilles tendon may increase the amount of load the structure is able to withstand without sensing pain, compared with high mechanical pain sensitivity. One explanation for the lack of findings in the present study may relate to different strategies for load management. The weekly training program varied between runners and runners were not managing the applied load in a similar manner. This may have introduced a source of bias as runners with lower pain sensitivity on average ran 1,050 km during the period, and the high pain sensitivity runners covered an average of 750 km in the same period. In future studies it will be necessary to control the management of load and volume of running.

The importance of identifying the range of progression has been demonstrated in e.g. team handball where the increased weekly progression of training increased the risk of shoulder related injury [48]. Moreover, the rate of progression of 20% increased the risk of shoulder-related injury the same as in handball players with and without normal scalpular function. However, a rate of progression in weekly training load between 20% and 60%, were increasing the risk of shoulder related injury in handball players with scalpula dyskinesia, while reducing the risk of shoulder related injury in handball players with a normal scalpula function. Based on these findings, it is plausible that runners with a high mechanical pain sensitivity are at increased risk of developing Achilles tendinopathy at a lower progression compared to runners with a low mechanical pain sensitivity.

4.3 Limitations and methodological considerations

The present study has several strengths and limitations. The prospective design of the study employing GPS data for activity tracking, the clinical assessment as well as clinically diagnosing each injured runner improved the study's quality and face validity. However, a limitation to our study is that at least 10 injuries per variable are needed to establish robust models for estimating the injury risk [49].

Initially, the statistical model was meant to account for progression or regression in the training load but due to the few injuries that occurred, this was not possible. This may be one of many important factors to account for as mechanical pain sensitivity in the Achilles tendon may relate to the risk of Achilles tendinopathy within a certain range of progression. Moreover, the timescale in the present study was kilometers at risk whereas some studies indicate that Achilles tendinopathy is more related to sudden increases in running speed than the distance of running [50–52].

Participating in the study required the runners to wear shoes that were different from those they normally ran in. This may have caused biomechanical changes of e.g. loading of the Achilles tendon as shoes with a smaller heel-to-toe drop and flatter shoe-sole construction increases the ankle flexion moment [53, 54], which among other things may increase the loading of the Achilles tendon and plantar fascia. Allowing the runners to use their own footwear could have bypassed this factor.

With the limitations in mind, future studies should control the training volume, speed and running shoes in the design or account for it in the analysis.

5 Conclusion

With the limitations discussed, this study did not demonstrate a link between mechanical pressure pain sensitivity assessed over the Achilles tendon and an increased risk

of Achilles injury in recreational male runners. However, the risk difference indicated an association between a high mechanical pain sensitivity and an increased risk of developing Achilles tendinopathy.

Authors' statements
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Informed consent: Informed consent was obtained from all participants.
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