Posttraumatic Perfusion Analysis of Quadriceps, Patellar, and Achilles Tendon Regeneration With Dynamic Contrast-Enhanced Ultrasound and Dynamic Contrast-Enhanced Magnetic Resonance Imaging

Preliminary Results

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Objectives—The healing process of tendons after surgical treatment of tendon ruptures mainly depends on the perfusion of the tendon and its surrounding tissue. Dynamic contrast-enhanced ultrasound (DCE-US) and dynamic contrast-enhanced MRI (DCE-MRI) can provide additional information about the local microperfusion. In this pilot study, the feasibility of these techniques to assess the vascularization during tendon regeneration was evaluated.

Methods—Between 2013 and 2015, 23 patients with surgical treatment of traumatic rupture of quadriceps, patellar, and Achilles tendons were involved. All patients received clinical follow-up examinations at 6, 12, and at least 52 weeks postoperatively. Dynamic contrast-enhanced US and DCE-MRI examinations were performed 6 and 12 weeks postoperatively. Dynamic contrast-enhanced US perfusion was quantified by the parameters peak enhancement, wash-in area under the curve, rise time, and initial area under the curve. Correlations between these parameters were examined via the Spearman rank correlation. The clinical and functional outcomes were assessed via the Lysholm Knee Score and Knee and Osteoarthritis Outcome Score at 12 and 52 weeks postoperatively.

Results—Fourteen patients with quadriceps (n = 8), patellar (n = 4) and Achilles (n = 2) tendon ruptures with complete follow-up were available. The microperfusion could be successfully assessed. We could detect a strong correlation of DCE-US (peak enhancement) parameters with DCE-MRI (initial area under the curve) parameters after 6 and 12 weeks.

Conclusions—In this pilot study, DCE-US was able to visualize the microperfusion of healing tendons with a strong correlation with DCE-MRI. Our initial results are in favor of DCE-US as a potential quantitative imaging tool for evaluating the vascularization in tendon regeneration as a complementary method.

Key Words—dynamic contrast-enhanced ultrasound; dynamic contrast-enhanced magnetic resonance imaging; musculoskeletal ultrasound; quantification; tendon

Received December 2, 2019, from the Center of Orthopedics, Trauma Surgery, and Spinal Cord Injury, Heidelberg Trauma Research Group, Heidelberg University Hospital, Heidelberg, Germany (C.F., M.M., A.J., G.S., A.W., J.D.); Department of Diagnostic and Interventional Radiology, Heidelberg University Hospital, Heidelberg, Germany (M.-A.W.); Institute of Diagnostic and Interventional Radiology, Pediatric Radiology, and Neuroradiology, University Medical Center Rostock, Rostock, Germany (M.-A.W.); Institute of Medical Biometry, University of Heidelberg, Heidelberg, Germany (O.S.); and Aschaffenburg Trauma and Orthopedic Research Group, Center for Trauma Surgery, Orthopedics, and Sports Medicine, Aschaffenburg, Germany (A.M.). Manuscript accepted for publication June 12, 2020.

Parts of this study were presented at the 2019 Dreiländertreffen ultrasound conference; October 16–19, 2019, Leipzig, Germany. Drs. Fischer and Miska contributed equally to the manuscript. Open access funding enabled and organized by Projekt DEAL. All of the authors of this article have reported no disclosures.

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Abbreviations
a.u., arbitrary units; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; DCE-US, dynamic contrast-enhanced ultrasound; iAUC, initial area under the curve; KOOS, Knee and Osteoarthritis Outcome Score; MBI, magnetic resonance imaging; PE, peak enhancement; ROI, region of interest; RT, rise time; US, ultrasound; WiAUC, wash-in area under the curve

doi:10.1002/jum.15424

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Tendon ruptures are frequent musculoskeletal injuries and tend to occur after a sudden overload or a jumpy eccentric contraction of the muscle. In many cases, it is accompanied by a preexisting degenerative injury. The most frequent tendon rupture is localized in the Achilles tendon; other common tendon injuries include the quadriceps and patellar tendons. Tendon ruptures are common sports injuries affecting patients with high activity demands. There is adequate evidence in the literature that injured tendons never reach the same mechanical properties as before. The biomechanical structure of collagen is no longer organized in the original pattern after tendon healing. Patients can therefore have a loss of power in the affected leg, and the healing process can last up to 1 year before full function is recovered. Tendons are regarded as bradytrophic tissue with a problematic regeneration process, especially in patients with preexisting degeneration.

