INTERACTION OF SECRETORY IGA, IGG, AND GUT MICROBIOME PROFILE DURING METFORMIN THERAPY

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OBJECTIVES
Metformin is the most widely administered therapeutic drug for the treatment of type two diabetes (T2D) despite its variable therapeutic effects and side effects. In our previous research, we have found that secretory immunoglobulin A (sIgA) may be involved in mediating metformin and gut microbiome interaction, by playing a significant role in shaping the composition of the human gut microbiome and the geographical distribution of bacterial communities. To further this study, we aimed to investigate sIgA, IgG, and gut microbiome interactions during antidiabetic therapy.

METHODS
We involved a total of 40 newly diagnosed, treatment-naive T2D patients and 10 healthy individuals. Stool samples from T2D patients were collected at three consecutive time points: before metformin therapy, one week after metformin therapy, and three months after therapy, but for healthy individuals, stool samples were collected at two time points: before metformin therapy and one week after metformin administration. Stool samples were sorted into three fractions (pre-sort, sIgA+ fraction, and IgG+ fraction) using a novel magnetic bead-based cell separation method that utilizes anti-IgA and anti-IgG antibodies. For all fractions, microbial DNA was extracted, and massive parallel metagenome sequencing was performed.

RESULTS
In total 420 fractions prepared from stool samples were sequenced and analyzed. In the sIgA+ fraction, metformin administration induced an increase in abundance of *Escherichia fergusonii*, and *Escherichia marmotae* in both cohorts. Both species were previously described as potential human pathogens. Additionally, we observed that *Anaerobutyricumhallii*, *Anaerostipes hardus,* and *Blautia A faecis* were coated with both sIgA and IgG antibodies in T2D patients at all time points with pre-sorted samples, regardless of metformin therapy, signaling a strong immune response to these species.

CONCLUSIONS
Metformin administration in both cohorts increased an abundance of multiple species in the sIgA+ fraction, and some of these species were previously described as potential human pathogens, further research is needed to understand whether this relates to metformin side effects. Relative abundance changes for most significant species were consistent in most fractions, showing that the bead-based bacterial cell separation method can produce consistent results and could be used in similar studies.

Key words: T2D, Metformin, sIgA, metagenome, microbiome