Identifying radiographic phenotypes of early knee OA
Towards more targeted treatment

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OA phenotypes

- OA symptoms and radiography vary between patients, between disease stages, and over time
- This may prove important in determining optimum (potential) treatment
- Identifying radiographic phenotypes would expectedly be facilitated by use of quantitative evaluation of separate radiographic OA features
Current goal

- To investigate whether different longitudinal radiographic phenotypes of very early-stage knee OA can be recognized…
- … using continuous measures of individual radiographic OA features.

Cohort Hip & Cohort Knee

- 1002 Subjects
- Inclusion criteria:
  - Pain and/or stiffness of knee(s) and/or hip(s)
  - Never or no longer than 6 months ago visited a general physician because of these complaints
  - Age 45-65 years
Knee radiographs

- Weight-bearing, semiflexed, posteroanterior
- At baseline, 2 year, 5 year
- Scoring
  - One observer
  - Blinded to sequence and clinical characteristics

Knee Images Digital Analysis (KIDA)

Minimum JSW
Medial JSW
Lateral JSW
Varus angle
Sum osteophyte area
Sum eminence height
Mean bone density

Marijnissen et al. Osteoarthritis & Cartilage 2007
Overall progression

Mean with 95% confidence interval, right and left knees

Minimum JSW (mm)
Medial JSW (mm)
Lateral JSW (mm)
Varus angle (degrees)
Osteophyte area (mm²)
Eminentia height (mm)
Bone density (mmAl)

Identification of phenotypes

Hierarchical cluster analysis (N=417)
  – Radiographic parameters left and right at T0, T2, T5
  – Change in radiographic parameters
    (T2-T0 and T5-T2)
  – Standardized using z-scores
  – Ward’s method
### Radiographic progression phenotypes

<table>
<thead>
<tr>
<th>Metric</th>
<th>T0</th>
<th>T2y</th>
<th>T5y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min. JSW (mm)</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Medial JSW (mm)</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Lateral JSW (mm)</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Varus angle (grades)</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Osteophyte area (mm²)</td>
<td>30</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Eminence height (mm)</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Bone density (mmAl)</td>
<td>28</td>
<td>28</td>
<td>30</td>
</tr>
</tbody>
</table>

- **‘severe’**
- **‘no’**
- **‘bone density involvement’**
- **‘early’**
- **‘late’** progression
Identified phenotypes

- Severe progression (N=17; 4%)
- Bone density (N=113; 27%)
- Early progression (N=110; 26%)
- Late progression (N=69; 17%)
- No progression (N=108; 26%)

Can these longitudinal phenotypes be predicted by baseline characteristics?
## Characteristics of phenotypes

<table>
<thead>
<tr>
<th></th>
<th>‘Severe’ (n=17)</th>
<th>‘Bone density’ (n=113)</th>
<th>‘Early’ (n=110)</th>
<th>‘Late’ (n=69)</th>
<th>‘No’ (n=108)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>58 (4)</td>
<td>56 (5)</td>
<td>56 (5)</td>
<td>57 (5)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>82%</td>
<td>55%</td>
<td>81%</td>
<td>88%</td>
<td>92%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>K&amp;L score ≥II</td>
<td>26%</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain in knee</td>
<td>71%</td>
<td>44%</td>
<td>40%</td>
<td>30%</td>
<td>34%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

### Outcome T=5y

<p>| | | | | | | |</p>
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</thead>
<tbody>
<tr>
<td>K&amp;L score ≥II</td>
<td>39%</td>
<td>23%</td>
<td>16%</td>
<td>12%</td>
<td>6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain in knee</td>
<td>53%</td>
<td>29%</td>
<td>30%</td>
<td>27%</td>
<td>21%</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

Mean (SD) and median [25-75 percentile]

## Prediction of phenotype membership

<table>
<thead>
<tr>
<th></th>
<th>severe</th>
<th>bone</th>
<th>early</th>
<th>late</th>
<th>no</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>NA</td>
<td>0.91</td>
<td>0.79</td>
<td>0.76</td>
<td>0.72</td>
</tr>
</tbody>
</table>

### Radiographic feature
- Min JSW
- Medial JSW
- Lateral JSW
- Varus angle
- Osteophyte
- Eminence
- Bone density

### Demographic & clinical
- Age
- Female gender
- BMI
Conclusions and discussion

- Specific phenotypes of radiographic knee OA progression in early-stage OA
- Phenotypes represented the level (severe vs. no), the phase of progression (early vs. late), and the involvement of specific features (e.g., bone density)
- Baseline demographic and radiographic features could partly predict phenotypes

Conclusions and discussion

- Phenotypes might represent relevant subgroups for the evaluation of treatment strategies in clinical trials
- Validation needed
- Relation with long-term clinical outcome and treatment will determine usefulness
- Clustering on radiographical and clinical characteristics as next step
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MA Viergever
PJ Emans
PMJ Welsing
FPJG Lafeber

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