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ABSTRACT NUMBER: 1640

Tryptophan Metabolites Are Associated with Erosion and Symptoms in Hand Osteoarthritis: Results from the DIGICOD Cohort

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Meeting: ACR Convergence 2022

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SESSION INFORMATION

Date: Monday, November 14, 2022

Session Type: Abstract Session

Session Title: Abstracts: Osteoarthritis – Clinical

Session Time: 9:00AM-10:30AM

Background/Purpose: Tryptophan (Trp) and its metabolites have been linked to inflammatory processes and associated with gut dysbiosis. However, their role in osteoarthritis (OA) is unknown. We aimed to investigate Trp-derived metabolites in hand OA (HOA), a non-weight-bearing joints model.

Methods: In 418 baseline HOA patients from the HOA “DIGICOD” cohort (85% women, mean age 66 years, mean BMI 25 kg/m², 34% erosive HOA defined as ≥ 2 finger joints in erosive or remodelled phase, according to Verbruggen score) (1). 18 serum Trp metabolites (belonging to Kynurenine-IDO, indole or serotonin pathways) were assessed using high-performance liquid chromatography. Trp metabolites, metabolite-ratios (defined by a ratio between downstream and upstream metabolites) and metabolite-pathways (defined by the sum of metabolites of each pathway) were log-normalized. Multivariate Logistic regression adjusted on age, BMI and sex was performed and Odds Ratio (OR) were calculated between erosive and non-erosive HOA. Secondary analyses were performed using a Spearman correlation network on hand OA symptoms (AUSCAN sub-scores) and physical examination. Benjamini Hochberg was applied to p-values for multiple test correction.

Results: We identified four Trp metabolites, nine metabolite-ratios and one metabolite-pathway differentially associated with erosive HOA (figure 1). Trp was decreased in the erosive HOA (OR 0.41 [0.24,0.70] p = 0.007). The Kynurenine-IDO pathway was significantly upregulated in erosive HOA (OR 1.64 [1.14,2.35], p = 0.025), with an increase of 3-OH-Anthranilic acid, 3-OH-Anthranilic acid/3-OH-

Kynurenine and 3-OH-Kynurenine/Kynurenine ratios suggesting an enhancement of *Kynureninase* and *Kynurenine 3-mono oxygenase* enzymes (OR = 1.33 [1.14,1.56] p = 0.002, OR = 1.44 [1.87,1.76] p = 0.002 OR = 1.63 [1.16,2.30], p = 0.021). In the indole pathway, Indole-3-Aldehyde was decreased in erosive HOA (OR = 0.66 [0.50,0.88] p = 0.02) and Indoxyl-sulfate/Trp ratio was increased suggesting an enzymatic *Tryptophanase* activation (OR = 1.29 [1.05,1.58], p = 0.014). Finally, in the serotonin pathway, 5-OH-Trp and 5-OH-Tryptophane/Trp ratio were significantly increased in erosive HOA (OR = 1.43 [1.14,1.79], p = 0.01 and OR=1.52 [1.24,1.87] p = 0.002) suggesting an activation of *Trp hydroxylase*. Secondary analysis indicated 19 correlations between Trp metabolites and HOA symptoms and clinical features (figure 2).

Conclusion: Metabolites of the proinflammatory pathway Kynurenine-IDO were significantly increased in erosive HOA (figure 3) and were positively correlated with HOA symptoms. These results emphasize the role of Trp metabolites disturbances, and thus of low-grade inflammation and gut dysbiosis, in HOA.

