

## Zonulin; serum

Circulating zonulin is a clinically useful marker of intestinal permeability. Zonulin is a protein that reversibly regulates intestinal permeability; it is synthesized in intestinal and liver cells. High levels of zonulin have been associated with increased intestinal permeability, as it induces the breakdown of the tight junctions between intestinal epithelial cells. Several autoimmune, inflammatory and neoplastic diseases have been associated with elevated levels of zonulin, or evidence of increased intestinal permeability. Such diseases include Celiac disease, type I diabetes, juvenile nonalcoholic fatty liver disease; evidence is accumulating for multiple sclerosis, rheumatoid arthritis, asthma and inflammatory bowel disease. Zonulin levels may be higher in obese adults, and in adults with glucose intolerance. Elevated serum levels of zonulin and increased permeability are commonly observed in patients at risk of developing Crohn's disease and type 1 diabetes patients, prior to the onset of symptoms. Zonulin levels may increase with corticosteroid use.

### Analytes Tested

Analyte	CPT	ABN Required
Zonulin; serum	83520	Yes

### Detailed Information

Cellular receptors for zonulin are present in the small and large intestines, the heart and the brain. Zonulin release from the intestinal mucosa may be triggered by gliadin fragments, or by the adherence of bacteria to the epithelial cell surface. Simple sugars, sodium, emulsifiers, microbial transglutaminase (food additive) and nanoparticles are known to disrupt intestinal barrier function.

The use of some probiotics has been shown to reduce serum and fecal zonulin levels. Restoration of the gastrointestinal mucosal barrier may include dietary changes, treatment of dysbiosis, digestive supports and anti-inflammatory therapies. These may include supplements such as quercetin, vitamin C, curcumin, gamma-linoleic acid, omega-3 fatty acids (EPA, DHA), and aloe vera. Other nutrients such as zinc, beta-carotene, pantothenic acid, and L-glutamine may provide some support for rejuvenation of the GI mucosa. Consider a Comprehensive

Stool Analysis to further investigate potential causes of increased intestinal permeability.

Zonulin expression in the small intestine occurs when a chemokine receptor is stimulated by gliadin or chemokines and induces pro-inflammatory signaling pathways in gastrointestinal epithelial cells. The released zonulin activates the cell-signaling pathway via epidermal growth factor and protease-activated receptor 2, which disassembles the tight junctions between the GI epithelial cells. The loss of the tight junctions increases intestinal permeability and allows polypeptides and other macromolecules to pass between epithelial cells into the lamina propria layer of the gut wall. The macromolecules and polypeptides induce an antigen response and promote pro-inflammatory cytokine production in the enteric immune system.

Zonulin is a pre-haptoglobin; levels are modulated by the presence or absence of haptoglobin (HP) gene. When zonulin is cleaved by intestinal tryptase IV, it is converted into haptoglobulin, a protein with heme (iron)-binding and anti-microbial properties. HP-1-1 genotypes have zero (null) copies of the HP gene. HP-2-2 genotypes have two copies of the gene, and HP-1-2 genotypes have one copy of the gene. HP 1-1 (null) genotypes may have zonulin levels in the normal range, even if the presence of inflammatory or autoimmune disease is confirmed by other biomarkers. Zonulin levels may increase in nephrotic syndrome (Hp2-1 or 2-2 phenotypes).