Menopause and administration of bisphosphonate strongly affect values of these biomarkers as reported previously. It is quite interesting that urine CTX-II and NTX-I have a weak but positive correlation in both younger and elder groups in female. This indicates that cartilage degradation and bone resorption appear to develop in parallel.

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AUTOMATED ATLAS BASED SEGMENTATION OF KNEE MR IMAGES; REPRODUCIBILITY AND REPEATABILITY OF SIGNAL MEASUREMENTS

14Qimaging LLC, Rochester, NY; 2Inst. Tecnologico y de Estudios Superiores de Monterrey, Monterrey, Mexico; 3The Ohio State Univ., Columbus, OH; 4Mem. Hosp. of Rhode Island and Brown Medial Sch., Pawtucket, RI; 5Cleveland Clinic Fndtn., Cleveland, OH

Purpose: Most knee OA studies have focused on cartilage, but increasing evidence shows that cartilage loss is preceded by or accompanied with other changes in cartilage, bone and other soft tissues. Scoring systems developed for non-cartilage changes are based on changes in the structure’s MRI signal intensity as compared to normal. Preliminary data have shown that cartilage signal behavior separates normals from early OA. There is also evidence that subchondral bone and calcified cartilage vascularizes before cartilage loss and that calcified cartilage advances into non-calcified cartilage in the early phase of the disease. These events change the MRI signal intensity of the cartilage and underlying bone. Their longitudinal analysis would advance our understanding of OA. The Osteoarthritis Initiative (OAI) has a large clinical and radiological knee OA dataset. Only an automated approach would make such a large scale analysis feasible. We developed a fully automated, atlas based segmentation and analysis system to segment and analyze bones, cartilage and anatomic regions from knee MR image data. Here we compare the repeatability and reproducibility of the automated system and an expert radiologist for measuring average MRI signal intensity of cartilage and bone in several regions, as well as the within the tibiofemoral joint space.

Methods: The atlas for the automated system was created by manually tracing five subjects’ 3D DESS WE images from the 0.D1 OAI dataset and selecting the best performing atlas for further refinement and use. To test repeatability, 30 subjects’ images from the OAI were randomly chosen and anonymized. Of these, 10 were randomly selected and anonymized creating 40 blinded images. Automated measurements were generated with a trimmed average of five segmentations using varying initial parameters. Reproducibility was tested with 38 anonymized sagittal 3D DESS WE image sets of 19 subjects’ scan-rescan studies from the OAI pilot study. These were segmented both semi-manually and automatically as in the repeatability test.

Average signal intensity was automatically calculated for cartilage and bone in various regions as well as the tibiofemoral joint space. Reproducibility was calculated by computing mean-square (RMS) coefficient of variation (CV %) for each parameter.

Results: Automated segmentation produced identical re-analysis results for all measured parameters. CV% for manual segmentation varied between 2.3%-10%. Scan-rescan reproducibility for the automated method varied from 1.75% - 3.01%. Average signal intensities of cartilage plates were generally lower for femur than for tibia. Signal intensity of the deep layer of cartilage varied from 96 to 201, being higher for femur than for tibia. Average signal intensity of the superficial layer of subchondral bone was considerably lower for all areas. Reproducibility for tibiofemoral joint space signal intensity was 2.34% for lateral and 1.57 % for medial inter-bone regions using automated tools compared to 3.42 % and 3.34 % for manually edited regions.

Conclusions: The automated atlas based MR image analysis system provided repeatable and highly reproducible signal intensity measurements in the medial and lateral weight bearing regions of the knee. These automated tools provide a realistic opportunity to characterize the behavior of structural and compositional changes in cartilage and non-cartilage tissues in OA by analyzing large populations such as the OAI or other longitudinal datasets.

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OBJECTIVE IMAGE-BASED MULTIVARIABLE OA STAGE BIOMARKER: DEVELOPMENT AND CHARACTERIZATION USING THE OAI DATA SETS

J.G. Tamez-Pena1, E. Schreyer2, S. Totterman3, P. Gonzalez3, V. Trevino1
1ITESM, Monterrey, Nuevo Leon, Mexico; 24Qimaging, Rochester, NY; 3MITEK, Monterrey, Nuevo Leon, Mexico

Purpose: The objective evaluation of the OA stage will help in the development and evaluation of effective OA treatments. The purpose of this work is to develop and evaluate a multivariate quantitative image-based biomarker as a surrogate measurement of the OA stage using the publicly available OAI data sets.

