Architectural and functional alterations of the small intestinal mucosa in classical Whipple's disease

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Resumen

Classical Whipple's disease (CWD) affects the gastrointestinal tract and rather elicits regulatory than inflammatory immune reactions. Mechanisms of malabsorption, diarrhea, and systemic immune activation are unknown. We here analyzed mucosal architecture, barrier function, and immune activation as potential diarrheal trigger in specimens from 52 CWD patients. Our data demonstrate villus atrophy and crypt hyperplasia associated with epithelial apoptosis and reduced alkaline phosphatase expression in the duodenum of CWD patients. Electrophysiological and flux experiments revealed increased duodenal permeability to small solutes and macromolecules. Duodenal architecture and permeability ameliorated upon antibiotic treatment. Structural correlates for these alterations were concordant changes of membranous claudin-1, claudin-2, claudin-3, and tricellulin expression. Tumor necrosis factor-alpha and interleukin-13 were identified as probable mediators of epithelial apoptosis, and altered tight junction expression. Increased serum markers of microbial translocation and their decline following treatment corroborated the biological significance of the mucosal barrier defect. Hence, mucosal immune responses in CWD elicit barrier dysfunction. Diarrhea is caused by loss of absorptive capacity and leak flux of ions and water. Downregulation of tricellulin causes increased permeability to macromolecules and subsequent microbial translocation contributes to systemic inflammation. Thus, therapeutic strategies to reconstitute the mucosal barrier and control inflammation could assist symptomatic control of CWD.

Palabras clave

KeyWords Plus:HIV-INFECTED PATIENTS; TRICELLULAR TIGHT JUNCTIONS; ACTIVE CROHNS-DISEASE; NECROSIS-FACTOR-ALPHA; EPITHELIAL APOPTOSIS; CELIAC-DISEASE; CELL FUNCTION; BARRIER; PERMEABILITY; MACROMOLECULES

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