INTRODUCTION

Tendinopathies are a commonly occurring clinical problem in sports, which are characterized by chronic tendon pain and impaired functionality. Effective treatment options are difficult to develop, because etiology and progression of this disorder are still poorly understood. For many years, the disease, which is characterized by chronic tendon pain and impaired function, was considered to be mainly degenerative. However, recent research indicates that chronic inflammation may be a feature of Achilles tendinopathies.

For many years, tendinopathies were considered to be mainly degenerative. However, recent research indicates that chronic inflammation may be a feature of Achilles tendinopathy. Thus, the aim of this study was to investigate, if plasma levels of the inflammatory cytokine interleukin-6 (IL-6) are elevated in patients with chronic Achilles tendinopathy and if IL-6 levels are affected by physiotherapeutic treatment, duration of symptoms or anatomical localization. Male patients with chronic insertional (n = 16) or mid-portion (n = 15) Achilles tendinopathy were subjected to a physiotherapeutic intervention for 12 weeks. VISA-A scores and blood plasma IL-6 levels were determined before and after the intervention. From pre to post, VISA-A scores (57 ± 13 to 74 ± 18 points) increased while mean plasma IL-6 levels decreased significantly (2.5 ± 1.6 to 1.9 ± 0.7 ng/L). Patients with insertional did not significantly differ from patients with mid-portion Achilles tendinopathy. Of all investigated parameters, pre- and post-IL-6 levels correlated weakly with age only (r = 0.388 and r = 0.389). In a subgroup of patients, inflammation appears to play a role in the context of Achilles tendinopathies, making IL-6 a potential target for therapeutic interventions in this subgroup. Common factors leading to elevated IL-6 levels need to be identified in future studies.

KEYWORDS
Achilles tendinopathy, cytokines, exercise treatment, inflammation, non-steroidal anti-inflammatory drugs
the concentration of IL-6 has been found to increase dramatically in the peritendinous tissue around the Achilles tendon following running exercise. In vitro, IL-6 gene expression increased 16-fold upon cyclical loading of isolated tendon fascicles, being accompanied by a twofold increase in collagen I expression in bovine tendon. Since collagen I is the main constituent of tendon tissue and responsible for its tensile strength, this suggests that IL-6 may also play a role in the tendon’s structural adaptation to exercise. Indeed, IL-6 has been shown to stimulate collagen synthesis in human Achilles tendon, with infusion of recombinant human IL-6 in the peritendinous tissue of the Achilles tendon leading to increased levels of the procollagen type I N-terminal propeptide, a marker for collagen synthesis.

However, in contrast to short-term peaks in IL-6 levels possibly promoting structural adaptation in conjunction with the tendon’s response to exercise, long-term exposure to elevated IL-6 levels may be less beneficial. Chronically elevated IL-6 levels caused by regular injections of IL-6 in the peritendinous tissue around the rat Achilles tendon for 8 weeks led to a reduction in collagen I expression.

It remains to be established if chronic tendinopathy leads to chronically elevated levels of IL-6 which are measurable in the patients’ blood plasma and could thus be used as a Biomarker, and in addition, if those levels are affected by treatment. Furthermore, it remains to be established if the anatomical localization of the tendinopathy is associated with different levels of inflammation. It has already been described that different tendinopathic tendons show dissimilar changes in gene expression patterns (Achilles vs posterior tibialis tendon) and dissimilar changes in mechanical and material properties (Achilles vs Patellar tendon). It seems thus conceivable, that even within one tendon the different anatomical localization of the tendinopathy (mid-portion vs insertional) may be associated with different underlying pathophysiologies, and thus different cytokine levels.

The aim of this study was therefore to investigate blood plasma IL-6 levels in patients with chronic Achilles tendinopathy, hypothesizing that IL-6 levels are elevated with tendinopathy and that they are affected by physiotherapeutic treatment and anatomical localization of the tendinopathy.

## Materials and Methods

We recruited 43 male patients, aged between 20 and 55 years, with chronic Achilles tendinopathy (diagnosis verified by a medical doctor via ultrasound) and a VISA-A score lower than 80 points, suffering from tendon pain for at least 3 months (Table 1). During anamnesis by the medical doctor, potential subjects were questioned about patient history to exclude systemic diseases. Exclusion criteria were corticosteroid injections within the last 12 months prior to the study, antibiotics intake (particularly fluoroquinolone), surgery of the lower extremities, chronic inflammation, or systemic disease such as diabetes, gout, spondylitis, and arthritis. The study was approved by the Charité University hospital ethics committee (EA1/142/15) and performed in compliance with the Declaration of Helsinki. Written informed consent was obtained from the participants.

