Sodium MRI Predicts the Macromolecular Changes in Achilles tendon after Ciprofloxacin Administration

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Abstract. *The aim of this study was to determine if quantitative magnetic resonance (MR) imaging techniques (sodium MR imaging) could be used as potential markers for biochemical changes in the Achilles tendon induced by ciprofloxacin intake. The results demonstrated a ciprofloxacin-induced reversible reduction of the normalized sodium MR imaging signal in the Achilles tendon of healthy volunteers. Changes in sodium MR imaging in men may reflect a decrease of GAG content in the Achilles tendon after ciprofloxacin intake.*

Keywords: Sodium MRI, ciprofloxacin, MRI, glycosaminoglycan

1. Introduction

Fluoroquinolones (FQs) are frequently prescribed antibiotics and they are well established in both inpatient and outpatient settings for urinary and respiratory tract infections and skin, bone, joints, abdominal, and gastrointestinal infections [1]. In addition to gastrointestinal, central nervous system, and skin adverse effects, and prologantion of the QT interval prolongation, cumulative evidence suggests that FQ might be associated with Achilles tendinopathy [2, 3]. The occurrence of FQ-associated tendinopathy seems to be dose independent, and some risk factors were described in patients who develop FQ-related tendinopathy: age older than 60 years, (additional) glucocorticoid or immunosuppressive therapy, and renal failure [4]. However, cases of FQ-associated tendinopathy in the absence of these risk factors were described. Symptoms of tendinopathy include acute onset of tendon pain, tenderness, and swelling that affects the function of the tendon.

Because the biochemical composition of the Achilles tendon is closely related to its function, and biochemical alterations precede morphologic changes, the detection of biochemical changes can help elucidate the risk of developing tendinopathy. Pathologic alterations include an increase in the amount of glycosaminoglycans (GAGs), which is also accompanied by an increased sodium concentration. For proteoglycans, the sulfate and carboxyl groups associated with GAGs predominate, and they provide proteoglycans with a net negative charge. These negatively charged molecules preferentially attract positive counter ions. Recently, several MR imaging methods were introduced that are capable of noninvasive evaluation of the ultrastructural composition of the Achilles tendon. The similar principle of the direct proportion of the sodium ions and GAG content as known in cartilage was used to investigate the increase of GAG content in Achilles tendinopathy [5]. In addition, this method offers the opportunity to assess changes in the sodium concentration of the cartilage.

The aim of this study was to determine whether quantitative MR imaging technique (sodium MR imaging) could be used as potential markers for biochemical changes in the Achilles tendon induced by ciprofloxacin intake.

2. Subject and Methods

Patients

The ethics committee of the Medical University of Vienna approved the protocol (ethics committee number 1225/2012), and all subjects gave written, informed consent. Seven healthy men (mean age, 32 years ± 12 [standard deviation]) were recruited by advertisement in the public areas of the Medical University of Vienna between September 2012 and September 2013 and were included in our prospective study, and both ankles were measured. Exclusion criteria were as follows: known allergy against antibiotic agents; history of tendinopathy, tendon rupture, or joint diseases; and heavy exercise, which was defined as engaging in physical activity or sports for more than 3 hours per week. All patients underwent MR imaging at three time points: at baseline, at 10 days, and at 5 months after ciprofloxacin intake (1000 mg/day in two doses - 500 mg in the morning and 500 mg in the evening for 10 days). The first ciprofloxacin dose was taken after the baseline MR examination, and the last dose in the morning before the second MR examination.

