REVIEW

# Negative Effects of a High-Fat Diet on Intestinal Permeability: A Review

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**ABSTRACT**

The intestinal tract is the largest barrier between a person and the environment. In this role, the intestinal tract is responsible not only for absorbing essential dietary nutrients, but also for protecting the host from a variety of ingested toxins and microbes. The intestinal barrier system is composed of a mucus layer, intestinal epithelial cells (IECs), tight junctions (TJs), immune cells, and a gut microbiota, which are all susceptible to external factors such as dietary fats. When components of this barrier system are disrupted, intestinal permeability to luminal contents increases, which is implicated in intestinal pathologies such as inflammatory bowel disease, necrotizing enterocolitis, and celiac disease. Currently, there is mounting evidence that consumption of excess dietary fats can enhance intestinal permeability differentially. For example, dietary fat modulates the expression and distribution of TJs, stimulates a shift to barrier-disrupting hydrophobic bile acids, and even induces IEC oxidative stress and apoptosis. In addition, a high-fat diet (HFD) enhances intestinal permeability directly by stimulating proinflammatory signaling cascades and indirectly via increasing barrier-disrupting cytokines [TNF$\alpha$, interleukin (IL) 1B, IL6, and interferon $\gamma$ (IFN$\gamma$)] and decreasing barrier-forming cytokines (IL10, IL17, and IL22). Finally, an HFD negatively modulates the intestinal mucus composition and enriches the gut microflora with barrier-disrupting species. Although further research is necessary to understand the precise role HFDs play in intestinal permeability, current data suggest a stronger link between diet and intestinal disease than was first thought to exist. Therefore, this review seeks to highlight the various ways an HFD disrupts the gut barrier system and its many implications in human health. *Adv Nutr* 2020;11:77–91.

Keywords: high-fat diet, intestinal permeability, gut barrier, tight junction, inflammatory bowel disease, inflammation, bile acids, superficial unstirred mucus layer, shedding-proliferation axis, gut microbiota

## Introduction

The intestinal tract comprises the largest boundary between the host and its environment. In this role, the intestinal tract retains a robust barrier system in order to protect the host from external toxins, dietary antigens, bacteria, and other potentially hazardous substances. This barrier is multifaceted and comprises various protective mechanisms, such as a mucus layer, a constantly renewing epithelial boundary, tight junctions (TJs), and even the gut microbiome, to preserve intestinal health. Throughout the host's lifetime, these systems provide rigid protection yet remain malleable to allow normal physiological remodeling with minimal alteration to barrier integrity. However, stimuli such as dietary substances, especially fats, compromise the barrier and enhance permeation of luminal contents into the mucosal and submucosal layers in proximity to resident immune cells. These changes promote inflammatory responses that damage intestinal superstructures and predispose the host to various enteropathies like inflammatory bowel disease (IBD), celiac disease, and irritable bowel syndrome.

It is well known that dietary components substantially alter intestinal physiology and specifically modulate intestinal barrier integrity. For example, in celiac disease, permeability of hypersensitized intestines to gluten leads to profound mucosal inflammation, villous atrophy, and malabsorption diarrhea. Remarkably, simple removal of dietary gluten tends to ameliorate most intra- and extra-intestinal pathologies and symptoms (1). Like celiac disease, dietary components

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Abbreviations used: AJ, adherens junction; AJC, apical junctional complex; BA, bile acid; CCK, cholecystokinin; CD, Crohn's disease; CDCA, chenodeoxycholic acid; CLDN, claudin; CTFR, cystic fibrosis transmembrane receptor; CXCR3, C-X-C motif chemokine receptor; DCA, deoxycholic acid; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; FA, fatty acid; FAS, fatty acid synthase; GC, goblet cell; GI, gastrointestinal; HFD, high-fat diet; IBD, inflammatory bowel disease; IEC, intestinal epithelial cell; JAM, junctional adherens molecule; LCA, lithocholic acid; LFD, low-fat diet; LOOH, lipid peroxide; LP, lamina propria; MLC, myosin-light chain; MLCK, myosin-light chain kinase; MUC2, mucin 2; OCLN, occludin; OS, oxidative stress; PAR, perijunctional actinomyosin ring; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; ROS, reactive oxygen species; SUML, superficial unstirred mucus layer; TCA, taurocholic acid; TJ, tight junction; *TJP1*, zona-occludens 1 (*ZO1*) gene; TLR4, Toll-like receptor 4; UFA, unsaturated fatty acid; ZO, zona occludens.