The patients were subjected to a 12 week long physiotherapeutic intervention. All patients received a standard prescription of passive manual therapy, which entitled them to utilize up to 12 sessions with a physiotherapist of their choice. The content of the physiotherapy sessions depended on the individual physiotherapist and was documented in a training diary. The applied physiotherapy consisted mainly of massage, mobilization of soft tissue and joints, and to a lesser extent of friction and electrical stimulation. In addition, some of the patients were instructed to engage in active physiotherapeutic exercises, which they performed self-organized at home, while recording their activities in their training diary: a randomly chosen third of patients performed eccentric exercises according to the Alfredson protocol, consisting of three sets of 15 heel drops with bended and three sets of 15 heel drops with straight knee performed twice daily; a randomly chosen second third of patients performed heavy slow resistance training of the plantar flexors, consisting of five series of four isometric plantar flexions (four times per week) with 90% of the maximum voluntary contraction held for 3 seconds with 3 seconds rest between repetitions. All physiotherapeutic treatment approaches were equally effective in reducing tendinopathy symptoms; thus, the pre- to post-intervention analysis did not distinguish between different treatment approaches.

At baseline, most of the patients actively engaged in regular exercise activities, on average 6.3 ± 4.0 hour per week.
such as cycling and running. During the intervention period, the patients were allowed to continue with their normal exercise routine, as long as the pain during activity did not exceed level three on a numeric rating scale. The patients recorded their exercise activity daily in a training diary.

Before and after the intervention, VISA-A scores were determined and venous blood samples were taken to establish blood plasma IL-6 levels. Patients were advised not to train or to engage in any intense exercise activity before blood sampling, while they were allowed to walk or to cycle to the surgery. Blood samples were collected in LI-Heparin plasma Vacutainer tubes (5 mL), centrifuged (15 minutes) and directly analyzed. IL-6 levels were established applying the quantitative electrochemiluminescence method (ECLIA) (Roche Diagnostics) using a COBAS 8000 modular analyzer series (Roche Diagnostics) according to the manufacturer's instructions. The limit of detection was <1.5 ng/L. A study investigating the variability of IL-6 plasma levels estimated an intra-class correlation coefficient of 0.87 for one measurement and concluded that obtaining a single sample from a healthy subject would be fairly representative of that individual's level over an extended period of time.21

In seven patients, the post-intervention blood sample could not be obtained (eg, patients missed appointments or surgery closed during holidays). Blood samples from patients who had an orthopedic injury (n = 1) or an infection (n = 4) within the last 2 weeks prior to blood sampling were excluded from the analysis. Subtracting dropouts and exclusions, values of 16 patients with insertional and 15 patients with mid-portion tendinopathy were analyzed for this study.

### 2.1 Statistical analyses

For statistical analysis, SPSS statistics 22 was used. To test for differences between physiotherapeutic approaches regarding their effect on VISA-A scores and IL-6 levels, a one-way ANOVA with a Bonferroni post hoc analysis was used. To compare pre- and post-VISA-A scores as well as pre- and post-IL-6 levels, the non-parametric Wilcoxon signed-rank test was used. To compare patients with insertional to patients with mid-portion tendinopathy and to compare patients with rising IL-6 levels with patients with steady or dropping IL-6 levels, the Mann-Whitney U test was applied. To establish relationships between parameters, the Pearson correlation coefficient was calculated. Correlations below 0.4 were qualitatively interpreted as weak. For all statistical tests, significance was established at \( P < 0.05 \).

### 3 RESULTS

We could not detect any significant differences regarding the effect of the different treatment approaches in terms of VISA-A scores or IL-6 levels. As a consequence, the presented results on the effect of time (pre to post) and anatomical localization (mid-portion vs insertional) do not differentiate between different treatment approaches. Patients with insertional did not significantly differ from patients with mid-portion Achilles tendinopathy in any of the investigated parameters (Table 1 and Figure 1).

Overall, VISA-A scores significantly \((P < 0.001)\) increased from 57 ± 13 to 74 ± 18 points and plasma IL-6 levels significantly \((P < 0.05)\) decreased from 2.5 ± 1.6 to 1.9 ± 0.7 ng/L from pre- to post-measurement (Figure 1).

