

# EDITORIAL – MICROBIOME TRANSPLANTATION TRIALS: RESOLVING RARE ENDOCRINE DISRUPTIONS IN WHIPPLE’S DISEASE WITH MALABSORPTION

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Whipple’s disease (WD) is the result of an infection by *Tropheryma whipplei*, which impairs the small intestine, leading to villous atrophy, lymphatic obstruction, and fat deposition in the mucosa. The structural changes that develop cause severe nutrient malabsorption, resulting in the classical triad of weight loss, diarrhea, and steatorrhea<sup>1</sup>. Although gastrointestinal symptoms are primary, the disease has spread to endocrine systems in a few instances, and features such as hypothyroidism, pituitary involvement, and adrenal insufficiency have been reported. An isolated case report described transient primary hypothyroidism that resolved after antibiotic therapy<sup>2</sup>.

WD is not only a bacterial infection but also a breakdown of the patient’s immune system, in which dysbiosis has a major role in the pathogenesis. The presence of *T. whipplei* does not always lead to disease, since the pathogen can be found in 50% of healthy individuals<sup>3</sup>. Usually, the infection becomes chronic only in those with T-cell immune defects. From a pathological perspective, macrophages loaded with *T. whipplei* found in the lamina propria cause malabsorption and microbiome disruption. The bacterium enters intestinal epithelial cells, inducing apoptosis and weakening the gut barrier, thereby perpetuating dysbiosis even after therapy. Though eradication requires long-term antibiotic therapy (e.g., Trimethoprim-Sulfamethoxazole for 1-2 years), the treatment often worsens gut flora imbalance, leading to post-infection complications.

Dysbiosis and the resulting malnutrition (vitamin B12, D, and folate deficiencies have been reported in up to 90% of patients) may lead to secondary endocrine dysfunctions, such as hypopituitarism and adrenal insufficiency<sup>4</sup>. Considering that healthy microbiota is the main supplier of hormonal and metabolic homeostasis through the synthesis of short-chain fatty acids (SCFAs) and cofactors needed for nutrient absorption, microbiome restoration is highly recommended as a treatment.

Fecal Microbiota Transplantation (FMT), which restores the microbiome, has thus far been effective in regulating metabolism and the endocrine system. Experiments in animals and humans provide evidence of a positive impact of FMT on insulin resistance, glucose metabolism, and systemic inflammation in type 2 diabetes mellitus<sup>5</sup>. These results show that microbiome changes can indirectly lead to the correction of endocrine disorders caused by gut dysfunction. On top of that, FMT has resulted in cure rates of 87-92% in cases of recurrent *Clostridioides difficile* infection (rCDI), a condition characterized by antibiotic-induced dysbiosis<sup>6</sup>. The potential of FMT as a post-antibiotic recovery tool in WD is, therefore, very promising.



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A pilot Microbiome Transplantation (MT) trial would evaluate whether the reintroduction of a healthy microbiome post-*T. whipplei* eradication not only helps in gut barrier repair quickly but also normalizes bile acid and SCFA metabolism and resolves secondary endocrine dysfunctions faster than nutritional supplementation alone<sup>5</sup>. Nevertheless, since WD is an infectious disease, any microbiome-based treatments must be accompanied by strict donor screening protocols. According to the FDA, there have been deaths due to infections transmitted by donor stools without proper screening; hence, the utmost caution in safety monitoring and adherence to FDA-level screening standards is necessary<sup>7</sup>.

Today, there are no systematic investigations pertaining to endocrine recovery or microbiome restoration post-Whipple's disease treatment. Given that the microbiome is considered an "endocrine organ"<sup>8</sup>, clinician-led documentation of endocrine outcomes following WD therapy can set the direction for research. Only a few case reports have been published describing hypothyroidism, adrenal insufficiency, and hypogonadism as secondary to WD. However, these endocrine disruptions are still not well understood and are seldom reported<sup>9</sup>. There has never been a trial that considered microbiome transplantation to resolve endocrine sequelae, thereby constituting a significant area that can be cautiously explored further.

### Conflict of Interest

The author declares no competing interests.

### Authors' Contributions

Conceptualization, A.M.H., M.I., M.L.; Literature Review, A.M.H., M.I.; Original Draft, A.M.H.; Writing – Review & Editing, A.M.H., M.I., M.L.; Final Approval, A.M.H., M.I., M.L.

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