 

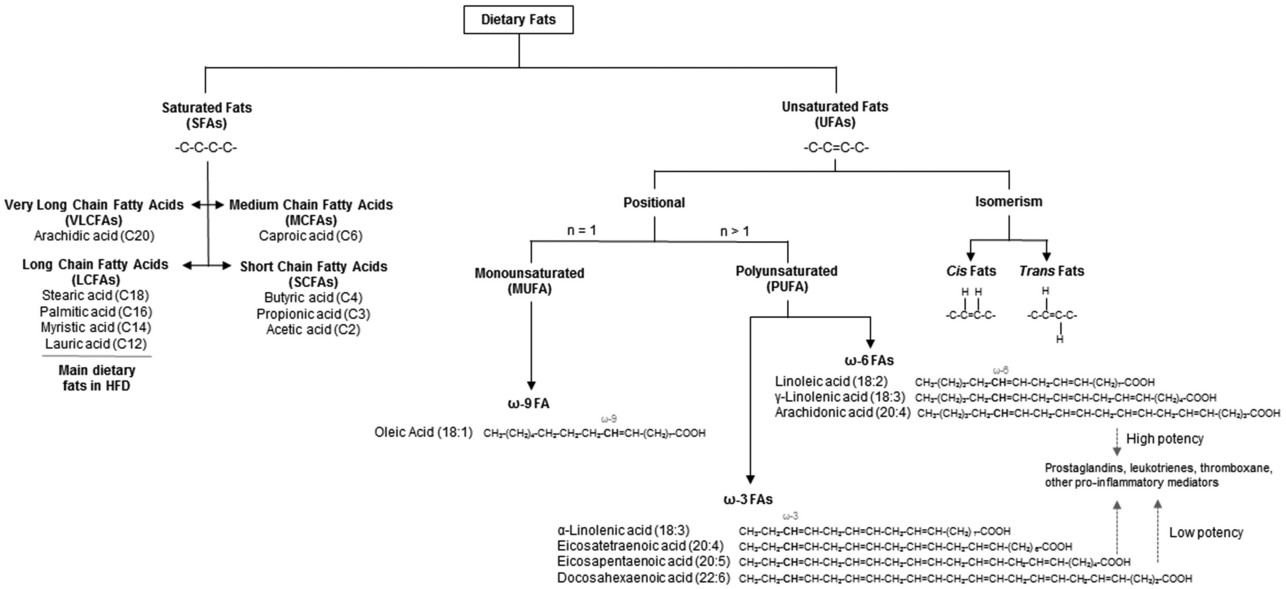


**FIGURE 1** Classification of dietary fats. Dietary fats come in a variety of forms and are classified based on the presence of double bonds in the hydrocarbon chain. SFAs have no double bonds while unsaturated fatty acids (UFAs) contain double bonds. UFAs are subcategorized based on the orientation, number, and position of the double bonds. *Cis* fats contain *cis*-oriented double bonds and are natural, while *trans* fats contain *trans*-oriented double bonds and are usually synthetic or processed. Fatty acids with one double bond are MUFAs, while PUFAs contain more than one double bond. Last, UFAs can be further classified depending on the position of the chain-terminal double bond. For example, $\omega$-3 PUFAs contain a double bond 3-carbons away from the terminal carbon on the fatty acid tail. PUFAs are usually regarded as safe and beneficial; but that depends on potency, concentration, and oxidizability. HFD, high-fat diet.

may play a larger role in the pathophysiology of other intestinal diseases than was initially thought. Differences in diet among various regions and cultures may explain the divergent incidence rates of intestinal diseases. For example, celiac disease, IBD, and even colorectal cancer tend to localize to Westernized countries, such as the United States, Canada, and Europe, where a diet high in fats and refined carbohydrates, and low in fiber, predominates (2). Underlying these diseases is gut barrier degeneration due to as yet unidentified reasons. Diet seems to play a major role in these observations and thus the need to understand how it modulates intestinal barrier integrity is of great significance.