In 14 patients (nine insertional and five mid-portion), IL-6 levels decreased from 3.5 ± 1.9 to 1.9 ± 0.8 ng/L, in seven patients (one insertional and six mid-portion) IL-6 levels did not change (1.7 ± 0.5 ng/L) and in 10 patients (six insertional and four mid-portion) IL-6 levels increased from 1.7 ± 0.5 to 1.9 ± 0.6 ng/L. Comparing patients with dropping IL-6 levels

![Figure 1](attachment:image.png)
to patients with steady or rising IL-6 levels, pre-VISA-A scores were similar (57 ± 12 and 57 ± 14 points, respectively) and the patients did not significantly differ in any of the investigated parameters. However, post-VISA-A scores tended (P = 0.084) to be lower in the group with dropping IL-6 levels (70 ± 15 points) compared to the other patients (78 ± 19 points).

Pre- and post-IL-6 levels correlated weakly but significantly (P = 0.031) with patients age (r = 0.388 and r = 0.389, respectively), while no correlations were detected between any of the other measured parameters such as duration of symptoms, height, body weight, or exercise activity (Figure 2).

4 | DISCUSSION

Inflammation appears to play a role in the context of Achilles tendinopathies in some patients. In agreement with our hypothesis, mean IL-6 levels were elevated with tendinopathy and dropped with treatment and an improvement of symptoms. With 1.9 ng/L postintervention, plasma IL-6 concentration had returned to levels similar to those which had been established in a healthy reference population (1.89 ng/L) of 125 healthy subjects with a mean age of 49 years.22 However, our data emphasize that the IL-6 response was not homogenous since IL-6 levels were elevated in some but not all patients with Achilles tendinopathy. This subgroup of patients with elevated IL-6 levels appeared to respond less well to physiotherapeutic treatment, as their post-VISA-A scores tended to be lower compared to the other patients. Inflammatory processes such as increased levels of IL-6 may be a potential target for therapeutic interventions in this subgroup.

Our study indicates that in the future it may be possible to use IL-6 as a Biomarker to identify patients in which low-grade inflammation may be involved in the representation of tendinopathy. Systemically elevated plasma IL-6 levels have been used in the context of other diseases to predict a poor clinical outcome.23 Higher circulating levels of IL-6 have even been associated with an increased risk of mortality in a diseased24 or healthy elderly population.25 Still, even if elevated IL-6 levels are detected in a patient, it has yet to be determined, if this finding should be interpreted as a surrogate marker, not warranting the treatment of inflammation, or if inflammation should be targeted. Targeting inflammation could then be accomplished by either treating inflammation in general, using, for example, non-steroidal anti-inflammatory medication, or selectively by blocking IL-6 or its receptor directly.2

There is no consensus if targeting inflammation in Achilles tendinopathy with a generalized approach using non-steroidal anti-inflammatory medication (NSAIDs) is an effective form of treatment. Short-term treatment as for example one week ibuprofen intake did not affect pain at rest26 or during running.8 Even treatment over several weeks investigated in a randomized controlled trial with 70 patients suffering from Achilles tendinopathy did not lead to any difference in terms of pain and function between the piroxicam and placebo-treated group.27 However, in a smaller study with 19 patients a topically applied diclofenac gel led to reductions in Achilles tendon pain during loading whereas a placebo gel did not.28
Differences in the effectiveness of NSAIDs on pain reduction in these studies may be related to the different active substances or the form of application. Another explanation may be that as in our study only a proportion of the analyzed population may have suffered from inflammatory responses and that NSAID treatment only had an effect in this specific subgroup.

In spite of possible positive effects on short-term pain control, the question yet remains if long-term the suppression of the inflammatory response may negatively affect tendon healing and thus contributes to the progression of tendinopathy.\(^3\) \(^2\) Despite on gene expression level, one week of NSAID treatment had no effect on collagen I gene expression in tendinopathic tissue at rest\(^2\) \(^6\) and after exercise,\(^8\) NSAID intake abolished the exercise-induced increase in collagen I synthesis in healthy human tendon.\(^3\) \(^0\) This suggests a reduced adaptive capacity which is likely to be disadvantageous for the healing process, particularly since exercise treatment is considered to be an effective form of treatment achieving good clinical results.\(^3\) \(^1\) \(^3\)

