Results: The proteomic analysis resulted in the identification of 558 proteins (10,468 peptides) in the serum samples. A label-free quantification algorithm was employed to quantify 468 proteins in the samples. Hierarchical clustering of the data showed the differences in protein abundance were more relevant longitudinally (BL to 24M) than in cross-sectional comparisons between the three groups under study (N, P or S). Thirty-six proteins were significantly altered (fold change >=1.5, p<0.05) when comparing BL to 24M in the N group (15 increased and 48 decreased), 53 in the P group (20 increased and 33 decreased) and 93 in the S group (19 increased and 74 decreased). Interestingly, two different endotypes were detected at baseline in the N and S groups, based on these protein modulations. The overlapping of these proteomic profiles was analyzed between groups and is shown in the Figure 1. Proteins modulated specifically in the N group may be associated with mechanisms related with joint repair. On the other hand, six proteins (including two apolipoproteins) were increased at 24M only in the P group. Finally, 30 proteins were modulated only in the S group: five of them increased and 25 decreased. Remarkably, this latter group includes lubricin, chaperones and proteins related with proteoglycan binding, such as COMP, fibronectin or histidine-rich glycoprotein.

Figure 1. Circulating proteins identified as modulated after 24M follow-up in 45 patients from the APPROACH cohort that progressed in structure (S group; n=15), pain (P group; n=15) or did not progress (N group; n=15). The numbers with arrows indicate those proteins that decrease (arrow pointing down) or increase (arrow pointing up) compared to baseline.

Conclusion: The modulation of specific protein profiles in serum were identified as associated with the progression in structure, pain or non-progression in patients from the APPROACH cohort. Proteomic changes found specifically in the S group may be interesting circulating markers of the structural affectation occurring in the joint.

REFERENCES:

Disclosure of Interests: Cristina Ruiz-Romero: None declared, Patrik Önerford: None declared, Valentina Calamia: None declared, Patricia Fernández-Puente: None declared, Lucía Lourido: None declared, Rocío Paz González: None declared, Pawel Widera: None declared, Jaume Bacardit: None declared, dez Puente: None declared, Lucía Lourido: None declared, Rocío Paz González: None declared, Cristina Ruiz-Romero: None declared, Patrik Önerford: None declared, Valentina Calamia: None declared, Patricia Fernández-Puente: None declared, Lucía Lourido: None declared, ROCío Paz González: None declared, Pawel Widera: None declared, Jaume Bacardit: None declared, dez Puente: None declared, Lucía Lourido: None declared, Rocío Paz González: None declared, Cristina Ruiz-Romero: None declared, Patrik Önerford: None declared, Valentina Calamia: None declared, Patricia Fernández-Puente: None declared, Lucía Lourido: None declared, ROCío Paz González: None declared, Pawel Widera: None declared, Jaume Bacardit: None declared, dez Puente: None declared, Lucía Lourido: None declared, Rocío Paz González: None declared, Cristina Ruiz-Romero: None declared.
if the trajectory is changed, ** PAFs and related 95%CIs were calculated by the Stata punafcc package using the formula ∑pKRi[(HRi − 1)/HRi], where pKRi is the proportion of total knee replace-

