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Age- and Sex-Specific Gut Microbiome Alterations in IgA Nephropathy: Implications for Disease Pathogenesis and Progression

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Objectives : IgA nephropathy (IgAN) is a heterogeneous disease influenced by age and sex, with gut dysbiosis potentially contributing to its onset and progression through galactose-deficient IgA1 (Gd-IgA1) production in the gut mucosa-associated lymphoid tissue, although the definite mechanism remains unclear.

Methods : We analyzed shotgun metagenome sequencing from fecal samples of 85 biopsy-proven IgAN patients and 51 kidney donors. Gut microbiome composition and pathways were analyzed using MaAslin2 for covariates and Random Forest regression, with performance assessed via AUC-ROC curves and SHAP values. Then, we validated these age/sex specific metagenomic findings from the independent validation cohort consisting of 147 IgAN, serum Gd-IgA1 levels, and glomerular immunofluorescence findings. The clinical significance of age and sex was further explored in a separate multi-center IgAN cohort using multivariable Cox proportional hazards modeling.

Results : IgAN patients showed dysregulated age-dependent gut microbiome shifts compared to healthy controls, which was more pronounced in males than females. Significant taxonomic and functional gene differences were observed in specific age groups (males ≤47 years; females ≤44 years). Younger patients exhibited upregulated galactose metabolism genes suggesting reduced galactose availability and subsequent elevation of serum Gd-IgA1 production, while older patients showed downregulated immune and signaling pathways, suggesting age-related immune dysregulation. Parallelly, young IgAN patients showed more elevated serum Gd-IgA1 levels than healthy controls ($p<0.001$) as well as more prominent mesangial IgA and C3 deposition than older IgAN patients. Finally, older age was associated with faster renal progression in younger patients, whereas the opposite trend in older IgAN patients

Conclusions : The impact of the gut microbiome on IgAN pathogenesis differs by age and sex, with a more pronounced effect observed in younger patients. Younger patients exhibit distinct metagenomic features associated with dysregulated galactose metabolism, that might be associated with enhanced Gd-IgA1 production, increased mesangial IgA and C3 deposition, and rapid kidney progression.