To be able to recommend or to advise against treatment of inflammation and particularly the suppression of raised IL-6 levels in tendinopathic patients, a better understanding of cause and effect of its induction in tendinopathic tendon may help. Thus, one aim of our study was to identify common factors which were associated with elevated IL-6 levels. Age was the only covariate that correlated weakly with pre- and post-IL-6 levels. While the cause of age-related changes in plasma IL-6 levels remains unclear, weak associations \((r = 0.28)\) were also found in a group of 55 healthy adults between 26 and 75 years of age.\(^3\) \(^\text{33}\) This correlation was mainly based on a significant IL-6 increase in the male population, as levels did not increase significantly in the female population.\(^3\) \(^\text{33}\) Higher IL-6 levels have also been detected in the healthy elderly when subjects over 80 years of age were compared to 71- to 72 year-olds. And again, male sex was associated with higher IL-6 levels.\(^2\) \(^5\) However, raised IL-6 levels may not be associated with age itself but with underlying comorbidities or with age and sex-linked habits. Greater IL-6 levels in these healthy elderly subjects were also associated with cigarette smoking, greater body mass index, and history of cardiovascular disease.\(^2\) \(^5\) The fact that IL-6 levels are not necessarily raised with age and are rather associated with age-related disease is underlined by a study detecting no difference in plasma IL-6 concentration between young adults (mean age 26 years) compared with healthy normoxic elderly (mean age 83 years), while older people (mean age 85 years) with hypoxia, defined as a oxyhemoglobin saturation lower than 95%, represented with significantly elevated IL-6 levels.\(^3\) \(^4\)

In contrast to our expectations, IL-6 levels were neither differentially affected by anatomical localization of the tendinopathy nor associated with factors such as the duration of symptoms or exercise activity. While acute exercise has repeatedly been shown to induce a rapid rise in plasma IL-6 concentration followed by a similarly rapid decline upon cessation of the exercise (see \(^3\) \(^5\) for review), long-term higher exercise activity does not appear to lead to constantly elevated IL-6 levels even in patients with tendinopathy. Furthermore, it has been discussed, that inflammation may predominantly play a role in the early stages of tendinopathy.\(^4\) It appears though, that once the tendinopathy has become chronic and patients are suffering from it for more than 3 months, in terms of low-level inflammation it does not make a difference if the tendinopathy is persisting for months or years.

A limitation of this study is that the content of the treatment varied between patients and that the patients performed different forms of active physiotherapeutic exercises at home. While this reflects current clinical practice, different therapeutic approaches may affect tendon healing differently. However, VISA-A score improvements were similar, irrespective of the applied treatment approach, indicating a comparable therapeutic effectiveness regarding tendinopathic symptoms. With VISA-A score improvements of 14 points in the passive physiotherapy group, 16 points in the group performing additional eccentric exercises and 22 points in the group which performed additional heavy slow resistance exercises the improvements were comparable to a previous study, which reported improvements of 14 points after eccentric training and 22 points after heavy slow resistance training.\(^3\) \(^6\) Similarly, this study did not detect differences in the clinical outcome irrespective of the applied physiotherapeutic approach.\(^3\) \(^6\)

Another critical point is the biological variability of the IL-6 blood plasma levels. Although a single blood sample may be sufficient to indicate a general effect in a pilot study,\(^2\) \(^1\) for a more accurate description of the intervention associated IL-6 kinetics, better accounting for the biological variability, repeated blood samples are recommended.\(^3\) \(^7\) Furthermore, the investigation of additional biomarkers in the blood plasma, hinting on acute or chronic disease, may help to identify other factors leading to fluctuation in IL-6 levels. This would allow to better distinguish between intervention related and unrelated effects while also leading to a more precise description of the patient characteristics.

## Perspectives

Our study highlights the importance of taking more cofactors into account when trying to uncover the reasons for the highly individual representation of tendinopathies. Inflammation appears to play a role in the context of Achilles tendinopathies in some patients, making IL-6 a potential target for therapeutic interventions in this subgroup. Future studies...
may show if NSAIDs are effective in the treatment of pain in tendinopathic patients presenting with elevated IL-6 levels and if suppression of the proinflammatory response will promote the healing process.

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CONFLICTS OF INTEREST

In accordance with ethical obligations as researchers, the authors report no conflicts of interest that may affect the research reported in the enclosed paper. We declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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