Table 1. Comorbidities with significant HRs of exposure to knee or hip OA

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>HR</th>
<th>99.9% CI</th>
<th>Comorbidity</th>
<th>HR</th>
<th>99.9% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>1.33</td>
<td>1.09</td>
<td>1.64</td>
<td>Anemia</td>
<td>1.29</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.28</td>
<td>1.04</td>
<td>1.57</td>
<td>Atrial fibrillation</td>
<td>1.46</td>
</tr>
<tr>
<td>Cataract</td>
<td>1.27</td>
<td>1.02</td>
<td>1.59</td>
<td>Fibromyalgia</td>
<td>6.09</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.30</td>
<td>1.06</td>
<td>1.59</td>
<td>Peripheral vascular disease</td>
<td>1.64</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.34</td>
<td>1.03</td>
<td>1.75</td>
<td>Sleeping disorder</td>
<td>1.44</td>
</tr>
<tr>
<td>Gout</td>
<td>1.43</td>
<td>1.01</td>
<td>2.03</td>
<td>Solid malignancy</td>
<td>1.32</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>1.34</td>
<td>1.00</td>
<td>1.79</td>
<td>Spinal disc herniation</td>
<td>2.03</td>
</tr>
<tr>
<td>Neck pain</td>
<td>1.58</td>
<td>1.16</td>
<td>2.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>2.02</td>
<td>1.06</td>
<td>3.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeping disorder</td>
<td>1.33</td>
<td>1.04</td>
<td>1.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolic disease</td>
<td>1.40</td>
<td>1.01</td>
<td>1.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.46</td>
<td>1.14</td>
<td>1.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>6.09</td>
<td>1.25</td>
<td>29.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.64</td>
<td>1.09</td>
<td>2.49</td>
<td></td>
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<tr>
<td>Sleeping disorder</td>
<td>1.44</td>
<td>1.10</td>
<td>1.87</td>
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<tr>
<td>Solid malignancy</td>
<td>1.32</td>
<td>1.11</td>
<td>1.55</td>
<td></td>
<td></td>
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<tr>
<td>Spinal disc herniation</td>
<td>2.03</td>
<td>1.46</td>
<td>2.83</td>
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<td></td>
</tr>
</tbody>
</table>

Conclusion: This study showed that certain comorbidities were diagnosed more often in patients exposed to knee or hip OA, and none were less frequently diagnosed in patients exposed OA. This suggests that the management of OA should consider the risk of other long-term-conditions and that further research on causality between OA and comorbidity is needed.

REFERENCES:

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Disclosure of Interests: None declared

Table 1. Reduction in TKA if individuals followed the trajectory that was one lower

<table>
<thead>
<tr>
<th>Population counterfactuals</th>
<th>Population at risk, n (%)</th>
<th>TKA under the original scenario, n (%)</th>
<th>TKA under the new scenario*, n (%)</th>
<th>Difference in risk, n (%)</th>
<th>PAF** (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR1</td>
<td>4811 (19.7)</td>
<td>124 (2.6%)</td>
<td>No change 124 (2.6%)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>TR2 followed TR1 trajectory and rate of TKA*</td>
<td>8943 (36.7)</td>
<td>378 (4.2%)</td>
<td>2.6% of 8943 = 233</td>
<td>145 (10.9)</td>
<td>379 (26.7, 47.3)</td>
</tr>
<tr>
<td>TR3 followed TR2 trajectory and rate of TKA*</td>
<td>6526 (26.8)</td>
<td>416 (6.4%)</td>
<td>4.2% of 6526 = 274</td>
<td>142 (10.7)</td>
<td>26.8 (20.0, 31.2)</td>
</tr>
<tr>
<td>TR4 followed TR3 trajectory and rate of TKA*</td>
<td>845 (3.5)</td>
<td>64 (7.6%)</td>
<td>8.6% of 845 = 54</td>
<td>10 (0.8)</td>
<td>3.1 (0, 6.0)</td>
</tr>
<tr>
<td>TR5 followed TR4 trajectory and rate of TKA*</td>
<td>2466 (10.1)</td>
<td>253 (10.3%)</td>
<td>76% of 2466 = 187</td>
<td>66 (5.0)</td>
<td>20.2 (0, 36.3)</td>
</tr>
<tr>
<td>TR6 followed TR5 trajectory and rate of TKA*</td>
<td>777 (3.2)</td>
<td>93 (12.0%)</td>
<td>10.3% of 777 = 80</td>
<td>13 (1.0)</td>
<td>0.4 (0.0, 10.0)</td>
</tr>
<tr>
<td>Total population</td>
<td>24368</td>
<td>1328</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If the trajectory is changed. ** PAFs and related 95%CIs were calculated by the Stata punafcc package using the formula ∑pKRi[(HRi − 1)/HRi], where pKRi is the proportion of total knee replacements observed in the ith obesity trajectory and HRi is the hazard ratio (HR) associated with that category. PAFs were calculated using pKRi and HRi estimated from the entire sample. All HRi values were generated from Cox proportional hazards regression models adjusted for covariates (age at baseline, sex, country of birth, physical activity, smoking history, and comorbidity) and postestimation analyses.