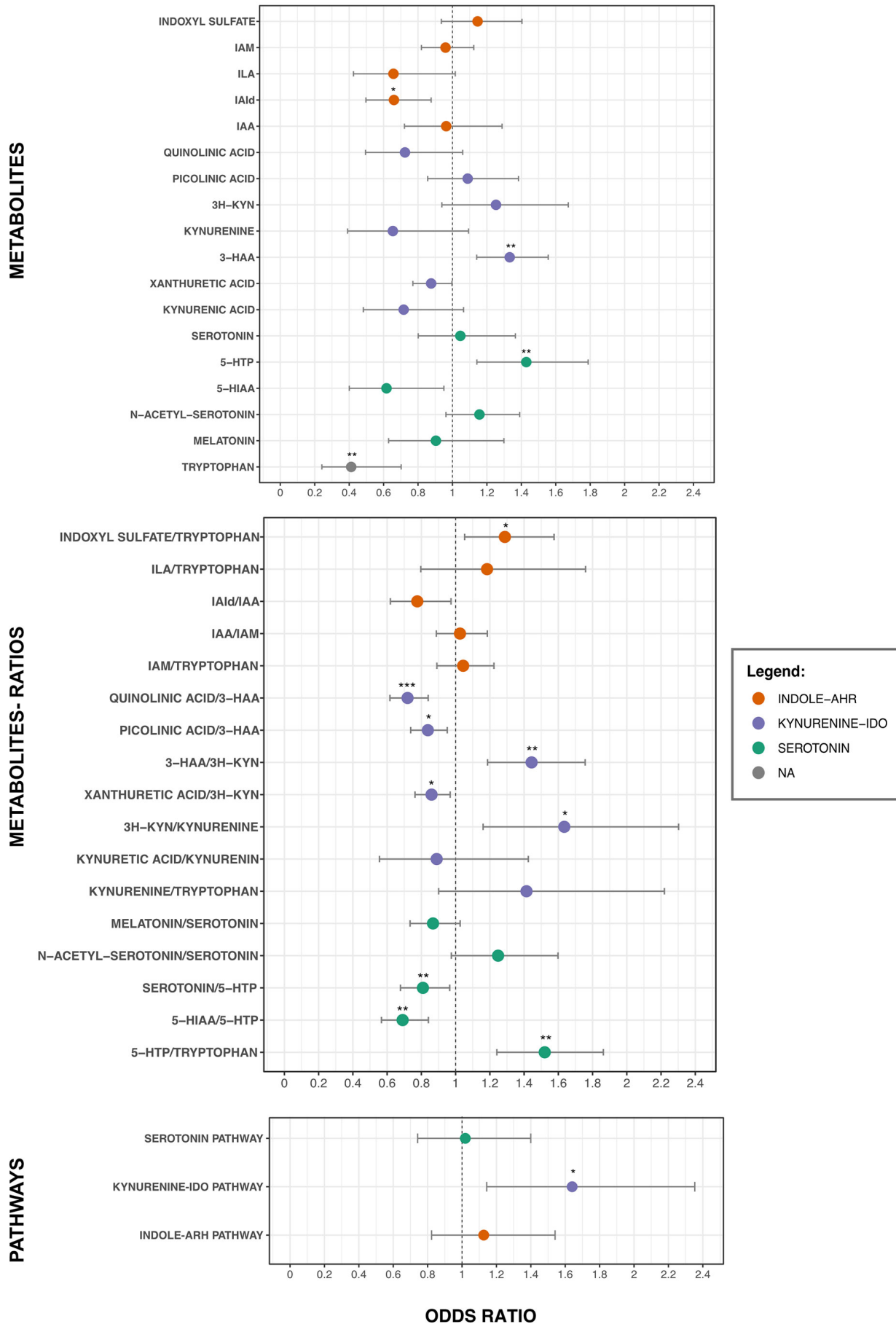


Figure 1: Odds ratio analyses of Trp metabolites, Trp metabolites ratio and pathways between erosive and non-erosive hand OA, results are adjusted on BMI, age and gender and p-values corrected for multiple- testing. 3-HAA : 3-Hydroxyanthranilic Acid 3H-KYN: 3-Hydroxykynurenine 5-HTP: 5 Hydroxytryptophan IIAA: Indole Acetic Acid IAld: Indole_3-Aldehyde IAM: Indole_3-Acetamide IDO: Indoleamine 2,3-Dioxygenase ILA: Indole_3-Lactic Acid

