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THE PECULIARITIES OF INTESTINAL MICROBIOME IN PATIENTS WITH OSTEOARTHRITIS

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Introduction: Osteoarthritis (OA) requires frequent nonsteroidal anti-inflammatory drugs (NSAIDs), harmful to the gastrointestinal tract. Intestinal microbiome (IM) disturbance can result from NSAID use, amplifying NSAID-enteropathy, but some evidence shows that IM disturbance can relate to OA directly.

Aims & Methods: To study the peculiarities of the intestinal microbiome in patients with OA. We investigated 91 patients with OA of different localizations and degrees divided into three subgroups depending on NSAIDs use and their selectivity. 30 people without OA were recruited as a control group (CG). We studied major phyla of intestinal bacteria (*Bacteroidetes*, *Firmicutes*, *Actinobacteria*), then calculated the *Firmicutes/Bacteroidetes* (F/B) ratio and content of "other" in feces; PCR-SSP method. Among "others," we determined the content of *Gamma-proteobacteria* class and *Akkermansia muciniphila* species.

Results:

| Phyla content | OA | OA subgroups | | | CG |
|-----------------------|----------------------------|----------------------------|----------------------------|----------------------------|--------------------------|
| | | "non-NSAIDs" | non-selective NSAIDs | selective NSAIDs | |
| <i>Firmicutes</i> | 51.80% (IQR 45.37-58.64) § | 51.47% (IQR 48.11-56.21) § | 57.21% (IQR 49.98-69.05)*# | 47.83% (IQR 32.24-52.92) § | 66.66% (IQR 58.57-73.66) |
| <i>Bacteroidetes</i> | 15.86% (IQR 8.25-20.54) § | 15.08% (IQR 8.03-29.21) § | 18.04% (IQR 9.36-17.75) § | 13.50% (IQR 9.24-17.75) § | 6.06% (IQR 3.23-8.57) |
| <i>Actinobacteria</i> | 9.99% (IQR 6.55-13.61) * | 8.41% (IQR 5.59-10.02) £& | 7.75% (IQR 5.51-10.56) £& | 13.66% (IQR 13.26-14.56) | 12.16% (IQR 8.09-16.54) |
| "other" | 22.33% (IQR 13.39-33.95) | 25.04% (IQR 19.51-34.48) & | 17.00% (IQR 12.54-25.69) § | 25.02% (IQR 12.85-36.16) & | 15.12% (IQR 12.10-19.57) |
| F/B ratio | 3.32 (IQR 2.18-5.47) § | 3.33 (IQR 1.79-6.74) § | 3.27 (IQR 2.65-5.25) § | 3.65 (IQR 1.63-4.84) § | 11.60 (IQR 6.56-20.76) |

§ - a significant difference from CG (p<0.0001)

* - a significant difference from CG (p<0.05)

& - a significant difference from CG (p<0.01)

- a significant difference from selective NSAIDs (p<0.01)

£ - a significant difference from selective NSAIDs (p<0.0001)

§ - a significant difference from "non-NSAIDs" (p<0.05)

There was a negative correlation between *Firmicutes* content and the stage of OA (p=0.521); the F/B ratio correlated with the body mass index (BMI) (p=0.455) and patient's age (p=0.562); a negative correlation in *Actinobacteria* content with the patient's age was found (p=0.300); p<0.05.

| Bacteria class/specie | "non-NSAIDs" | non-selective NSAIDs | selective NSAIDs |
|--------------------------------|-----------------------|------------------------|------------------------|
| <i>Gamma-proteobacteria</i> | 1.44% (IQR 0.81-2.03) | 1.96% (IQR 1.52-2.57)# | 2.19% (IQR 1.08-2.51) |
| <i>Akkermansia muciniphila</i> | 2.55% (IQR 1.63-4.30) | 1.35% (IQR 1.20-1.64)* | 1.22% (IQR 0.99-1.50)* |

§ - a significant difference from "non-NSAIDs" (p<0.01)

* - a significant difference from "non-NSAIDs" (p<0.001)

We found a correlation in the *Gamma-proteobacteria* content with the stage of OA (p=0.526) and with BMI (p=0.356), p<0.05. The *Akkermansia muciniphila* content correlated with the patient's age (p=0.402; p<0.05).

Conclusion: There is a significant difference in the IM composition among subjects with OA and without this disease. Patients with OA have higher levels of *Bacteroidetes* and "other" bacteria and lower *Firmicutes* and *Actinobacteria* content. The F/B ratio is the most sensitive indicator of the difference. The NSAIDs intake and its selectivity affect some bacterial taxonomical units, but we did not find apparent regularity. The most explicit changes were found in *Akkermansia muciniphila* levels: NSAIDs intake decreased its level, regardless of NSAID's selectivity.