The EISER Study: Identifying Microbial Factors Associated with Subclinical Gut Inflammation in Psoriatic Arthritis Patients Who Develop Inflammatory Bowel Disease

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BACKGROUND

- Nearly 8% of patients with spondyloarthritis (SpA) manifest symptoms that are compatible with inflammatory bowel disease (IBD), despite not having any previous diagnosis of chronic intestinal pathologies.
- There is growing evidence showing that the microbiome is associated with immune-mediated diseases, particularly in IBD, which is characterized by an aberrant microbiome composition and function. We hypothesize that the gut microbiome could modulate intestinal inflammation and pathogenesis of IBD in SpA patients.

METHODS

- **Subjects**: We selected 193 subjects in the EISER study diagnosed with axial (n=9), peripheral (n=144) or mixed (n=40) forms of psoriatic arthritis (PsA), a subset of SpA, with no prior diagnosis of IBD or other chronic intestinal disorders.
- **IBD diagnosis**: Subjects with fecal calprotectin (fCAL) levels <80µg/g were considered negative for IBD. For patients with fCAL levels ≥80 µg/g and/or with clinical symptoms compatible with IBD, IBD was diagnosed based on colonoscopy and histological analysis of biopsies.
- **Microbiome analysis:** Stool microbiome was characterized using shotgun metagenomic sequencing (Illumina HiSeq). Data was processed using MetaPhlAn 4, MMEDS and R. Blood samples were collected for proteomic analysis using ELISA and Multiplex methods.

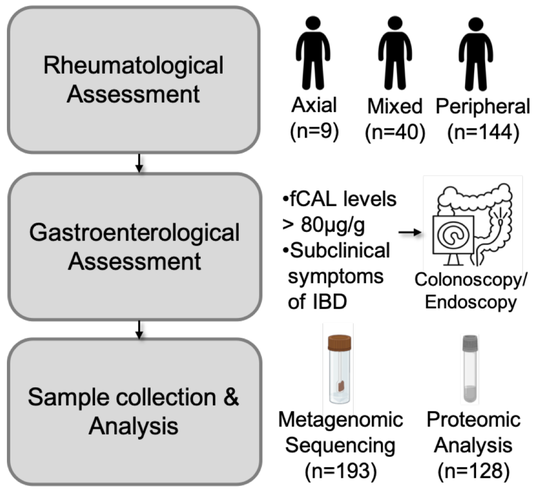

Figure 1. Study Design

RESULTS

- Twenty-five out of 193 subjects (12.95%) had symptoms compatible with subclinical IBD (sxIBD) and five patients (2.6% of total) were diagnosed with IBD (dxIBD). Nonsteroidal anti-inflammatory drugs (NSAIDs) resulted in significant differences in microbial alpha (p=0.03) and beta diversity (p=0.043), while proton-pump inhibitors (PPI) resulted in significant differences in beta diversity (p=0.036).
- Patients diagnosed with IBD had higher fCAL (p=0.016), and significant enrichment of *Prevotella copri, P. stercorea, P. distasonis, Clostridium fessum* and *Blautia stercoris* (p<0.05). Several of these taxa had a larger effect size (Cohen's D) compared to fCAL for diagnosis of IBD. While fCAL was significantly elevated in patients using PPIs*, P. copri, P. stercorea* and *B. stercoris* were not (p>0.05). (**Fig. 2**).
- *Blautia caecimuris, Romboutsia timonensis, Eubacterium ventriosum and Bacteroides nordii* were enriched in axial PsA*, Veillonella atypica* in mixed PsA, and *Eubacterium spp* and *Enterocloster lavalensis* in peripheral PsA (**Fig. 3A)**.

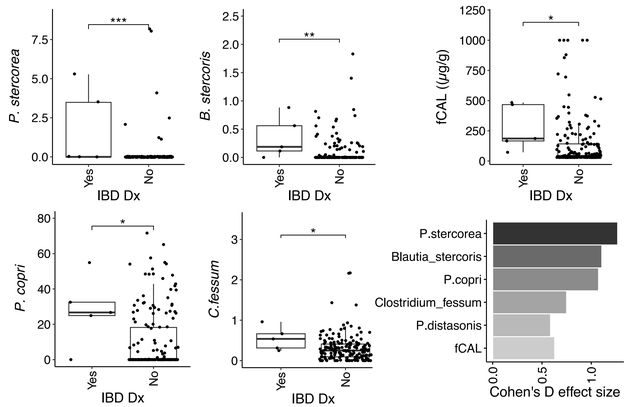

Figure 2. **Potential biomarkers of IBD in PsA patients.** Cohen's D effect size show that *P.stercorea* has the biggest effect on IBD diagnosis, followed by *B.stercoris* and *P.copri*, compared to other bacteria and the levels of fCAL.

- Patients presenting mixed PsA had elevated levels of serum IL-8 compared to axial and peripheral PsA patients, and of IL-17F and IL-13 compared to peripheral PsA (p<0.05) (**Fig. 3B**).

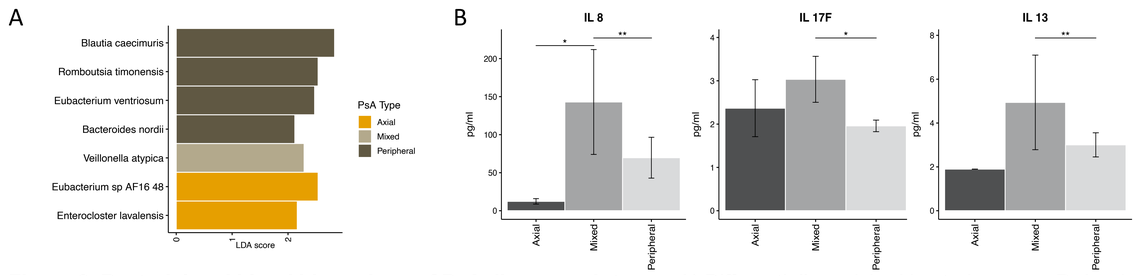

Figure 3. **Bacterial and blood biomarkers of PsA disease sub-types.** A) Differentially enriched bacteria across PsA sub-types, assessed with linear discriminant analysis Effect Size (LefSe). B) Levels of serum cytokines across PsA sub-types.

DISCUSSION

In this cohort of PsA patients, 2.6% were diagnosed with IBD. We identified taxa differentially enriched in IBD, including *P. copri*, which has been linked to other rheumatic diseases. Importantly, while fCAL was significantly higher in IBD, its discriminatory power was not as strong as that of *P. stercorea*, *B. stercoris, P. copri* or *C. fessum*, suggesting that these taxa could be used as additional biomarkers of IBD in PsA patients. Moreover, we identified enrichment of specific taxa in PsA subtypes and elevated levels of cytokines in patients with mixed PsA, which could have additional predictive value to distinguish disease subtypes.

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