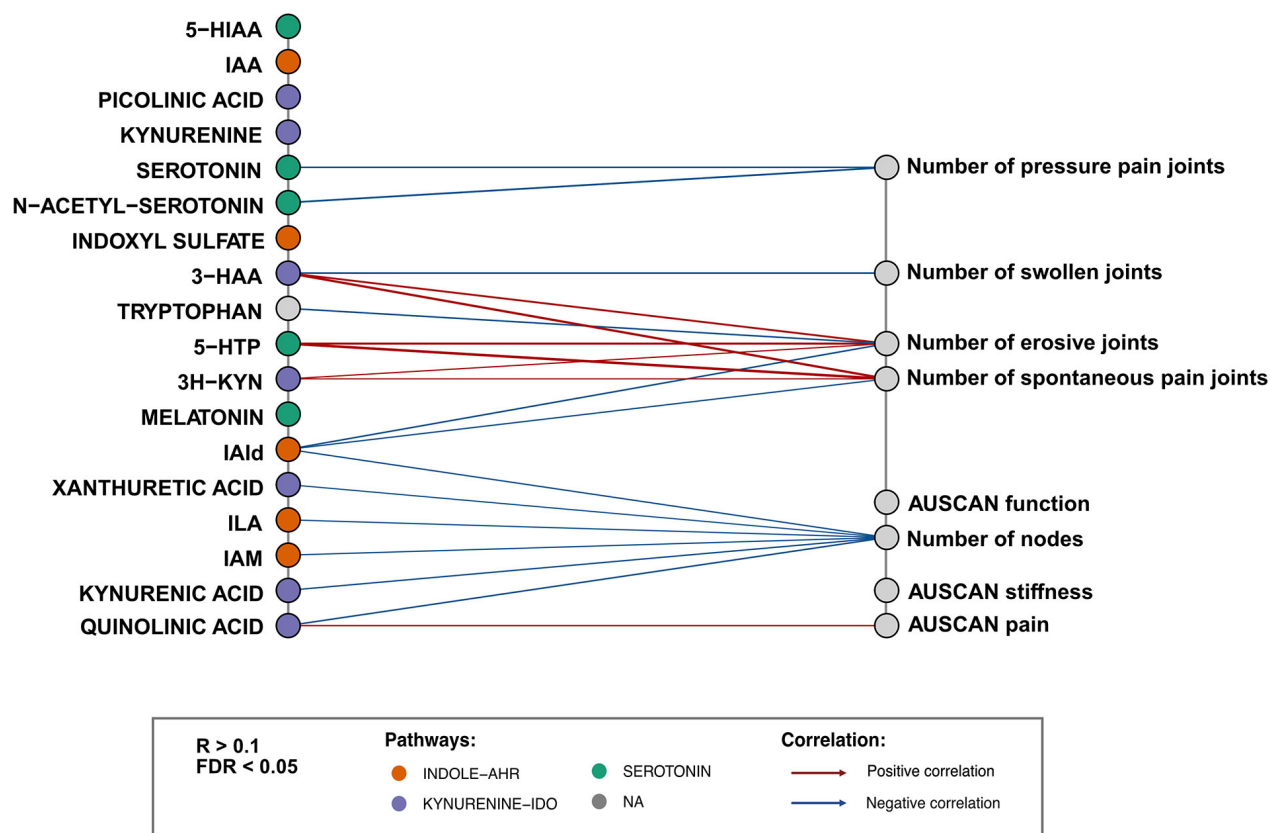


Figure 2: Correlation network of Trp metabolites and hand OA symptoms. Odds ratio analyses of Trp metabolites, Trp metabolites ratio and pathways. 3-HAA : 3-Hydroxyanthranilic Acid 3H-KYN: 3-Hydroxykynurenine 5-HTP: 5 Hydroxytryptophan IIAA: Indole Acetic Acid IAld: Indole_3-Aldehyde IAM: Indole_3-Acetamide IDO: Indoleamine 2,3-Dioxygenase ILA: Indole_3-Lactic Acid