Standard radiologic examinations for diagnosis of a tendon rupture are magnetic resonance imaging (MRI) and ultrasound (US). In the follow-up examination after conservative or surgical treatment, it can be challenging to visualize adequate healing. Recent radiologic techniques such as dynamic contrast-enhanced ultrasound (DCE-US) and dynamic contrast-enhanced MRI (DCE-MRI) are able to visualize the microcirculation of healing soft tissues.

The use of DCE-US has expeditiously increased in clinical practice since the first European Federation of Societies for Ultrasound in Medicine and Biology guidelines in 2004 and their last update for nonhepatic applications in 2017. Especially, the application for musculoskeletal issues has spread rapidly. The ability of DCE-US to assess microvascular perfusion in musculoskeletal issues as a surrogate parameter of tissue vitality and metabolism could be a promising new standard diagnostic method for the evaluation of post-traumatic tendon regeneration.

The US contrast agent SonoVue (Bracco SpA, Milan, Italy) used for DCE-US consists of sulfur hexafluoride bubbles with almost a size of an erythrocyte and has a low incidence of side effects (complication rate, <0.01%). After intravenous injection, the bubbles remain intravascular, enhancing blood echogenicity and not influencing renal function. Therefore, the demand for laboratory testing of renal function before administration is not necessary.

The aim of this pilot study was to assess tendon regeneration of unilateral quadriceps, patellar, and Achilles tendon ruptures in humans in a prospective approach via visualization and quantification of the vascularization during tendon healing with DCE-US and DCE-MRI. Clinical and functional outcomes were correlated as well with the quantification results.

Materials and Methods

Patient Population and Study Protocol
This study was approved by the local Ethics Committee (S-371/2012) and was performed according to the Declaration of Helsinki (World Medical Association) in its current form. All individuals accorded with the study protocol and gave their written informed consent before any relevant study procedures.

Between November 2013 and July 2015, a total of 23 patients with unilateral traumatic rupture of quadriceps, patellar, and Achilles tendons were included. Inclusion criteria were a minimum age of 18 years and unilaterally ruptured quadriceps, patellar, and Achilles tendons with scheduled surgical treatment. General exclusion criteria were multiple associated injuries, known intolerance or allergies to contrast agents, recent myocardial infarction, massive cardiac, pulmonary, and renal insufficiency, disorders in galactose metabolism, uncontrollable hypertension, marcuramization (warfarin), bleeding disorders, and pregnancy. Missing follow-up data and technical difficulties were also exclusion criteria and had to be applied to 9 patients.

All patients were treated surgically with minimally invasive suture of the Achilles tendon, direct suture of the patellar tendon, or transosseous refixation of the quadriceps tendon by experienced senior orthopedic surgeons. The postoperative treatment was realized with partial weight bearing for 6 weeks in a functional orthosis with an increasing range of motion for quadriceps and patellar tendon ruptures and 20° plantar flexion with early mobilization in a foot and ankle orthosis for Achilles tendon ruptures.

Follow-up examinations with DCE-US and DCE-MRI were realized 6 and 12 weeks after initial treatment. Patients visited the outpatient clinic at
least 12 months after surgery for a final clinical examination.

**Clinical and Functional Evaluation**

The tendon healing process was monitored during regular clinical follow-up examinations; the functional assessment consisted of the following questionnaires: Lysholm Knee Score\textsuperscript{19,20} and Knee and Osteoarthritis Outcome Score (KOOS). The KOOS is subdivided in 5 separately scored subscales: pain, other symptoms, function in daily living, function in sport and recreation (sport/rec), and knee-related quality of life.\textsuperscript{21} These scores were applied 12 weeks and at least 12 months after surgery. At the last follow-up and at least 12 months after surgery, we finally examined our patients, measuring the extension strength of the treated leg in comparison to the healthy leg by using a commercially available dynamometer, using the mean of 5 repetitions on both sides.

**Dynamic Contrast-Enhanced US Evaluation**

With this examination, we intended to display the neovascularization during tendon regeneration in the ruptured area (Figure 1). The examination and measurement by DCE-US were performed 6 and 12 weeks after surgery, using settings established during previous studies recently described by Fischer et al.\textsuperscript{11,12,22} All contrast-enhanced US examinations were performed at the local university US center by the same experienced orthopedic and trauma consultant with German Society for Ultrasound in Medicine level III qualification. The contrast-enhanced US video clips were postprocessed and analyzed by the same experienced orthopedic and trauma resident. Both were blinded to any clinical information.

