Changes in Cartilage and Tendon Composition of Patients With Type 1 Diabetes Mellitus

Identification by Quantitative Sodium Magnetic Resonance Imaging at 7 T

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Objective: The aim of this study was to investigate possible biochemical alterations in tendons and cartilage caused by type 1 diabetes mellitus (DM1), using quantitative in vivo 7 T sodium magnetic resonance (MR) imaging.

Materials and Methods: The institutional review board approved this prospective study, and written informed consent was obtained. Eight DM1 patients with no history of knee trauma and 9 healthy age- and weight-matched volunteers were examined at 7 T using dedicated knee coils.

All participants underwent morphological and sodium MR imaging. Region-of-interest analysis was performed manually for the non-weight-bearing area of the femoral condyle cartilage and for the patellar tendon. Two readers read the image data sets independently, twice, for intrareader and interreader agreement. Normalized mean sodium signal intensity (NMSI) values were compared between patients and volunteers for each reader using analysis of variance.

Results: On morphological images, cartilage in the non-weight-bearing area and the patellar tendon was intact in all patients. On sodium MR imaging, bivariate analysis of variance showed significantly lower normalized mean NMSI values in the cartilage (P = 0.008) and significantly higher values in the tendons (P = 0.025) of patients compared with those of volunteers.

Conclusion: Our study showed significantly different NMSI values between DM1 patients and matched volunteers. Differences observed in the cartilage and tendon might be associated with a DM1-related alteration of biochemical composition that occurs before it can be visualized on morphological MR sequences.

Key Words: quantitative sodium MRI, 7 tesla, diabetes mellitus, tendon, cartilage

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Diabetes mellitus is a systemic metabolic disorder, characterized by hyperglycemia, which results in microvascular damage and glycosylation of proteins in multiple organ systems.1–3

Recent data obtained from mice models show that reduced insulin production in diabetes mellitus results in accelerated loss of joint cartilage during fracture repair.4 The reduced production of insulin may cause a decrease in the proliferation and differentiation of chondrocytes, whereas insulin and insulin treatment each may have a positive effect on the differentiation of the precursor cells of chondrocytes.4,5 In rat models with induced diabetes mellitus, impaired tendon-bone healing was found after rotator cuff repair. This observation is explained by the assumption that hyperglycemia induces changes in cartilage and tendons due to increased deposition of glycosylisation end products (AGE) at the tendon-bone interface.2,6 This deposition of AGEs may again result in alterations of the extracellular glycosaminoglycan (GAG) content, which represents a major component of articular cartilage and tendons.

The biochemical composition of cartilage and tendons can now be visualized using different methods with the ability to show biochemical tissue alterations.6,12–15 Jungmann et al13 used T2 techniques to report that metabolic risk factors, such as high abdominal circumference, hypertension, high fat consumption, and diabetes mellitus, were associated with increased baseline T2. When more of these factors were present, higher T2 values were found, suggesting an abnormal biochemical composition of cartilage in these individuals.

Sodium imaging, however, with its potential to directly determine the cartilage GAG content, is a sensitive method with which to measure these tissue alterations.1,12–13 The sodium magnetic resonance (MR) signal correlates directly with the GAG concentration in these tissues because the positive counterpart of the negatively charged GAG molecules are sodium ions. Therefore, the biochemical tissue composition can now be quantified by using in vivo sodium MR imaging (MRI). Furthermore, sodium MRI has been demonstrated as a non-invasive method for the evaluation of changes in the GAG content of patients after different cartilage repair surgery techniques and in patients with osteoarthritis (OA).11,13–15 These studies showed a decrease in sodium values in patients after cartilage repair and in OA patients that was associated with a lower GAG content after cartilage repair and loss of GAG in OA. In contrast, Juras et al4,5 found increased normalized mean sodium values in tendons in patients with tendinopathy. This corresponds to the work of Samiric et al,14 which suggested that this effect might be primarily due to changes in the metabolic turnover of GAG, with increased deposition of large aggregating proteoglycans.