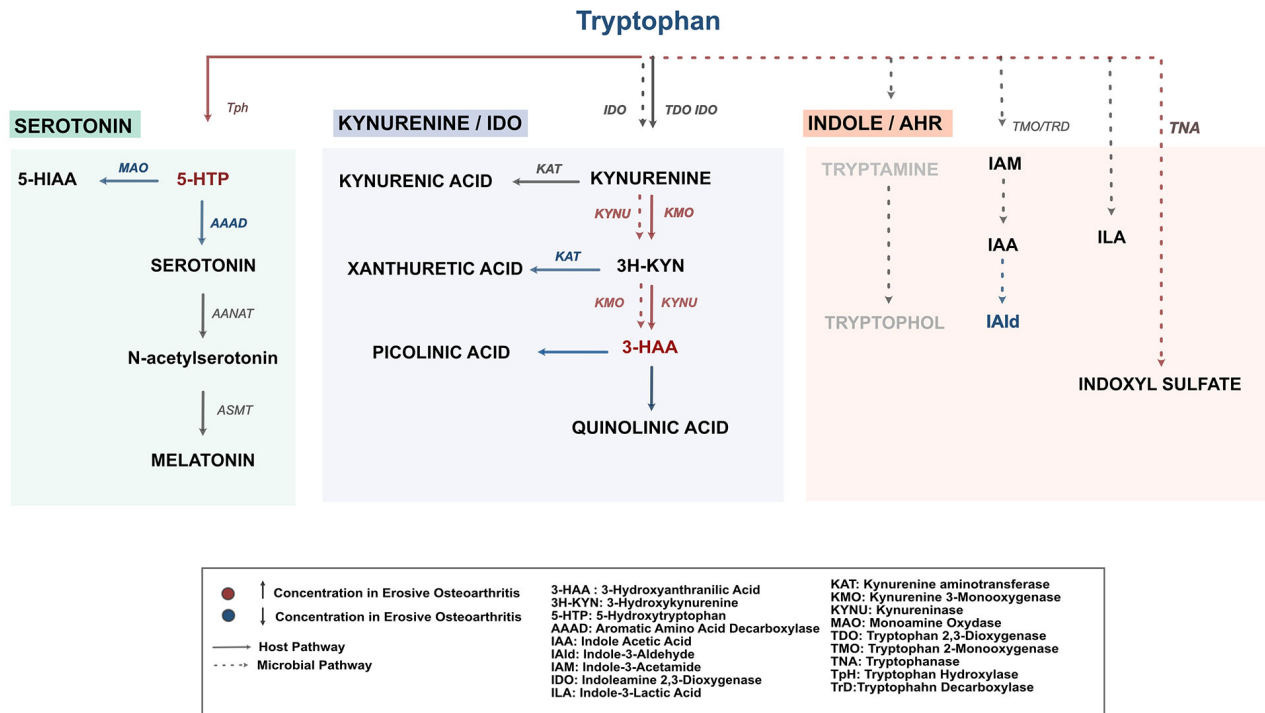


Figure 3: Identification of upregulated and downregulated Trp metabolites in erosive hand OA.

Disclosures: **M. Binvinat**, None; **P. Emond**, None; **B. Miao**, None; **A. Courties**, None; **E. Maheu**, None; **M. Kloppenburg**, None; **P. Richette**, AbbVie, Amgen, Biogen, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, Roche, Sanofi-Aventis, UCB; **A. Butte**, Genentech, Northrup Grumman, Johnson and Johnson, Personalis, NuMedii, Samsung, Mango Tree Corporation; **E. Mariotti-Ferrandiz**, None; **F. Berenbaum**, 4Moving Biotech; **H. Sokol**, None; **J. SELLAM**, None.

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