Dietary fat has been a focus of research into gut barrier regulation due to its ubiquitous nature, particularly in Western countries. For example, high-fat diet (HFD) consumption promotes and exacerbates experimental colitis in dietary and genetic mouse models of IBD (3, 4). In humans, consuming a Western-style diet is associated with an increased risk of developing IBD, a condition characterized by intestinal hyperpermeability (5–7). In addition, high dietary fat consumption enhances the number and intensity of IBD flares, presumably due to enhanced mucosal permeation of gut microbes or dietary antigens (3). Specifically, there is a striking positive correlation between IBD incidence rates and the industrialization status of a country, as diets in these societies tend to be richer in processed fats and sugars (8). Similarly, migrants traveling from countries with low IBD incidence rates to countries with high incidence rates adopt the risk of developing IBD with the latter (9). Taken together, dietary fats play an integral role in intestinal disease pathogenesis, prompting a need to understand the molecular mechanisms underlying dietary fat–mediated intestinal permeability. Indeed, knowledge of diet-induced intestinal changes may prove invaluable for successful treatment of intestinal disease, such as IBD. Diet alteration is not only a simpler choice for therapeutic targeting, it is relatively inexpensive, carries less risk of adverse effects, and can be fine-tuned by either the physician or patient. Moreover, a regimen consisting of dietary changes enhances treatment adherence as patients are more involved and have greater control of their treatment compared to conventional pharmacologic regimens (10). Therefore, this review explores the various mechanisms underlying the effects of dietary fat on intestinal permeability.

## The Western-Style Diet

Dietary fats come in many forms and are classified based on the number and position of double bonds within the hydrocarbon chain (**Figure 1**). For example, SFAs have no double bonds whereas MUFAs contain one and PUFAs contain more than one double bond. Additionally, unsaturated fatty acids (UFAs) can be configured in the *cis*- or *trans*-orientation with respect to their double bonds, where the former is natural, and the latter is processed. Diets rich in UFAs, such as in a Mediterranean diet, are associated with anti-inflammatory