To date, imaging in diabetic patients has been used mainly to document the extent or complications of long-standing disease. These changes were thought to be caused primarily by different factors, such as weight, neural loss, or microangiopathy. Therefore, morphological imaging of bones and joints was chiefly used to show secondary osteoarthritic effects, such as cartilage degradation or tendinopathy. In addition, conventional imaging was used to differentiate between the effects due to neuropathy, such as Charcot joints, and changes from infectious diseases, such as osteomyelitis and soft-tissue infection in diabetic patients.

Therefore, the detection of early OA stages, when the disease is potentially reversible, is of major interest in cartilage imaging and in the clinical development of potential disease-modifying OA drugs. These stages are often missed by conventional morphological imaging techniques, as early stages of OA are related to changes in the organization and composition of the extracellular matrix only, such as a decrease in GAG content, which cannot be visualized properly using morphological imaging alone.

Today, evidence derived from current studies suggests that diabetes mellitus itself may adversely affect the homeostasis and repair of articular tissues and tendons and therefore may have an impact on the development, severity, and therapeutic outcomes of OA.11,17–19
Thus, sodium imaging, with its potential to directly determine and quantify the GAG content in cartilage and tendon, seems to be the method of choice for the visualization of changes in the GAG content of patients with systemic metabolic disease, such as type 1 diabetes mellitus (DM1), which alters tissue homeostasis.2,12,18

The purpose of this study was to evaluate changes in tendons and cartilage associated with DM1, using quantitative in vivo sodium MRI at 7 T.

MATERIALS AND METHODS

Study Population

Our hospital’s institutional review board approved the protocol for this prospective study, and written, informed consent was obtained from all study participants. From July 2012 to January 2013, patients volunteered in response to a public notice at the outpatient clinic of our endocrinology department and were included in our study based on the following inclusion criteria: (1) body mass index less than 30 kg/m², (2) no known history of knee trauma or inflammation, and (3) proven history of DM1. Exclusion criteria included (1) morbid obesity, (2) known history of knee injury or surgery, or (3) other systemic metabolic diseases. Diagnosis and treatment of diabetes in patients were made at the outpatient clinic of the Department of Internal Medicine III, Division of Endocrinology and Metabolism, using a plasma glucose test, a glucose tolerance test, and glycated hemoglobin values. In volunteers, diabetes and metabolic syndrome were excluded by questioning, by asking for a known history of diabetes, any first-degree relative with diabetes, overweight, elevated blood pressure, and height for body mass index calculation.

According to these criteria, 8 patients (4 women, 4 men; mean [SD] age, 43 [16.9] years; age range, 22–68 years; median duration of DM1, 11.4 years; minimum, 0.75 years; maximum, 54 years) were enrolled in the study. The control group consisted of 9 healthy age- and weight-matched volunteers (3 women, 6 men; mean [SD] age, 40 [17.2] years; age range, 23–69 years) for further details, see Table 1).

MRI Protocol

The MR examinations were performed on a 7 T whole-body MR scanner (Magnetom, Siemens Healthcare, Erlangen, Germany) with a gradient strength of 40 mT/m, using a dedicated 28-channel knee coil (Quality Electrodynamics LLC, Cleveland, OH) for morphological imaging. For sodium MRI of the knee, a dedicated 15-channel Na-only knee coil (Quality Electrodynamics LLC) was used. Care was taken to keep the patients’ knees in an identical position for morphological and sodium imaging; both coils have exactly the same housing and the subject did not leave the patient table during the coil change. A reference sample containing 308 mmol/L sodium chloride solution was fixed to the knee coil and served for normalization of the sodium signal intensities. Patients were examined in the supine position with the knee extended and tightly fixed, and the joint space was placed in the center of the coil.

Axial, sagittal, and coronal proton density-weighted turbo spin echo (PD-TSE) sequences with fat suppression were performed for morphological diagnosis and localization of anatomical sites for a region-of-interest (ROI) analysis. T2 maps were acquired using a double echo steady-state free precession (DESS) technique. The DESS sequence generates 2 signal echoes that are characterized by different contrast behaviors. Based on these 2 contrasts, the underlying T2 can be calculated. The DESS sequence combines both the steady state free precession with free induction decay and the SSFP-echo signals to produce an image. The DESS measurements were performed with a field of view of 140 × 140 mm, a matrix size of 320 × 320, and a voxel size of 0.44 × 0.44 × 3.00 mm. Repetition time was 8.46 milliseconds, echo time was 4.23 milliseconds for the S-echo, and 2*repetition time-echo time was 12.69 milliseconds for the S-echo. Bandwidth was 211 Hz/pixel, and acquisition time was 2:07 minutes for 32 slices. Double echo steady-state free precession-T2 maps were calculated on a pixel-by-pixel basis from the 2 contrasts of the DESS sequence.

