Analysis of serum biomarkers and their correlation with pain and quality of life in the rare disease alkaptonuria

Alkaptonuria (AKU) is an ultra-rare disease causing an early onset, chronically debilitating spondylo-arthropathy due to deposition of an ochronotic pigment in joints and spine, which causes severe pain and greatly reduces patients' quality of life. Despite an evident clinical interest and recent efforts to characterize the molecular mechanisms of the disease, AKU still lacks appropriate biomarkers (i.e. characteristics that are objectively measured and evaluated as indicators of a condition or a response to treatment) to monitor severity and progression excepting for an AKU Severity Score Index (AKUSSI).

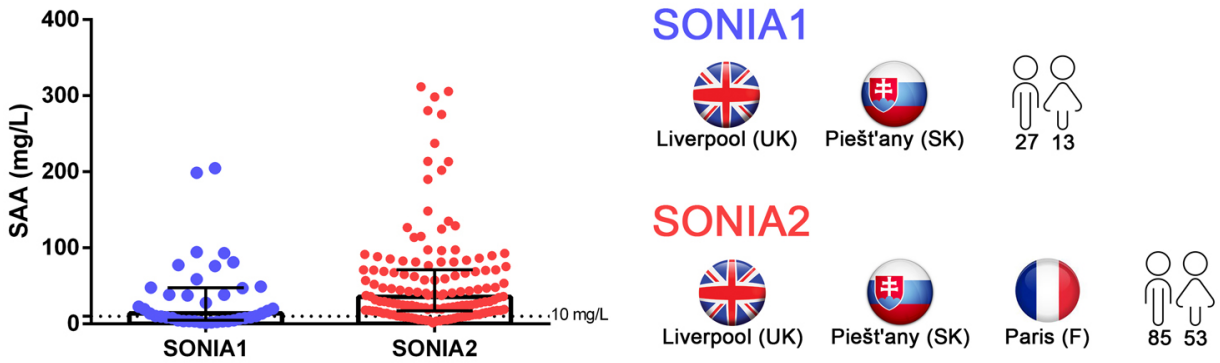

Fig. 1. Serum levels of the protein SAA in SONIA1 and SONIA2 patients were above the reference threshold of 10 mg/L 57.5% and 86% of samples, respectively.

Thanks to an international collaboration (www.developakure.eu) and an EU-funded project (7th Framework Programme funding granted in 2012 "DevelopAKUre" project number: 304985), we had the possibility to test for the very first time a high number of serum specimens (collected and stored under standardised procedures) from alkaptonuric individuals. Serum represents an excellent and easily accessible source of protein biomarkers that can reflect either physiological or pathological conditions. We used these serum samples to assess the levels of established biomarkers related to inflammation and oxidative stress. Samples were collected at the beginning of SONIA1 (enrolling 40 patients) and SONIA2 (enrolling 138 patients) clinical studies.

Our analyses showed that levels of a serum protein named Serum Amyloid A (SAA) were significantly elevated in the majority of samples: 57.5% and 86% of SONIA1 and SONIA2 samples, respectively (Fig. 1), regardless of sex or age. SAA play a role in inflammation, oxidative stress, and persistently elevated SAA is a risk factor for the development of AA amyloidosis, a process where insoluble fibrous protein aggregates are deposited leading to tissue degeneration and dysfunction. Similarly, another biomarker related to inflammation (chitotriosidase activity) was

above the reference threshold in half of SONIA2 samples. Other biomarkers used to assess inflammation (C-reactive protein, interleukin 1? and 6, tumour necrosis factor ?), tissue remodelling (metalloproteinase 3) or oxidative stress (advanced oxidation protein products, thiols, S-thiolated proteins and protein thiolation index-PTI) showed no statistically significant differences from a control healthy population.

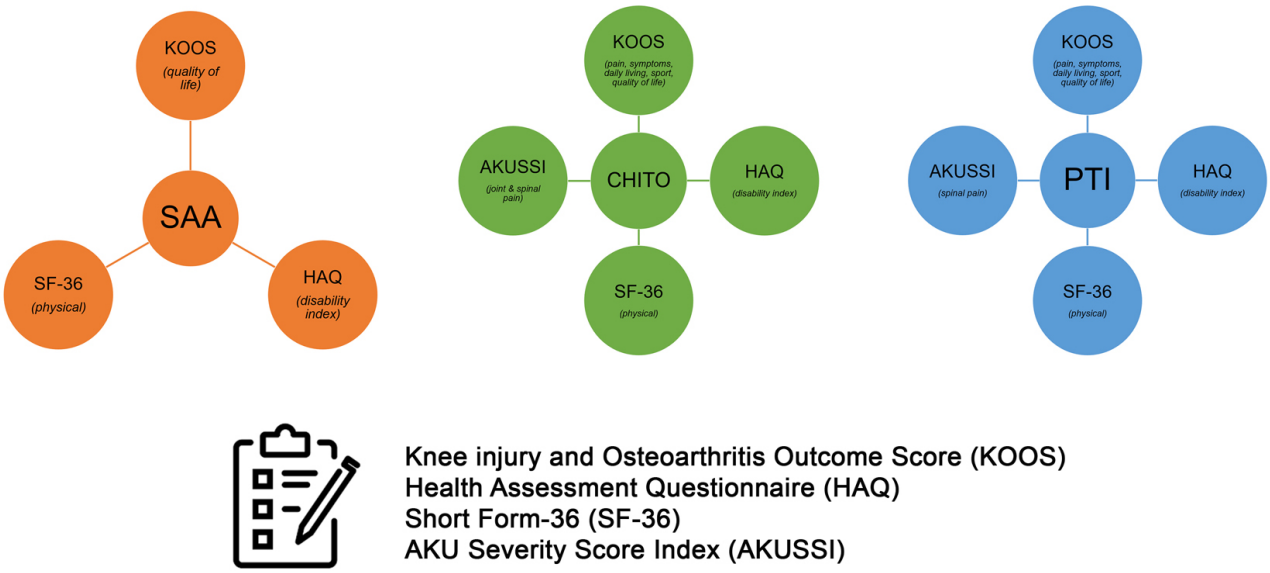

Fig. 2. SONIA2 patients with significantly high SAA, chitotriosidase activity and PTI reported more often a decreased quality of life (as assessed through patients' self-reports in established health questionnaires) and scored higher in the AKUSSI scale for joint and spinal pain.

Notably, we found that alkaptonuric individuals presenting with significantly higher SAA, chitotriosidase activity and PTI reported more often a decreased quality of life (as assessed through patients' self-reports in established health questionnaires) and scored higher in the AKUSSI scale for joint and spinal pain (Fig. 2). This suggests that increased inflammation and oxidative stress may cause worsening of symptoms in AKU, and that SAA, chitotriosidase activity and PTI might be proposed as disease activity and severity markers in AKU.

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Publication

Inflammatory and oxidative stress biomarkers in alkaptonuria: data from the DevelopAKUre project.

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