All patients were examined with the same Acuson S3000 US device (Siemens Healthineers, Erlangen, Germany). Patients were in the supine position with slight flexion of the knee for quadriceps and patellar tendons and in the prone position for the Achilles tendon. We localized the area of the tendon rupture with a linear transducer (9 L4, 4–9 MHz) in the sagittal plane perpendicular to the tendon; a live dual-view B-mode image in the Siemens-specific contrast Cadence mode was set. To achieve best image quality, we adjusted the gain at 3 dB and the mechanical index individually (0.07–0.11). After that, a bolus of 2.4 mL of SonoVue (sulfur hexafluoride microbubbles with a phospholipid shell) was intravenously applied, directly followed by 10 mL of a 0.9% saline solution (sodium chloride). A video clip of 90 seconds with a frame rate of 5 Hz was digitally recorded, beginning directly after injection of the contrast agent. During the video, no motion of the patient or the transducer was allowed to reduce artifacts. The described settings complied with the recommendations of the European Federation of Societies for Ultrasound in Medicine and Biology\textsuperscript{10} and were standardized for each DCE-US examination.

For quantification of the data sets, we used the dedicated, well-established, and commercially available offline quantification software VueBox 7.2 (Bracco SpA) because of its variate examination options, although other kinds of perfusion software may equally be applied. Furthermore, VueBox was also successful used in internal medicine and abdominal surgery for other indications.\textsuperscript{23,24} The region of interest (ROI) was positioned and customized to reduce artifacts from reflecting fascia or large vessels. Time-intensity curves were generated by VueBox software and the following quantified parameters were generated in arbitrary units (a.u.): peak enhancement (PE), the maximum signal intensity of the enhancement curve; wash-in area under the curve (WiAUC), the definite integral of the signal intensity against time until PE; and rise time (RT), the wash-in duration of contrast agent in seconds. All DCE-US parameters were correlated with the DCE-MRI parameter initial area under the curve (iAUC).

**Dynamic Contrast-Enhanced MRI Examination and Evaluation**

Dynamic contrast-enhanced MRI as an established imaging technique has already been applied in previous studies on nonunion perfusion.\textsuperscript{22,25} It noninvasively assesses tissue microcirculation via serial MR images before, during, and after the administration of an intravenous contrast agent and was used for the evaluation of tendon regeneration in this study.

The examination and measurement by DCE-MRI were equally performed by using the same protocol as recently described in another musculoskeletal DCE-MRI study.\textsuperscript{22,25} At the 6- and 12-week follow-ups, the examination was monitored by a senior musculoskeletal radiologist, who was blinded to any clinical information.
We used a 3-T MRI system (Magnetom Verio; Siemens Healthineers), and coronal T1-weighted, fat-saturated, volume-interpolated breath hold examination sequences were used for the T1-weighted dynamic images (repetition time/echo time, 3.75/1.35 milliseconds; 17 measurements; 48 slices each; 2-mm slice thickness). The contrast agent was injected with a flow of 2 mL/s (0.2-mmol/kg body weight gadoterate meglumine; Dotarem; Guerbet, Villepinte, France).

The same senior musculoskeletal radiologist evaluated DCE-MRI recordings and measured the time-intensity curves. The parameter iAUC was calculated. The postprocessed quantification of the DCE-MRI data sets was performed with Syngo Tissue 4D software of the MRI manufacturer (Siemens Healthineers). One ROI was placed into the area of the initial rupture as described for the DCE-US examination before. Consequently, the iAUC parameters were assessed for the ROI (Figure 2).

**Statistical Data Analysis**

The empirical distributions of continuous data and scores were reported with means and standard deviations and with absolute and relative frequencies for categorical data. An analysis of correlations between the evaluated techniques DCE-US and DCE-MRI as well as the clinical scores was performed with the
Spearman rank correlation giving the coefficient ($r$) and the 2-sided Wilcoxon test giving the $P$ value for significance. All $P$ values quoted are to be interpreted in a descriptive way, as they were not adjusted for multiple testing because this was an exploratory post hoc analysis. Every statistical analysis was staged out by using SPSS version 23.0 software for Windows (IBM Corporation, Armonk, NY). $P < .05$ was used to indicate statistical significance.