### TABLE 1. Shows Patients and Volunteer Characteristics With NMSI Values

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Height, m</th>
<th>Weight, kg</th>
<th>BMI</th>
<th>Complications</th>
<th>HbA1c, %</th>
<th>Disease Duration, y</th>
<th>NMSI, a.u.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>F</td>
<td>1.7</td>
<td>71</td>
<td>25</td>
<td>Retinopathy</td>
<td>7.2</td>
<td>54</td>
<td>100.32</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>M</td>
<td>1.74</td>
<td>71</td>
<td>23</td>
<td>Retinopathy</td>
<td>7.3</td>
<td>47</td>
<td>118.09</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>M</td>
<td>1.65</td>
<td>79</td>
<td>29</td>
<td>No</td>
<td>6.8</td>
<td>26</td>
<td>148.01</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>F</td>
<td>1.69</td>
<td>57</td>
<td>20</td>
<td>No</td>
<td>6.9</td>
<td>10</td>
<td>143.79</td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>M</td>
<td>1.92</td>
<td>88</td>
<td>24</td>
<td>No</td>
<td>11.3</td>
<td>0.8</td>
<td>138.26</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>F</td>
<td>1.65</td>
<td>56</td>
<td>21</td>
<td>No</td>
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<td>2.2</td>
<td>147.51</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>M</td>
<td>1.88</td>
<td>56</td>
<td>16</td>
<td>No</td>
<td>7.8</td>
<td>13</td>
<td>133.97</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>M</td>
<td>1.85</td>
<td>100</td>
<td>29</td>
<td>No</td>
<td>7.7</td>
<td>9</td>
<td>143.84</td>
</tr>
<tr>
<td>Volunteer no.</td>
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<td>F</td>
<td>1.6</td>
<td>58</td>
<td>22.66</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>148.97</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>M</td>
<td>1.88</td>
<td>80</td>
<td>22.63</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>161.42</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>F</td>
<td>1.62</td>
<td>46</td>
<td>17.53</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>144.60</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>M</td>
<td>1.84</td>
<td>73</td>
<td>21.56</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>178.93</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>M</td>
<td>1.86</td>
<td>84</td>
<td>24.28</td>
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<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>6</td>
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<td>1.65</td>
<td>72</td>
<td>26.45</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>139.31</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>M</td>
<td>1.83</td>
<td>65</td>
<td>19.41</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>168.01</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>M</td>
<td>1.83</td>
<td>72</td>
<td>21.50</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>161.00</td>
</tr>
<tr>
<td>9</td>
<td>69</td>
<td>M</td>
<td>1.6</td>
<td>59</td>
<td>23.05</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>148.91</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HbA1c, glycated hemoglobin; NMSI, normalized mean sodium signal intensity.
For sodium MRI, a 3-dimensional Cartesian spoiled gradient echo sequence with a variable echo time scheme was used (Table 2).20

### Image Analysis

All MR examinations were randomly presented to a senior radiologist who specialized in musculoskeletal imaging (S.F.N., with 12 years of experience). First, all participants were evaluated for chondropathy and tendinopathy on morphological sequences. Although all participants reported that they had no knee injury or pain, there was mild chondropathy (grades 1–2 according to the international cartilage repair society classification21) in the weight-bearing zone of 1 volunteer and 3 patients only. Therefore, the non–weight-bearing zone of the femoral condyle was used in further evaluations according to the criteria defined by Raynauld et al.22 to avoid signal alterations due to cartilage degeneration.

