Editorial

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Gut permeability, obesity, and metabolic disorders: who is the chicken and who is the egg?

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Improved hygiene that leads to a reduced exposure to microorganisms has been implicated as one possible cause for the "epidemic" of chronic inflammatory and metabolic diseases in industrialized countries during the past 3–4 decades. In addition to a genetic predisposition and exposure to environmental triggers, a third key element, increased intestinal permeability, which may be influenced by the composition of the gut microbiota, has been proposed in the pathogenesis of these diseases (1). An imbalance between caloric intake and energy expenditure, both of which coexist with unhealthy lifestyles, is the most frequent cause of obesity. However, intestinal factors that influence gut mucosal biological and immunologic functions, including modification of the microbiota composition and barrier function, seem to play a crucial role as well in causing obesity and its associated metabolic complications. The symbiotic lifestyle of enteric bacteria colonizing the gastrointestinal tract contributes to the human host metabolic needs with the elaboration of enzymes not produced by humans to the catabolism of dietary fibers. A specific microbiota composition highly influenced by a Western diet and characterized by a decreased ratio of Bacteroidetes to Firmicutes or an increase in specific microbiota species has been described (2). It is becoming increasingly evident from animal studies and metagenomic and metabolomic studies that, in obesity, a specific gut microbiota may be responsible for a more efficient intestinal absorption of calories and increased lipid deposition by the digestion and absorption of plant polysaccharides that are usually poorly digestible (3), which influences body weight and interferes with metabolic changes. Studies in children have shown that the success of specific dietary interventions to lose weight are dependent on the type of initial host microbiota, and that the microbiota in childhood is strongly influenced by the type of delivery, the neonatal feeding regimen, and the exposure to antibiotics (4).

Another key intestinal biological function influenced by diet and microbiota composition is the gut permeability by macromolecules. In mice, a high-fat diet reduced Bifidobacteria and increased plasma concentrations of LPS and liver fat, along with the expression of a number of proinflammatory cytokines. High-fat meal–related hypertriglyceridemia and a concurrent acute increase in plasma endotoxin concentrations seem to be due to an increase in intestinal permeability secondary to reduced expression of 2 epithelial tight junction (TJ) proteins, occludin and zonula occludens-1 (5). Microbiota dysbiosis may trigger the release of zonulin, a modulation of intercellular TJs (6), leading to increased trafficking of endotoxins and other nonself antigens. The access of LPS and other endotoxins to the intestinal lamina propria initiates a mucosal immune response that causes chronic low-grade inflammation and possible liver insult, triggering metabolic disorders characterized by nonalcoholic fatty liver disease, insulin resistance, the onset of type 2 diabetes, and ultimately, obesity (7). Indeed, in obese adult patients, circulating zonulin is increased in association with obesity-associated insulin resistance, which is probably mediated through obesity-related circulating IL-6, a cytokine that has been suggested to act as a promotor of the zonulin gene (8).

The article by Damms-Machado et al. (9) in this issue of the Journal presents a possible different explanation of the chain of events involving the liver-gut axis leading to metabolic disturbance. The investigators monitored gut permeability in 27 obese individuals with and without liver steatosis who underwent a weight-reduction program. They reported that gut permeability [measured by the lactulose/mannitol (Lac/Man) test] was elevated at baseline, particularly in those patients with liver steatosis, and that, by the end of the dietary intervention trial, the enrolled subjects lost an average of 23.5 kg and their gut permeability decreased along with serum IL-6 concentrations, whereas serum endotoxin load and fecal zonulin concentrations did not. These permeability changes showed a trend, which did not reach significance, toward an improvement in insulin resistance assessed by the homeostatic model assessment index, whereas a significant correlation was detected between homeostatic model assessment index improvement and decreased liver steatosis assessed by sonography and the fatty liver index.

On the basis of these results, the authors concluded that intestinal permeability increases in obese patients with steatosis (already reported in the literature) and returns within normal limits after successful weight reduction secondary dietary intervention (which is a novel aspect of this report). These results suggest that increased gut permeability is a consequence rather than the cause

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of obesity and associated metabolic disorders, because partial correction of overweight and liver steatosis by dietary intervention corrected the intestinal barrier defect as measured by the Lac/Man test. However, other biomarkers of impaired gut barrier, including fecal zonulin and serum LPS load, were unchanged after dietary intervention, even if a trend of elevated zonulin in obese patients with steatosis (either at baseline or after the dietary intervention) was detected when compared with patients without steatosis.

To explain the lack of fecal zonulin changes after the intervention, the authors postulated the existence of a zonulin-independent pathway that regulates the TJ dynamic in the course of weight reduction, which leads to the documented changes in gut permeability. Although this is a possibility, the persistent high concentrations of endotoxins after dietary intervention suggest ongoing antigen trafficking through an impaired gut barrier. This apparent dichotomy may be partially due to the low number of subjects who completed the study; ~50% of the enrolled patients (13 of 27) dropped out and therefore were not included in the analysis. Alternatively, the Lac/Man test may not be sensitive enough to detect ongoing functional barrier defects (as measured by persistent high fecal zonulin concentrations) that still cause LPS trafficking. These results are also at odds with another recent report that showed that a reduction in body fat mass in obese adults by targeting the gut microbiota through prebiotic and probiotic administration rather than dietary intervention was significantly correlated with serum zonulin concentrations (10).

Finally, a non–mutually exclusive explanation that compromises these findings is that a microbiota-driven, zonulin-dependent pathway is involved in the pathogenesis of metabolic disorders leading to nonalcoholic fatty liver disease, insulin resistance, and obesity in genetically susceptible individuals through the mechanisms outlined above. Once established, this metabolic imbalance may aggravate impairment of the gut barrier through the production of proinflammatory cytokines (interferon-γ and TNF-α) sensitive to dietary change. Large, well-designed randomized studies are necessary to challenge this hypothesis. Whether or not gut permeability is the cause, the consequence, or both of these metabolic disorders, it may represent a novel target to influence adipose tissue plasticity and, ultimately, the treatment and prevention of the metabolic imbalance associated with obesity.

The author is a co-founder and stockholder of Alba Therapeutics.

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