MR Examination

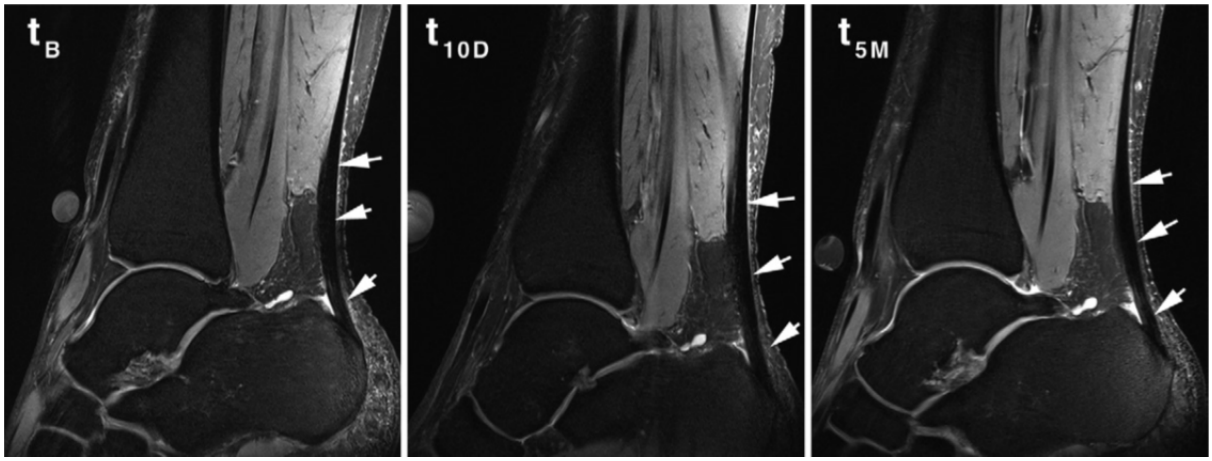

Fig. 1. Morphologic image of a patient at baseline before ciprofloxacin intake (t_B), 10 days after ciprofloxacin intake (t_{10D}), and at the 5-month follow-up examination (t_{5M}). There were no significant morphologic changes observed in any of the patients at 10 days and 3 months after ciprofloxacin intake (arrows show the top, middle, and bottom tendon parts, which are the insertion, mid portion, and musculotendinous junction, respectively).

All participants underwent MR examinations on a 7-T investigational MR unit (Siemens, Erlangen, Germany) with a 28-channel knee coil (Quality Electrodynamics, Mayfield Village, Ohio) for proton imaging and a 15-channel knee coil (Qed; Quality Electrodynamics) for sodium imaging. Morphologic imaging sequences and collagen- and GAGspecific MR imaging methods were used. Morphologic assessment was determined with a sagittal intermediateweighted turbo spin-echo sequence with fat saturation by using the Vienna Morphologic Achilles Tendon Score. This score is based on four characteristics of the Achilles tendon (thickness, continuity, signal intensity, and associated pathologies), and the scores from 0 to 100, with 0 being the worst and 100 being the best. For sodium imaging, the variable echo-time sequence adapted to x-nuclei capabilities was used. In the interest of time, the two-dimensional mode with three sections was used, and the echo time was 2.45 msec.

Data Processing

MR imaging parameters were calculated with a manually drawn region-ofinterest (ROI) analysis in the three regions of the Achilles tendon (insertion, middle, and muscle-tendon

junction; Fig 1). ROIs were drawn on two and three consecutive sections for sodium images. The length of each of the parts was defined as a third of the total Achilles tendon length, measured from the most proximal to the most distal. Values were also recorded for the sum of all three regions, hereafter referred to as the whole tendon. The sodium signal was normalized by the signal from the reference tube measured along each ankle with a known sodium concentration.

Statistical Analysis

All statistical calculations were performed by using statistical software (SPSS version 21.0, SPSS, Chicago, Ill; pROC version 1.5.4 of R Statistical Package, R Foundation, Vienna, Austria). Descriptive statistics were performed to calculate the mean and standard deviation of age and normalized sodium signal in the Achilles tendon and cartilage separately for various time points. To compare average normalized sodium signal in different ankles (right and left), we used a repeat-measure analysis of variance. The longitudinal aspect was modelled by using time points as level 1 and laterality as level 2 nested within individuals (level 3) and by modelling covariance structures. We also applied a diagonal, unstructured first-order autoregressive covariance matrix but presented only the results from the unstructured covariance matrix as it provided the best model fit. The relationship among three variables (MR parameter, time points, and laterality) is referred to as interaction. A P value equal to or below .05 was considered to indicate statistically significant results.