Then, on the sagittal PD-TSE sequence, 3 slices in a row were selected for each participant, covering morphologically intact-appearing femoral cartilage in the mid portion of the non–weight-bearing zones of the medial and lateral femoral condyle. Subsequently, 3 slices in a row for each participant were chosen, covering the midportion of the patellar tendon. Then, in each of the selected slices, a single ROI was manually drawn, covering the patellar tendon and the cartilage of the femoral condyle. Regions of interest had to be at least 0.2 cm² in size. The ROIs defined on PD-TSE images were transferred to the corresponding sodium MR images, and, for cartilage, also to the T2 maps for further analysis. First, corresponding images were selected by an experienced radiologist according to gross anatomical features. Then ROIs were placed on the T2 maps using the Osirix DICOM Viewer (Osirix 4.0, Pixmeo Sarl, Switzerland).

After that, sodium images were rescaled to the resolution of morphological images and overlaid with the corresponding sagittal PD-TSE images.

Sodium signal intensity in each of these ROIs was measured using the Osirix DICOM Viewer (Osirix 4.0, Pixmeo Sarl, Switzerland). Sodium-normalized signal intensities (NMSIs) were calculated by multiplying the mean signal intensity from an ROI in the cartilage or tendon by a factor derived from the signal intensity of an ROI placed in the reference sample attached to the knee coil. For the assessment of intrareader and interreader agreement, the same image data were reevaluated. The cartilage condyle side was randomly chosen by the study administrator and provided to both readers before their additional readings. For the assessment of interreader agreement, the senior radiologist performed ROI-based measurements in a subjective assessment, 8 weeks after the first evaluation. For the assessment of the interreader agreement, another reader (W.M., with 1 year of experience in musculoskeletal MRI) independently evaluated the same examinations, performing ROI measurements and a subjective assessment.

### Statistical Analysis

All statistical analyses and graphs were created using SPSS software (version 22.0 for Windows; SPSS, Chicago, IL) by a statistician with 16 years of experience (M.W.). The normality of distributions of sodium values, T2 map values, and volumes was assessed by the Kolmogorov-Smirnov test. Analyses using intraclass correlation (ICC) and bivariate analysis of variance were performed. Subsequently, Spearman ρ correlation and receiver operating characteristic (ROC) were performed for sodium imaging. The significance for all statistical tests was set at the P < 0.05 level.

### RESULTS

#### Morphological Sequences

We found early stages of chondropathy (grades 1–2 according to the international cartilage repair society classification of cartilage lesions23) on morphological images in the weight-bearing zones in 1 volunteer and in 3 patients. Excellent interreader and intrareader agreement was reached (ICC of 1) when comparing the non–weight-bearing areas of cartilage and the patellar tendon. Only slight differences in the grading (grade 1 and 2) of cartilage degradation in the weight-bearing area were seen between the 2 readers but did not reach statistical significance.

#### Sodium MRI

The interobserver reliability for both structures was substantial, with an ICC of 0.93 (95% confidence interval, 0.82–0.97) in cartilage and 0.97 (95% confidence interval, 0.91–0.99) in tendons; the intrareader reliability was 0.97 (95% confidence interval, 0.92–0.99) in cartilage and 0.97 (95% confidence interval, 0.92–0.99) in tendons (Table 3).

In patients with DM1, the mean size of the ROI in cartilage was 0.39 cm² (range, 0.22–0.46 cm²). In the control group of healthy volunteers, the mean size of the ROIs was 0.41 cm² (range, 0.23–0.95 cm²).

Mean (SD) sodium NMSI values in the femoral cartilage of the medial and lateral condyle were 156.4 (18.23) arbitrary units (a.u.) and 138.96 (15.6) a.u. in DM1 patients, respectively (see also Table 4 and Fig. 1).

Mean (SD) T2 map values in the femoral cartilage of the medial and lateral condyle were 34.53 (7.29) milliseconds and 36.08 (7.88) milliseconds in healthy volunteers and 32.71 (7) milliseconds and 38.68 (7.88) milliseconds in DM1 patients, respectively (see Fig. 1).