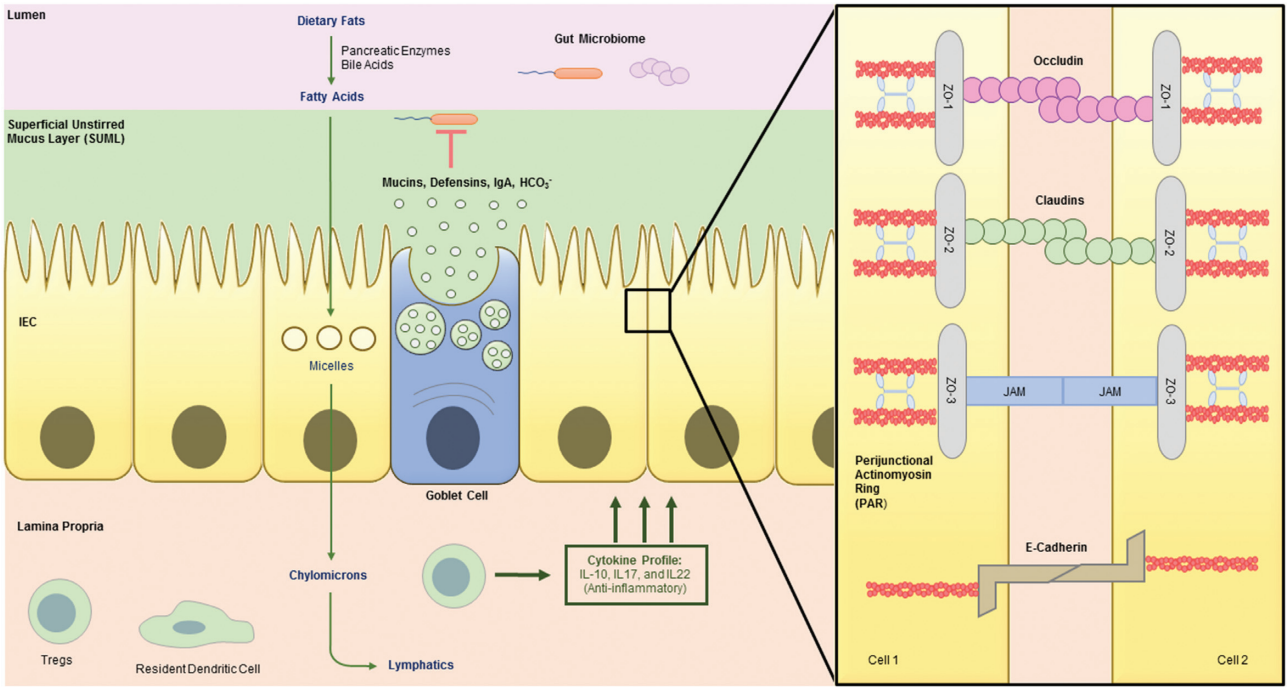


**FIGURE 2** Intestinal barrier system under normal dietary conditions. In steady state, the intestinal tract utilizes various strategies to prevent foreign material translocating from the lumen into the lamina propria (LP). The goblet cell–derived mucus prevents bacterial breach of the enterocyte monolayer by forming a physical barrier, enhancing degradation via defensins, and stimulating regulated immune responses through secreted IgA. In addition, the LP is maintained under an anti-inflammatory state due to the presence of anti-inflammatory dendritic cells and associated cytokines. Last, tight junctions (TJs) formed between enterocytes are numerous and selectively allow permeation of molecules while simultaneously walling the LP from the lumen. There are many proteins involved in TJ maintenance. including occludin, claudins, cadherins, etc. and these proteins are integral in gut barrier maintenance. IEC, intestinal epithelial cell.

properties (11, 12). In contrast, diets rich in SFAs, such as with a Western-style diet, are associated with negative health impacts including obesity, diabetes, cardiovascular disease, and even IBD (8, 13–15).

The "Western-style diet," as it is known colloquially, began around the time of the Industrial Revolution and developed throughout the 20th century as meats rich in SFAs became available year-round, refined vegetable oils and dairy products became more affordable, and foods containing sugars and grains were heavily processed (16). Today, 35–45% of calories derived from a Western-style diet is from fat, to which 11.1% is from SFAs alone (17). As of 2015, the American Heart Association recommends reducing SFA intake as a percentage of daily calories to 5–6% (13.1 g in a typical 2000-kcal/d diet) and to replace SFAs for PUFAs in the diet at a 1:1 ratio where possible in order to reduce cardiovascular disease risk (18). Unfortunately, these fats are mainly derived from dairy and lard-based foodstuffs, which are ubiquitous and culturally ingrained in Westernized countries.

In order to study how dietary fats affect biochemical processes and impact human health, researchers feed mice various diets with different fat contents designated as a percentage of total daily energy intake in kilocalories. Typically, control low-fat diets (LFDs) derive approximately 8–15% kcals from fats while HFDs derive either 40–50% kcals (models a Western-style diet) or 60–80% kcals (models diet-induced obesity) from fats (19). For simplicity, in this article "LFD" is used only to refer to diets deriving ≤15% kcal from fat, and "HFD" is used to refer to deriving ≥35% kcals from fat unless noted otherwise.

## Dietary Fat Disrupts Tight Junctions in Intestinal Epithelium

One mechanism by which dietary fat modulates intestinal permeability is through altering the distribution and expression of intestinal tight junctions (TJs), directly or indirectly. TJs and adherens junctions (AJs) comprise the apical junctional complex (AJC), one of the best understood components of the intestinal barrier system (for an extensive review on TJs see references 20 and 21). TJ and AJ components exist as multimeric complexes consisting of transmembrane proteins such as E-cadherin, occludin (OCLN), claudin (CLDN), and junctional adherens molecule (JAM). The structure of these proteins includes extracellular and intracellular domains (**Figure 2**). The extracellular domain binds the lateral-apical epithelial surface with adjacent intestinal epithelial cells (IECs) harboring TJ proteins of the same type, while the intracellular domains bind "bridging" proteins such as catenins, zona occludens (ZO, *TJP1*) −1, −2, and −3, that anchor the TJs directly to F-actin (22). Thus,