Results

Patient Characteristics

Of 23 study patients, 7 had to be excluded because of missing clinical and radiologic follow-up examinations (Figure 3). Furthermore, 2 patients were excluded because of technical difficulties during the administration of the contrast agent or quantification via VueBox (due to excessive movement). There were no adverse events from the contrast agent. The remaining 14 patients (Figure 3; 13 male and 1 female) had a mean age of 52.4 ± 12.8 years (range, 27–73 years). The tendon ruptures were distributed as follows: quadriceps, $n = 8$; patellar, $n = 4$; and Achilles, $n = 2$. All patients showed satisfying functional results after complete follow-up with healed tendons and no recurrent ruptures. Patient characteristics are shown in Table 1.

Clinical and Functional Outcomes

A significant improvement of clinical scores could be observed from follow-up at 12 weeks until the final examination after at least 12 months. The Lysholm Knee Score had been created to give information about how patients’ knee pain impairs everyday life. In total, 9 patients showed an excellent (>90%) outcome, 3 patients a good (84%–90%) outcome, and 2 patients a fair (65%–83%) outcome after at least 1 year. In detail, the Lysholm Knee Score was evaluated as 72.7% ± 15.9% after 12 weeks and 90.0% ± 8.3% ($P = .006$) after 52 weeks, with an improvement of 17.3%.

The KOOS is an instrument to assess patients’ opinions about their knee and associated problems. A score of 100% indicates no symptoms or any problems, whereby 0% indicates extreme symptoms or severe problems. The mean KOOS score 12 weeks after surgery was 77.6% ± 8.4%, and 52 weeks after surgery, it was 88.8% ± 6.7% ($P = .006$), with a mean improvement of 11.1%.

Figure 2. Dynamic contrast-enhanced MRI examination 6 weeks after surgical reconstruction of the quadriceps tendon. A, Dynamic contrast-enhanced MRI with contrast agent inflow. B, Absolute enhancement of the contrast agent inflow. Red label indicates the ROI (quadriceps tendon).
The final follow-up investigation included the extension strength measurement of the affected leg in comparison to the contralateral healthy leg; the mean values resulted from 5 repetitions of each leg. The strength measurements between both legs (affected and contralateral healthy leg) 12 months postoperatively differed significantly ($P = .002$) and amounted to $26.9 \pm 8.2$ kg (affected leg) and $30.6 \pm 11.7$ kg (contralateral healthy leg).

Eight of all patients reached an extension strength almost equivalent to that of the healthy leg ($>90\%$) of $95.2\% \pm 0.04\%$, and the other 6 patients reached an extension strength ($<90\%$) of $76.6\% \pm 19.5\%$. In sum, the strength of the affected legs did not completely reach full recovery with $100\%$ of the healthy legs’ extensional strength during tendon regeneration within 1 year of follow-up. They reached nearly $89\% \pm 7.3\%$ extensional strength and showed a satisfying healing process.

**Correlation of Scores With DCE-US and DCE-MRI**

Scores were correlated (KOOS and Lysholm) 12 months postoperatively with $iAUC$ (DCE-MRI; $r = 0.011; r = 0.307$) and $PE$ ($r = 0.200; r = 0.339$) as well as $WiAUC$ ($r = -0.158; r = 0.014$), $RT$ (DCE-US; $r = -0.193; r = -0.342$) 6 weeks postoperatively. In sum, the clinical scores showed only low correlations with DCE-US and DCE-MRI.

**Measurement by DCE-US and DCE-MRI**

In DCE-US, the quantification value $PE$ increased from $1103.9 \pm 959.6$ a.u. at the 6-week follow-up to $1875.6 \pm 2187.0$ a.u. ($P = .198$) at the 12-week follow-up, whereas $WiAUC$ increased from $10,233.4 \pm 5427.4$ to $15,645.6 \pm 16267.5$ a.u. ($P = .331$) and $RT$ decreased from $25.2 \pm 17.9$ to $17.0 \pm 7.7$ seconds ($P = .245$). In DCE-MRI, the mean $iAUC$ was $45.04 \pm 13.00$ a.u. 6 weeks postoperatively and increased to $45.51 \pm 19.02$ a.u. ($P = .975$) 12 weeks after surgery.