<table>
<thead>
<tr>
<th>CARTILAGE</th>
<th>TENDON</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICC</td>
<td>CI</td>
</tr>
<tr>
<td>Interobserver</td>
<td>0.93</td>
</tr>
<tr>
<td>Intraobserver</td>
<td>0.97</td>
</tr>
</tbody>
</table>

### Table 2: Sequence Parameters of Morphological Sequences and of the Sodium Sequence

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR/TE, ms</th>
<th>Flip Angle, °</th>
<th>Bandwidth, Hz/pixel</th>
<th>Field of View, mm²</th>
<th>Resolution, mm</th>
<th>No. Slices</th>
<th>Acquisition Time, min:s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sag. 2D-PD TSE fs</td>
<td>4010/18</td>
<td>159</td>
<td>248</td>
<td>160</td>
<td>0.4 × 0.4 × 2.5</td>
<td>25</td>
<td>4:30</td>
</tr>
<tr>
<td>Axial 2D-PD TSE fs</td>
<td>4010/18</td>
<td>159</td>
<td>248</td>
<td>160</td>
<td>0.4 × 0.4 × 0.5</td>
<td>14</td>
<td>4:42</td>
</tr>
<tr>
<td>Cor. 2D-PD TSE fs</td>
<td>4010/18</td>
<td>140</td>
<td>248</td>
<td>160</td>
<td>0.4 × 0.4 × 2.5</td>
<td>25</td>
<td>4:42</td>
</tr>
<tr>
<td>DESS (T2 maps)</td>
<td>4.86/4.23</td>
<td>159</td>
<td>211</td>
<td>140</td>
<td>0.44 × 0.44 × 3</td>
<td>32</td>
<td>2:07</td>
</tr>
<tr>
<td>23Na-3D-TE-GRE</td>
<td>12/1.6</td>
<td>50</td>
<td>80</td>
<td>200</td>
<td>1.5 × 1.4 × 3</td>
<td>40</td>
<td>28:07</td>
</tr>
</tbody>
</table>

TR indicates repetition time; TE, echo time; Sag., sagittal; 2D, 2-dimensional; PD-TSE, proton density-weighted turbo spin echo; fs, fat saturation; Cor., coronal; DESS, double echo steady-state free precession; 3D, 3-dimensional; vTE-GRE, gradient echo sequence with a variable echo time.

For sodium MRI, a 3-dimensional Cartesian spoiled gradient echo sequence with a variable echo time scheme was used (Table 2).
In patients with DM1, the mean size of the ROI in tendons was 0.35 cm$^2$ (range, 0.22–0.46 cm$^2$). In the control group of healthy volunteers, the mean size of the ROIs was 0.41 cm$^2$ (range, 0.23–0.95 cm$^2$).

Mean (SD) NMSI values for the patellar tendon were 61.19 (8.65) a.u. in healthy volunteers, whereas patients showed a mean (SD) NMSI value of 76.47 (15.94) a.u. (see also Table 5, Fig. 2). Bivariate analysis of variance revealed significantly lower sodium NMSI values in the medial condyle ($P=0.014$) and in the lateral condyle ($P=0.003$) in patients with DM1 compared with volunteers (see Table 4). No significantly different values were found in T2 maps in the medial ($P=0.623$) and in the lateral condyle ($P=0.499$) in patients.

An ROC analysis of cartilage measurements showed a mean NMSI of 142.22 a.u. as the best threshold value for the differentiation of patients and volunteers. The area under the curve value was 0.861, with a 95% confidence interval of 0.75 as the lower boundary and 1.0 as the upper boundary. The sensitivity was 87.5%, the specificity was 88.9%, the positive predictive value was 87.5%, and the negative predictive value was 88.9%, with a diagnostic accuracy of 88.24%.

In the patellar tendon, significantly higher sodium NMSI values were found in patients with DM1 compared with volunteers ($P=0.025$) (Table 5).

The ROC analysis of the tendon measurement showed a mean NMSI of 59.03 a.u. as the best threshold value for the differentiation of diabetic patients and healthy volunteers. The area under the curve value was 0.875, with a 95% confidence interval of 0.73 as the lower boundary and 1.0 as the upper boundary. The sensitivity was 87.5%, the specificity was 88.9%, the positive predictive value was 87.5%, and the negative predictive value was 88.9%, with a diagnostic accuracy of 88.24%.

Figure 3 provide the ROC curves, using a mean NMSI of 142.22 a.u. as the threshold value in cartilage and a mean NMSI of 59.03 a.u. as the threshold value in tendon.

Spearman $\rho$ correlation between NMSI values and disease duration of DM1 was $R=-0.381$ ($P=0.352$) for cartilage and $R=0.429$ ($P=0.289$) for tendon. Although associations were not strong, a tendency toward lower values in cartilage and higher values in tendons in the diabetic patients with increasing duration of disease was observed.