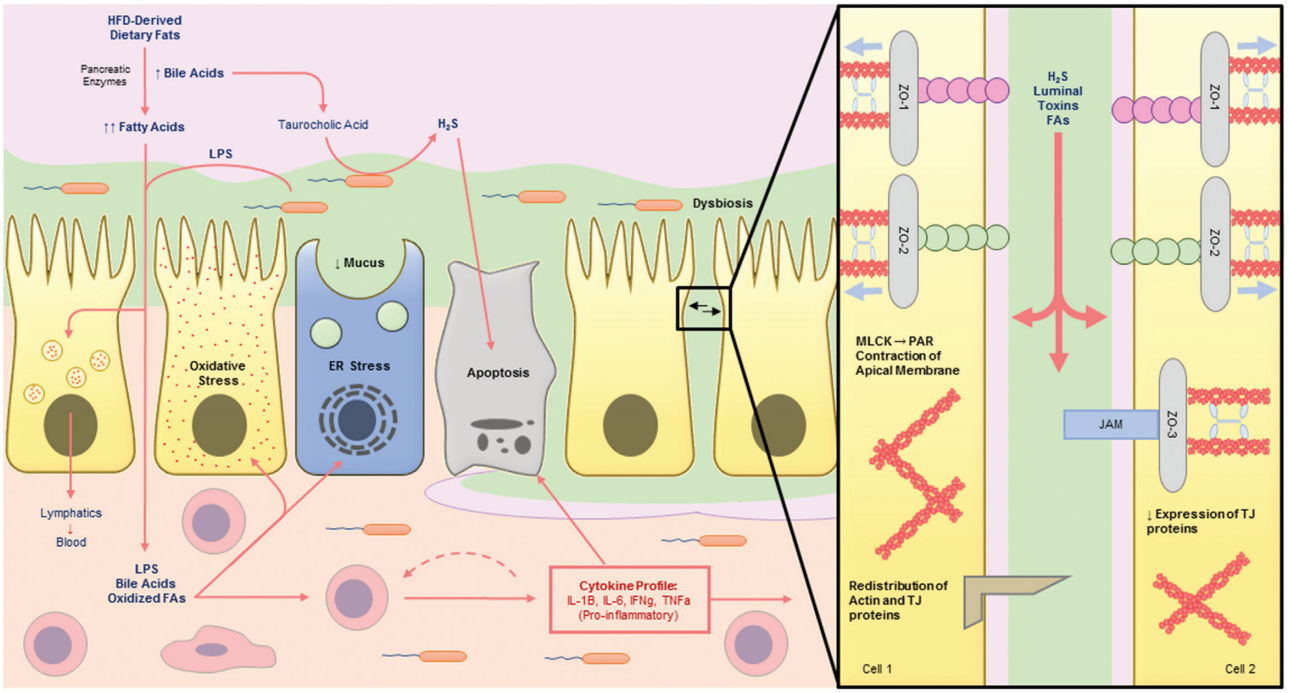


**FIGURE 3** Intestinal barrier system under a chronic high-fat diet (HFD). Chronically consuming an HFD has many detrimental effects on intestinal barrier integrity. An HFD reduces tight-junction (TJ) tightness by downregulating expression of TJ proteins or stimulating aberrant perijunctional-actinomyosin ring (PAR) contraction, permitting influx of luminal components to the lamina propria (LP). Translocated BAs and fatty acids induce enterocyte oxidative stress and apoptosis, further reducing the lumen tight seal. Additionally, fatty acid–induced unfolded protein response (UPR) stress in goblet cells inhibits the secretion of mucus, which in addition to elevated hydrophobic BA load, negatively impacts both the quality and quantity of mucus, permitting gut microbiota invasion. Changes to the bacterial flora by HFD increases the abundance of pathogenic strains, such as *Desulfovibrio* spp., which deconjugate TCA-producing genotoxic $H_2S$ gas. All these factors promote an inflammatory response which furthers the cycle of intestinal barrier degeneration, predisposing the host to gastrointestinal pathologies. BA, bile acid; ER, endoplasmic reticulum; MLCK, myosin-light chain kinase; PAR, perijunctional actinomyosin ring; TCA, taurocholic acid.

the AJC connects adjacent IECs to form a lumen-tight seal that selectively allows nutrients to permeate paracellularly. Indeed, this barrier inhibits unwarranted permeation of environmental toxins, luminal antigens, and bacteria, which prevents potential focal enteropathy or systemic disease (**Figure 3**). Moreover, IEC permeability can be dynamically altered through rearrangement of cellular cytoskeletal elements, expression of AJC proteins, or posttranslational modifications. Therefore, disruption of AJC complexes results in intestinal hyperpermeability.

