the ACR criteria for symptomatic OA of at least one knee and radiographic criteria for OA with a Kellgren-Lawrence (KL) score of 1-4 in at least one knee.

**Radiographic Imaging:** Posteroanterior semi-flexed knee radiographs were obtained and read for KL grade and individual radiographic features of OA, including joint space narrowing (JSN) and osteophytes (OST).

**Scintigraphic Imaging:** Scintigraphic images of the knee were obtained at 2 mins. (early phase) and 2.5 hrs. (late phase) after injection of technetium-99m methylene diphosphonate. The intensity of bone uptake was scored for the tibiofemoral and patellofemoral compartments of each knee.

**Biochemical measurements:** Matched serum and SF samples were analyzed for UA using HPLC. Cytokines were measured in the SF using the Bio-Rad human cytokine multiplex immunoassay for IL-5, IL-6, IL-7, IL-8, IL-13, MCP-1, and MIP-1 beta. Statistical Analysis: Descriptive statistics and univariate analyses were performed using Graphpad Prism software. Relationships between SF analytes and OA were analyzed using the GenMOD procedure with the addition of a repeated statement (GLM, SAS Enterprise Guide). Multivariate modeling was used to assess independent effects of SF analytes and to control for BMI, age, and gender.

**Results:**

- This study was limited to 69 study participants (49 women and 20 men) with knee OA and adequate SF volume for these analyses. The mean (±SD) age was 64.5±10.1 years. The mean (±SD) body mass index was 32.4±7.1 kg/m². Knee OA was graded 1-4 in severity (23.1%, 14.6%, 49.2%, 13.1% for each KL grade).
- SF measurements were possible for both knees of 63 participants, and for single knees of 6 participants.

**Late Phase**

<table>
<thead>
<tr>
<th></th>
<th>Bone Scan*</th>
<th>JSN</th>
<th>OST</th>
<th>JSN + OST</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF UA</td>
<td>0.04</td>
<td>0.03</td>
<td>0.29</td>
<td>0.05</td>
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<tr>
<td>SF Inh-L</td>
<td>0.06</td>
<td>0.01</td>
<td>0.04</td>
<td>0.007</td>
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<tr>
<td>Serum UA</td>
<td>0.02</td>
<td>0.04</td>
<td>0.08</td>
<td>0.83</td>
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</table>

*Early Phase Bone Scan controlled for in model. Total = Tibiofemoral (TF) + Patellofemoral. JSN = Joint Space Narrowing. OST = Osteophytes.

**Outcomes**

<table>
<thead>
<tr>
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<th>Bone Scan*</th>
<th>JSN</th>
<th>OST</th>
<th>JSN + OST</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF UA</td>
<td>0.02</td>
<td>0.02</td>
<td>0.34</td>
<td>0.06</td>
</tr>
<tr>
<td>Early Phase</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;0.0001</td>
<td>0.005</td>
<td>0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>0.03</td>
<td>0.21</td>
<td>0.08</td>
<td>0.13</td>
</tr>
<tr>
<td>Gender</td>
<td>0.41</td>
<td>0.98</td>
<td>0.21</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Early Phase Bone Scan controlled for in model. Total = Tibiofemoral (TF) + Patellofemoral. JSN = Joint Space Narrowing. OST = Osteophytes.

**Conclusions:** The strong association shown here between OA severity, particularly osteophytes, and SF UA, demonstrates that UA may be a factor contributing to the pathological process of OA. The constitutive release of UA from injured and dying cells in the OA joint may exacerbate joint tissue inflammation through sub-acute macrophage activation. Urate crystallization in the presence of nucleating agents released from degrading cartilage extracellular matrix may also contribute to joint tissue inflammation.

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**THE RELATIONSHIP BETWEEN RADIOLOGICAL GRADE OF KNEE OSTEOARTHRITIS AND BIOCHEMICAL MARKERS OF CARTILAGE AND BONE DEGRADATION (URINE CTX-II AND NTX-I): THE MATSUDAI KNEE OSTEOARTHRITIS SURVEY 2007**

H. Yamagiwa1, T. Hayami2, G. Omoni3, N. Tanishi1, H. Mera1, Y. Koga4, N. Endo1

1Dept. of Orthopedic Surgery, Niigata Univ, Niigata, Japan;
2Dept. of Orthopedic Surgery, Saiseikai Niigata Daini Hosp, Niigata, Japan;
3Ctr. for Transdisciplinary Res., Niigata Univ, Niigata, Japan; 4Dept. of Orthopedic Surgery, Niigata Kobari Hosp, Niigata, Japan

**Purpose:** Biochemical markers of cartilage and bone degradation are becoming increasingly important in the evaluation of knee Osteoarthritis (OA). The correlation between radiological knee OA and urine CTX-II (C-terminal crosslinking telopeptide of collagen type II) or urine NTX-I (N-terminal crosslinking telopeptide of type I collagen) needs to be evaluated how these markers are useful in the health check-up in a large population-based study.

**Methods:** We have performed the epidemiological knee survey in a rural Japanese population every 7 years at the Matsudai district in Niigata Prefecture, Japan since 1979. In 2007 (5th survey), a cross-sectional study of biomarkers was conducted with informed consent in the historical cohorts. Urine specimens were collected from 1040 subjects (605 females and 435 males), and CTX-II and NTX-I were measured using ELISA. Menstruation status and oral administration of bisphosphonate were checked. Standing knee AP X-rays were obtained and graded according to the Kellgren-Lawrence (K-L) classification. The subjects were then divided by gender, age (40- to 59-year-old group and 60- to 79-year-old group), and the X-ray grade (K-L Grade 0,1, Grade 2, and Grade 3,4). The values of CTX-II and NTX-I were compared between age groups and OA grade groups. Mann Whitney U test, Kruskal-Wallis test, and Spearman’s rank correlation test were used, and p<0.05 was considered statistically significant.

**Results:** In non-OA (Grade 0,1) subjects, there was no significant difference in CTX-II values between two age groups in males. However, in female, the 40- to 59-year-old postmenopausal group and the 60- to 79-year-old group had significantly higher CTX-II values than the 40- to 59-year-old premenopausal group. Administration of bisphosphonate also affected strongly both CTX-II and NTX-I values, so subjects taking bisphosphonate were excluded from further analysis.

In the male subjects aged over 60 years, knee OA Grade 3,4 group had significantly higher CTX-II values than the Grade 0, 1 group or the Grade 2 group (Fig. 1). In female subjects aged over 60 years, CTX-II values significantly increased according to the severity of knee OA (Fig. 1). For NTX-I, there were no significant differences between each OA grade. However, weak but positive correlations were observed between the urine CTX-II and urine NTX-I values in the 40- to 59-year-old female group and the 60- to 79-year-old male and female groups (r=0.23, 0.10, 0.14, respectively).

**Conclusions:** Urine CTX-II can be a useful biomarker of knee OA stages even by the single measurement in people older than 60 years although it would be difficult for 40-59-year-old people to evaluate knee OA changes using single urine CTX-II values.
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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; 6Cleveland 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 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 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 comparing 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 tibia than for femur. 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. Totterman2, P. Gonzalez3, V. Trevino1
1ITESM, Monterrey, Nuevo Leon, Mexico; 24Qimaging, Rochester, NY; 3IMITEK, 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, and 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 REexcel add-in (Erich Neuwirth). Excel was then used to identify all the subjects with a full set of successful measure-