**DISCUSSION**

The primary finding of our study shows that there are significant differences in sodium NMSI values in the non-weight-bearing femoral cartilage and patellar tendon of patients with DM1 compared with healthy age- and weight-matched volunteers. Although functional imaging is not used routinely, it has become more accepted in the literature for the evaluation of biochemical alterations in cartilage and tendons because of changes that occur during different repair techniques and for the evaluation of the early stages of OA. In particular, sodium MRI remains challenging, compared with conventional proton MRI or even H1 techniques, such as T2 mapping, because of the very
low natural abundance of sodium and the lower gyromagnetic ratio. Recent developments, particularly the use of ultra-high-field scanners and improved sodium sequences,\textsuperscript{20} allow reproducible evaluation of cartilage biochemical composition. Nevertheless, sodium MRI has proven its sensitivity to changes in the GAG content of cartilage and tendons in patients with OA\textsuperscript{25} and chronic tendinopathy.\textsuperscript{26} Our results therefore suggest that biochemical changes might occur before any changes are apparent on morphological images or even on T2 maps where the tendons and the non–weight-bearing segments of cartilage appear normal. Interestingly, our results revealed no significant differences between diabetes mellitus patients and volunteers using T2 maps. However, Jungmann et al\textsuperscript{11} reported that metabolic risk factors, such as high abdominal circumference, hypertension, high fat consumption, and diabetes mellitus, were associated with increased baseline T2 values. Nevertheless, it must be taken into account that there is no uniform definition for the early stages of OA, as these changes refer to changes that can often be seen with histological methods or arthroscopy, but not with conventional MRI techniques.

For example, Onur et al\textsuperscript{27} found that diabetes mellitus type 2 caused global degeneration in University of California, Davis, type 2 diabetes mellitus rat knee joints, but immunohistochemistry stains showed little to no change in collagen II degeneration between diabetes mellitus type 2 and control rats. This might suggest that changes caused by diabetes are primarily a result of AGE-altered GAG content rather than of changes in the collagen network. We found increased sodium NMSI values in cartilage and decreased values in tendons. These results support our hypotheses that diabetes affects cartilage and tendons directly, in addition to indirect effects, such as obesity and polyneuropathy. It has been reported that hyperglycemia increases AGE production through a unifying mechanism in diabetic patients.\textsuperscript{25,28} This leads to an altered GAG content of the extracellular matrix of cartilage and tendons. As proteoglycans and, therefore, GAG, are vital components of the extracellular matrix in both tissue types, changes in these macromolecules lead to altered charges and concentrations of these tissue components. On the basis of previous reports that have demonstrated a high sensitivity of sodium MRI to changes in GAG content in cartilage and tendon, we believe that sodium imaging can also detect the changes in GAG content caused by a systemic disease, such as diabetes mellitus.\textsuperscript{12–33}

The increased sodium NMSI values in the cartilage and decreased values in the tendons described in this work correspond to recently published work.\textsuperscript{12,26,30} Several papers have shown lower sodium values in the repair tissue than in native cartilage in patients who have undergone cartilage repair surgery.\textsuperscript{13,25,30,34,35} suggesting an incomplete maturation of repair tissue by matrix synthesis. Therefore, no amount of GAG equal to that of normal hyaline cartilage was produced in the repair tissue, which resulted in an overall lower GAG

| TABLE 5. ANOVA Analysis of the Mean Sodium NMSI Values in Tendon Measurements |
|-------------------------------|-------------------|---------------|------|
| Tendon                        | Count | NMSI, a.u. | SD   | t Test (P) |
| Patient                       | 8     | 76.47      | 15.94 | 0.025     |
| Reference                     | 9     | 61.19      | 8.65  |           |

ANOVA indicates analysis of variance; NMSI, normalized mean sodium signal intensity; a.u., arbitrary units.