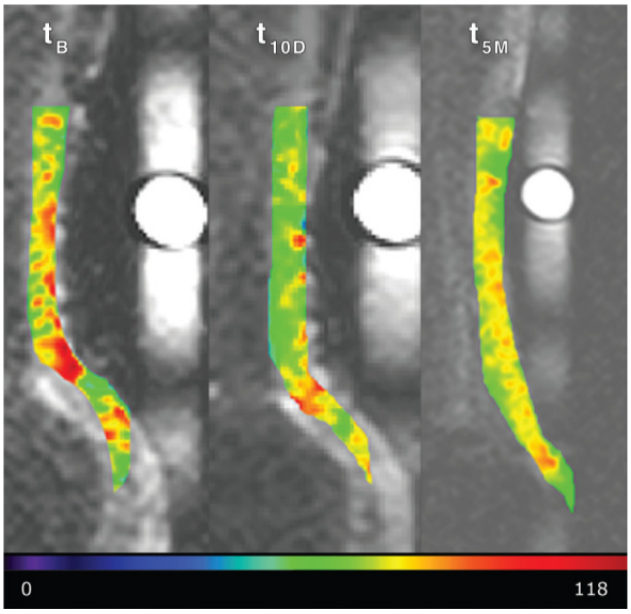

Fig. 2. The normalized sodium signal in the Achilles tendon at baseline before ciprofloxacin intake (t_B), 10 days after ciprofloxacin intake (t_{10D}), and at the 5-month follow-up examination (t_{5M}). Images were scaled equally. The decrease in the sodium signal in the tendon after intake is shown. The scale at the bottom of the image indicates the normalized sodium signal in arbitrary units.

3. Results

The mean Vienna Morphological Achilles Tendon Score was 89.6 ± 6.9 for the baseline, 93.75 ± 5.96 10 days after ciprofloxacin intake, and 93.75 ± 5.69 5 months thereafter. None of the volunteers experienced any clinical symptoms from the intake of ciprofloxacin. At the three time points for the whole tendon, the mean normalized sodium signal was 130 arbitrary units (au) ± 8, 98 au ± 5, and 116 au ± 10, respectively. Using the repeated measures analysis of variance, a statistically significant difference was found between imaging at baseline and 10 days after for both whole tendon and the insertion in normalized sodium signal. Five months after ciprofloxacin intake, there was no significant change compared with baseline.

4. Discussion

Our study demonstrates that sodium MR imaging is likely to detect changes in GAG content in the Achilles tendon after ciprofloxacin intake in healthy men. The changes were observed 10 days after ciprofloxacin intake, while the sodium signal returned to normal after 5 months. There were no visible morphologic changes in the Achilles tendon between the respective

time points. Our study further links ciprofloxacin intake to Achilles tendinopathy. Of interest, while previous studies offered suspicions that FQ-associated Achilles tendinopathy is closely related to the age of the patient, cortisone treatment, and renal failure, our study demonstrates that changes in the Achilles tendon can also be observed in healthy young men. Although verified by MR imaging, the changes did not lead to clinical symptoms of tendinopathy or tendon injury; however, all subjects were asked to refrain from intense physical activity at least 14 days after ciprofloxacin initiation. Ciprofloxacin-associated tendinopathy and accompanying tendon rupture most commonly occur in the Achilles tendon, which is likely related to the weight-bearing role of the Achilles tendon [6]. Other tendons, including the supraspinatus, patellar, and quadriceps tendons, may also be occasionally affected by FQ drugs [7]. It is possible that the tendinitis observed in certain patients treated with FQs is secondary to an alteration in fibroblast cell homeostasis that results in the structural compromise of the tendon. The correlation coefficients of test-retest reliability showed high values for all three MR parameters, which suggests that there is no spontaneous change of the parameters over time. However, this is a confirmation rather than a proof of that expectation.

5. Conclusions

In conclusion, our study demonstrates the changes in sodium MR imaging in men after ciprofloxacin intake were very likely caused by a decrease of GAG content in the Achilles tendon. The observed changes in GAG content may contribute to the characterization of the pathomechanism of FQ-associated tendinopathy in the future.

Acknowledgements

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