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Metformin promotes regulatory T and B cells and suppresses Th17 via multiple pathways including microbiome modulation in liver transplant patients

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Introduction: In a previous study, we documented that a combination treatment with metformin and tacrolimus may improve immune homeostasis by modulating regulatory T cells (Tregs) and T helper17 cells (Th17). In the present study, we aim to observe serial changes in immune cells, including Tregs, regulatory B cells (Bregs), and Th17 cells, following the addition of metformin in liver transplant (LT) patients. Furthermore, we seek to elucidate the underlying pathways driving these changes in immune homeostasis, including the analysis of gut microbial changes in LT patients.

Methods: We prospectively enrolled 23 LT patients with newly diagnosed diabetes or pre-diabetes and administered metformin (500-1000mg/day). Subsequently, 12 patients gradually tapered their immunosuppressants (ISs) to half dose (tapering group), while the remaining 11 maintained there IS dosage (maintenance group). The proportion of various immune cells, including Tregs, Bregs, Th1, and Th17, were analyzed in every 3 months. Fecal microbiome analyses were also performed before and after metformin treatment. RNA sequencing analyses were conducted to evaluate differences in gene expression in response to metformin and functional microbiome changes (Figure A).

Results: After administering metformin, the proportions of Tregs, Bregs, Th1 cells gradually increased, while Th17 cells decreased over time in the maintenance group (Figure B). These trends were consistently observed in the tapering group, further supporting the immunomodulatory effects of metformin (Figure C). The maintenance group also showed a marginal increase in the abundance of Akkermansia and Bifidobacterium after metformin administration. Meanwhile, in the tapering group, the abundance of Faecalibacterium tended to increase after metformin treatment. RNA sequencing analysis revealed that these microbiomes increased the expression of the IL-10 gene. Moreover, the expression of STAT3 decreased, while CTLA-4 expression increased after metformin therapy.

Conclusion: This study demonstrated that metformin increases Tregs and Breg cells and suppresses Th17 via multiple pathways, including functional microbiomes, in LT patients.