FIGURE 2. Magnetic resonance images of a healthy volunteer with morphological images (A) showing colored sodium regions of interest (ROIs) in the tendon (B) and corresponding patient images with morphological images (C) and colored sodium ROI in tendon (D). Figure 2 can be viewed online in color at www.investigativeradiology.com.
in which a significant increase in sulfated GAG content/C2 reported an increase in sodium values in www.investigativeradiology.com at 7 T. Because sodium relaxation © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

versus healthy controls, as seen on MRI over time. Newbould et al reported significantly different sodium values in knee cartilage in OA concentration in patients with OA, with a signal decrease of 30% to 60% depending on the degree of cartilage degeneration. Newbould et al reported significantly different sodium values in knee cartilage in OA versus healthy controls, as seen on MRI over time. Conversely, Juras et al reported an increase in sodium values in patients with chronic achillotendinitis, corresponding to an increase in GAG concentration within the Achilles tendon. Several authors have verified these findings by comparing sodium measurements with histologically evaluated GAG content in cadaver tendons, which served as a standard of reference. Those findings were supported by a study by Samiric et al, in which a significant increase in sulfated GAG content was observed in diseased tendons, primarily because of changes in the metabolic turnover of these macromolecules.

We expected small differences in sodium values between DM1 and tendon. Therefore, to increase the sensitivity of sodium imaging, we used a T1-weighted sodium sequence with a relatively high resolution of $1.4 \times 1.5 \times 3.0$ mm$^3$ at 7 T. Because sodium relaxation times in the tendon are still unknown, quantification of sodium concentration is not possible, and we report NMSI values in the cartilage and tendon. However, sodium relaxation times in the cartilage and tendon of patients were expected to be similar to those of volunteers. Thus, the observed decrease in sodium NMSI values primarily represents differences in GAG concentration in cartilage, which reflects early cartilage degeneration. Conversely, an increase in the sodium signal seen in tendons is probably a result of changes in the metabolism of proteoglycans, reflecting tendinopathy.7 As analogous tendencies were seen in our patients, we assume that a decrease in the NMSI values in the cartilage and an increase in tendons in diabetic patients might represent underlying changes similar to those seen in patients with OA or chronic tendinopathy. Therefore, this might reflect the metabolic activity of AGEs in diabetic patients that lead to early changes that are also associated with OA, in accordance with the findings of Schett et al, who reported that diabetes was an independent risk factor for OA.

We believe that changes caused by diabetes are primarily a result of AGE-altered GAG content rather than of changes in the collagen network. As T2 relaxation times show cartilage tissue alterations primarily based on changes in the collagen matrix and water content, this might explain why we were able to observe changes only by using sodium imaging while morphological imaging and functional T2 mapping did not detect any significant differences. Thus, sodium MRI, with its potential to directly determine the cartilage GAG content in cartilage and tendons, seems to be more sensitive in the detection of early degenerative changes, owing to the loss of small amounts of GAG, while the collagen network remains mainly unaffected.

Although we did not observe a strong association between sodium values and the duration of DM1, a tendency toward lower values in cartilage and higher values in tendons in the patients who were diabetic for a longer duration was observed, compared with the volunteers.

Our study has several limitations. First, there is the small number of patients, although, even in this small cohort, statistically significant differences could be detected. Therefore, we tried to create a cutoff value with ROC analysis for cartilage and tendons. However, any defined cutoff value must be judged with caution, as a larger cohort of patients is needed to allow the definition of a reliable cutoff value for diabetic patients at risk for chondropathy and tendinopathy. Second, it should be noted that, because of the small number of patients, our patient group might be too inhomogeneous in age and duration of disease. We tried to overcome these problems by matching the control group in age and weight (using body mass index) to our diabetic patients. Still, age-related changes in cartilage and tendons should be considered when interpreting these results. In future studies on larger cohorts, we plan to divide the diabetic patients into additional subgroups according to their glycated hemoglobin values and already-present, long-term damages, such as retinopathy or nephropathy, or even different therapeutic strategies.

In summary, our study showed a statistically significant difference in sodium NMSI values in patients with DM1, compared with a healthy control group. As observed changes are probably associated with alterations in biochemical composition, they may be indicative of biochemical alterations that occur before any morphological changes can be seen on routinely performed MRI sequences.

**SUMMARY STATEMENT**

Quantitative sodium MR can help identify patients with biochemical changes in cartilage and tendons that are thought to occur because of systemic diseases, such as diabetes mellitus, before these changes can be visualized on routinely performed MRI sequences.

**REFERENCES**