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**Table 1. Patient Characteristics**

| Patient | Sex | Age, y | Location | Side | Trauma         |
|---------|-----|--------|----------|------|----------------|
| 1       | Male| 39     | Quadriceps | Left | Soccer         |
| 2       | Male| 49     | Patella   | Right| Walking downstairs |
| 3       | Male| 48     | Quadriceps | Right| Walking downstairs |
| 4       | Male| 69     | Quadriceps | Right| Accidental fall |
| 5       | Male| 38     | Patella   | Left | Walking downstairs |
| 6       | Male| 56     | Quadriceps | Right| Accidental fall |
| 7       | Male| 57     | Quadriceps | Left | Walking downstairs |
| 8       | Male| 27     | Achilles  | Right| Badminton      |
| 9       | Male| 48     | Patella   | Right| Walking downstairs |
| 10      | Male| 64     | Quadriceps | Left | Accidental fall |
| 11      | Male| 56     | Achilles  | Left | Accidental fall |
| 12      | Female| 73    | Quadriceps | Right| Accidental fall |
| 13      | Male| 64     | Quadriceps | Right| Accidental fall |
| 14      | Male| 46     | Patella   | Right| Salto jump     |
Correlation of DCE-US With DCE-MRI

Six and 12 weeks postoperatively, all DCE-US parameters showed a strong correlation with the iAUC of DCE-MRI. Peak enhancement showed the strongest correlation with ($r = .829; P < .001$) after 6 weeks (Figure 4) and remained significant after 12 weeks with ($r = 0.556; P = .039$). After 6 weeks, WiAUC correlated significantly ($r = 0.789; P < .001$; Figure 5) as well as after 12 weeks, yet was lower ($r = 0.521; P = .056$). The RT showed a correlation of $r = -0.635 (P = .015)$ at 6 weeks and $r = -0.301 (P = .296)$ at 12 weeks.

Discussion

In this pilot study, primary tendon regeneration was investigated concerning the visualization of microperfusion with DCE-US and DCE-MRI. Clinical and functional outcomes were correlated with the quantified perfusion parameters from DCE-US and DCE-MRI.

Our results revealed a satisfying clinical outcome and healing of the injured tendons in the study cohort. The feasibility of the DCE-US and DCE-MRI methods could be demonstrated and showed strong correlations with each other.

To our knowledge, this was the first study to evaluate and correlate microperfusion during tendon regeneration in humans comparing DCE-US and DCE-MRI as well as the functional outcome. Dynamic contrast-enhanced US and DCE-MRI are well-established imaging techniques in our trauma center and were successfully applied in previous studies to assess the microperfusion of tendons and muscles\textsuperscript{12,13} as well as osseous perfusion of healing bone\textsuperscript{26,27}, infected nonunions, and their surrounding tissue\textsuperscript{28,29} for various clinical issues, showing reliable results.

In this pilot study, large intraindividual differences between the investigated patients could be detected. However, there was no significant correlation with the clinical outcome after 1 year. This might have been in part related to the small and inhomogeneous sample size without comparable groups regarding the outcome.

Nevertheless, we detected strong correlations between the quantification parameters of both evaluated methods (DCE-US and DCE-MRI) 6 and 12 weeks postoperatively. Interestingly, a lower
correlation between both imaging methods could be observed at the 12-week follow-up. With regard to the quantification parameters from DCE-US and DCE-MRI, it is noteworthy that they increased significantly more strongly in DCE-US than in DCE-MRI. That might be one reason for the worse correlation after 12 weeks.

It is recognized from the literature that proliferative tissue regeneration during tendon healing is almost completed after 12 weeks. In particular, the remodeling phase of the affected tissue begins after 6 to 8 weeks. The existing increase of quantification parameters after 12 weeks by DCE-US might imply that an examination of microperfusion by DCE-US might better reflect the regenerative potential of tendons than by DCE-MRI at the 12-week follow-up and might therefore more accurately identify changes in microperfusion over time.

Additionally, Doral et al. reported that type III collagen emerged during tendon regeneration, before the neosynthesis of type I collagen, leading to a change in tendon biomechanics. This abnormal collagen composition is recognized as a cause of intrinsic tissue weakness.

Furthermore, Don et al. noted that torn tendons had increased stiffness at 3 and 6 months postoperatively. However, Gigante et al. observed, in addition to the above-mentioned increased stiffness, a peak in thickness 6 months postoperatively during tendon regeneration process due to scar maturation and remodeling inside the treated tendon. Since DCE-US is believed to be more sensitive to tissue changes in visualization of microperfusion, these above-mentioned tissue changes may not be detectable by DCE-MRI, represented by the slight increase of the quantification parameter at the 12-week follow-up.

