

Gut microbiome associated with Graves' disease and Graves' orbitopathy: the INDIGO* multi-centre European study

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Abstract

Context: Gut bacteria can influence host immune responses but little is known about their role in tolerance-loss mechanisms in Graves' disease (GD; hyperthyroidism caused by autoantibodies, TRAB, to the thyrotropin receptor, TSHR) and its progression to Graves' orbitopathy (GO).

Objective: To compare the fecal microbiota in GD patients, with GO of varying severity, and healthy controls (HC).

Design, setting and patients: Patients were recruited from four European countries (105 GD patients, 41 HC) for an observational study with cross-sectional and longitudinal components.

Results: At recruitment, when patients were hyperthyroid and TRAB positive, Actinobacteria were significantly increased and Bacteroidetes significantly decreased in GD/GO compared with HC. The Firmicutes to Bacteroidetes (F:B) ratio was significantly higher in GD/GO than in HC. Differential abundance of 15 genera was observed in patients, being most skewed in mild GO. Bacteroides displayed positive and negative correlations with TSH and FT4 respectively and was also significantly associated with smoking in GO, smoking is a risk factor for GO but not GD. Longitudinal analyses revealed that the presence of certain bacteria (Clostridiales) at diagnosis correlated with the persistence of TRAB 200 + days after commencing anti-thyroid drug treatment.

Conclusions: The increased F:B ratio observed in GD/GO mirrors our finding in a murine model comparing TSHR-immunized with control mice. We defined a microbiome signature and identified changes associated with autoimmunity as distinct from those due to hyperthyroidism. Persistence of TRAB is predictive of relapse, identification of these patients at diagnosis, via their microbiome, could improve management with potential to eradicate Clostridiales.

Keywords: Firmicutes:Bacteroidetes ratio; Graves' disease; Graves' orbitopathy; autoimmunity; gut microbiota; hyperthyroidism.

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