Methods: OAI image data releases 0.D.1, 1.D.1, 2.D.1 and 3.C.1 were used in this study. OAI Biomarker0X, Joint0X, and Physicalexam0X datasets were also used. All right knee MRI DESS images of these data sets were automatically segmented and quantified five times using IPAS (Jose Tamez-Pena). The automated atlas-based segmentation extracted bone as well as cartilage tissue present in the knee joint using the 4Qimaging Knee Atlas (4Qimaging, Rochester, NY). The extracted tissue included definitions of the trochlea, and the medial and lateral weight bearing areas of the knee. Once the tissues were automatically segmented, measurements of volume, thickness, bone curvature, average boundary signal and inter-bone distances were computed for all regions and for all time points. All repeated measurements from each of the five runs were then exported to Excel (Microsoft) with the RExcel add-in (Erich Neuwirth). Excel was then used to identify all the subjects with a full set of successful measure-
ments for all four time points. Each one of the five repeated measurement were then summarized with the trimmed average (Average of the three middle measurements). The trimmed average measurements were used to compute the standardized femur curvature, the standardized minimum contrast, and the standardized minimum of medial and lateral tibia-to-femur bone distance. Those measurements were used as surrogate measurements for bone shape, tissue inflammation and unloaded tibia-femoral joint distance. Those measurements then were used to compute a tree variable linear composite metric associated to the OA grade (biomarker00 data set) and to the WOMAC score of the right knee (Joint0x data set). The weights of the linear combination of three variables were selected in such a way to provide a strong association to the total WOMAC score and the OA Grade score. The qMRI composite index then was evaluated for responsiveness to time using a linear model.

Results: From 196 subjects included in data release 3.0, only 179 subjects had the complete set of four time points with full MRI quantification. The computed qMRI composite index was associated to total WOMAC (r=0.33, t=4.6, p<0.001) and to the OA grade scores (Spearman rho=0.51, p<0.001). The coefficients of the linear model are shown in Table 1. The linear model of the responsiveness of the qMRI composite index reduced the longitudinal variability of the index in 12%. (r²=0.116, p<0.001). The index had an average annualized SRM of 0.14 for the 179 subjects.

Table 1. Responsiveness to time: qMRIIndex – BLqMRIIndex = BLqMRIIndex × Time + Time

<table>
<thead>
<tr>
<th>Coefficients</th>
<th>Value</th>
<th>Std Error</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>0.5054</td>
<td>0.0819</td>
<td>6.1755</td>
<td>0.00000000</td>
</tr>
<tr>
<td>BLqMRIIndex×Time</td>
<td>-0.121</td>
<td>0.0219</td>
<td>-5.518</td>
<td>0.00000000</td>
</tr>
</tbody>
</table>

Conclusions: The image-analysis methodology and biomarker discovery approach presented in this work was able to automatically segment the OAI DESS images and used to provide an objective index of the OA stage that is associated to the WOMAC scores and to the OA grade scores. Furthermore, this index has the potential to be used for automated objective screening for OA progressors. The methodology has still to be validated using more time points. It effectiveness and usefulness has still to be tested in independent OA study cohorts.

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MITOCHONDRIAL DNA HAPLOGROUUPS MODULATE THE SERUM LEVELS OF BIOMARKERS IN PATIENTS WITH OSTEOARTHRITIS

I. Rego1, M. Fernandez-Moreno1, M. Deberg1, S. Pertega1, N. Oreiro1, V. Bonome-Gonzalez1, Y. Henrotin1, F.J. Blanco1


Purpose: To analyze the influence of mitochondrial DNA (mtDNA) haplogroups on serum levels of molecular biomarkers in patients with osteoarthritis (OA).

Methods: We analyzed serum levels of molecular biomarkers of cartilage metabolism (collagen type II markers: Coll2-1, Coll2-1NO2, C2C, CPII), synovial metabolism (hyaluronic acid (HA)) and cartilage and synovial turnover (YKL-40) in 73 OA cases and 77 healthy controls using enzyme-linked immunosorbent assays (ELISAs). All subjects had been previously genotyped for the mtDNA haplogroups J, U, and H. Non-parametric and multivariate analysis were performed to test the effects of the clinical variables, including gender, age, smoking status, diagnosis, mtDNA haplogroups and radiologic Kellgren/Lawrence (K&L) grade on the serum levels of the molecular markers.

Results: Non parametric analysis showed increased serum levels of HA in patients with OA, meanwhile the values for Coll2-1, C2C and C2C/CPII ratio appeared statistically increased in healthy controls. Multivariate analysis showed a clear incidence of the mtDNA haplogroups in the serum levels of the typical type II collagen markers. Carriers of the mtDNA haplogroup H had higher levels and carriers of the mtDNA haplogroup J showed lower levels. Statistical interactions between mtDNA haplogroups and both diagnosis and radiologic K&L grade in the serum levels of the molecular markers were also detected.

Conclusions: A new role for mtDNA haplogroups emerges from this work. Our results suggest that the mtDNA haplogroups significantly interact with the serum levels of OA-related molecular markers, suggesting the possibility of their use as a complementary assay with these molecular markers.