Additionally, Genovese et al. and De Marchi et al. were able to demonstrate the superiority of DCE-US in detection of neovessels and neovascularization compared to power Doppler US in tendon tissues. Due to the overall strong correlation in this study, we can assume that DCE-US and DCE-MRI are feasible methods for assessment of neovascularization.
during tendon regeneration, whereas DCE-US may more accurately identify changes in microperfusion over time.

This might be encouraging, as US is the more cost-effective and less-afflicting examination tool for patients. A further strength is that the examination time for experienced investigators is shorter than that for a DCE-MRI scan. We used well-established examination protocols from our previous studies.\(^{12,13}\)

Regarding the side effects of contrast agents, there are fewer reported complications and better tolerability for the US contrast agent SonoVue\(^{17}\) compared to MRI contrast agents. SonoVue microbubbles remain strictly intravascular; therefore, the measurement of vascularization is not disturbed by cumulative effects in the examined tissues.\(^{13,36}\)

Although DCE-US is examiner dependent and therefore sensitive to bias, we were able to demonstrate that DCE-US is a reliable examination technique, which yields similar results as DCE-MRI. The real-time examination allows a subjective impression of the qualitative microvascularization in tendon tissue. The enhancement of the contrast agent creates a dynamic illustration that could indicate the extent of the rupture.

In contrast, DCE-MRI needs a longer evaluation and contains predefined sectional images, which may not reflect the rupture area adequately. Magnetic resonance imaging cannot be interpreted during the examination. It has to be postprocessed with computer-based quantification software, which relates the tendon rupture region to healthy muscle and tendon tissue. Eventually, the positioning of the ROI relies on the operator as well.

One main limitation of this pilot study was the small number of patients and the inhomogeneous study population with different kinds of posttraumatic tendinous lesions and follow-up treatments. A comparison of groups was not possible, especially because of the overall satisfying clinical outcome and lack of patients with clear therapy failure or an examination of the contralateral healthy leg. Another weakness was that in both techniques, the quantification depends on the examiner, who has to determine the ROI to exclude fascia and large vessels.

Further studies concerning the vascularization during tendon regeneration could possibly focus on DCE-US alone. To obtain better findings on the influence of the vascularization, a larger patient number is necessary, making a comparison of groups possible. The correlation between vascularization of the tendon tear side and a histologic examination could also be an aspect of further studies. A focus on a single anatomic area of tendon rupture would be helpful to eliminate possible sources of bias as well. Regarding a possible association of higher rerupture rates in patients with lower vascularization, long-time follow-up would be necessary.

In contrast to visualization of microperfusion with DCE-US and DCE-MRI, the relatively newly developed US-based imaging technique sonoelastography allows determination of elastic properties of tendon tissue by applying pressure.\(^{37}\) Gehmert et al\(^{38}\) were among the first who monitored the elasticity of injured Achilles tendons with sonoelastography. Furthermore, Frankewycz et al\(^{39}\) could show with sonoelastography that healed Achilles tendons had lower elasticity after traumatic rupture even after a long-term healing phase. In combination with DCE-US and DCE-MRI, sonoelastography might be an interesting novel method in the follow-up of surgically treated tendons for the evaluation of the regeneration process or the assessment of musculoskeletal alterations.

In conclusion, imaging modalities such as US and MRI are the reference standards for postoperative imaging of the healing process after tendon repair. Dynamic contrast-enhanced US and DCE-MRI allow additional information on microperfusion as a surrogate parameter for tendon quality as well as the possibility of a quantitative analysis of vascularization parameters. In our pilot study, we could demonstrate that DCE-US is a feasible method to assess the microperfusion in the reconstructed and healing tendon with a strong correlation with DCE-MRI. Furthermore, it is the faster, more cost-effective technique with fewer side effects related to the contrast agent used. In further studies, an influence of vascularization on long-time follow-up in a more-homogeneous and larger collective should be examined to establish DCE-US as standard diagnostic method for the posttraumatic perfusion analysis of tendon regeneration in daily clinical routines. After larger collectives with higher patient numbers are generated, a multicenter setup could be realized, similar to a recently published study, which evaluated the intraobserver and device-
dependent interobserver reliability of DCE-US for deltoid muscle perfusion quantification. Sectional plane standardization and the restriction to a single entity are decisive for reliability and transferability of DCE-US muscle and tendon perfusion quantifications. Existing landmarks should be considered to allow sufficient sectional plane reproduction.

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