Association of Synovial Fluid and Plasma Tryptophan-Kynurenine Pathway Metabolites with Osteoarthritis Pain and Severity

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INTRODUCTION: Altered tryptophan (Trp) metabolism, partially regulated by pro-inflammatory cytokines that are upregulated in osteoarthritis (OA), results in inflammation and neurotoxicity. This study examines the relationship between altered Trp metabolism and radiographic OA severity and pain.

METHODS: Knee synovial fluid (SF) and plasma samples from a previous study of participants with radiographic OA in at least one knee and self-reported knee pain were analyzed via LC/MS/MS for Trp, kynurenine (Kyn), kynurenic acid (KynA) and indoleamine 2,3-dioxygenase (IDO) activity calculated (kynurenine:tryptophan). SF and plasma concentrations were tested for an association with OA pain and severity and for correlation with one another.

RESULTS: Higher mean SF concentrations of Kyn (p=0.042) and IDO activity (p=0.026) were positively associated with OA radiographic severity (Kyn p=0.042, IDO p=0.026) and knee pain (Kyn p=0.007, IDO p=0.027). Compared with plasma levels, SF KynA (p<0.0001) and SF Trp (p=0.0005) were lower but SF IDO activity was higher (p=0.0019). SF Kyn (r^2=0.68, p=0.0002), SF KynA (r^2=0.36, p=0.023), SF Trp (r^2=0.31, p=0.032), and SF IDO activity (r^2=0.59, p=0.0009) were all significantly correlated with their corresponding plasma levels, and plasma Kyn was positively correlated with OA severity.

DISCUSSION AND CONCLUSION: Altered Trp metabolism was associated with both more severe structural damage and pain in OA. The higher IDO activity in SF suggests more conversion of Trp to pain-inducing Kyn in the joint than in the plasma. The strong correlations between SF and plasma concentrations of Trp metabolites suggests their clinical utility as biomarkers and targets for therapy.