### Dietary fat directly modulates TJ distribution and expression levels

Recent studies have shown that dietary fats directly modulate AJC integrity, and thus intestinal permeability. For example, a long-term HFD reduces expression of gut TJ proteins and correlates with intestinal hyperpermeability in mice (23, 24). In corroboration, continuous feeding of C57BL/6J mice with an unsaturated, but not saturated, fatty acid–enriched diet significantly reduced TJ expression and increased flux of fluorescein isothiocyanate–conjugated 4-kDa dextran, a measurable fluorescent marker of paracellular permeability (25). Similarly, Long-Evans Tokushima Otsuka and Otsuka Long-Evans Tokushima Fatty rats, which develop obesity as a result of enhanced neuropeptide Y–mediated hyperphagia, fed an HFD exhibited reduced expression of *Ocln*, *Jam2*, *Cldn1*, and *Cldn3*, which originated with the dietary fat itself and not the metabolic consequences of the diet (26).

Dietary fats may also modulate intestinal permeability through stimulation of intracellular signaling pathways. Notably, a typical Western-style diet contains an abundance of $\gamma$-linolenic (18:3, n–6) and docosahexaenoic acid (22:6, n–3), both of which are known potent signaling molecules (Figure 1). Direct supplementation of these fatty acids to differentiated human colon adenocarcinoma cell line (Caco2) monolayers, a well-established in vitro enterocyte model, enhanced intestinal permeability through protein kinase C (PKC)-mediated redistribution of actin and TJ proteins, an effect ameliorated with PKC inhibitors (27, 28). Additionally, Caco2 cells can convert eicosapentaenoic acid (20:5, n–3), another Western-style diet PUFA, into bioactive metabolites that enhance monolayer permeability through stimulation of endogenous cyclooxygenase and lipooxygenase activity (29). Taken together, these results confirm that dietary fats directly alter intestinal barrier integrity by interacting with intestinal epithelial cells.

### Dietary fat–induced bile acid production damages the gut mucosal barrier

It has long been known that dietary fat stimulates both bile acid (BA) synthesis and bile expulsion by the gallbladder. The BAs emulsify luminal fat and increase the total surface area for lipase-mediated digestion of micelles for absorption by intestinal epithelial cells. Multiple studies have shown a direct correlation between fat intake and BA secretion/synthesis (30–32), and this phenomenon can be explained briefly. First, digested chyme containing fat stimulates cholecystokinin (CCK) secretion by duodenal I-cells. Next, CCK stimulates gallbladder contraction and expulsion of stored bile. Following that, luminal BAs return to the liver via the entero-hepatic circulation, which reabsorbs and recycles 95% of the intraluminal bile at the ileum. Finally, recycled bile is reabsorbed by hepatocytes and secreted back into bile canaliculi [for a more thorough review on BA metabolism and signaling, see (33)]. Under normal physiologic conditions, IECs are usually resistant to the solubilizing effects of BAs. However, chronically high intraluminal and fecal BA levels, especially those seen in HFDs, may induce intestinal hyperpermeability through alteration of TJ dynamics (26, 34–36).

Stenman et al. (36) was one of the first to investigate the detrimental effects of BAs on intestinal permeability in vivo. This group showed that long-term HFD, but not LFD, increased BA synthesis 10-fold and enriched bile composition in hydrophobic BAs such as deoxycholic acid (DCA), lithocholic acid (LCA), and chenodeoxycholic acid (CDCA) (36). In particular, hydrophobic BAs induced intestinal hyperpermeability when administered at concentrations observed in HFD, but not LFD (36). One possible mechanism for DCA- and CDCA-induced intestinal hyperpermeability is by epidermal growth factor receptor (EGFR) stimulation (35). In Caco2 cells, treatment with supra-physiologic concentrations of DCA and CDCA led to rapid stimulation of EGFR-mediated signaling, resulting in *1*) SRC kinase activation; *2*) downstream serine-threonine dephosphorylation of the OCLN cytoplasmic tail; *3*) OCLN-ZO1 complex dissociation; and *4*) enhanced intestinal permeability (35). However, changes in intestinal permeability were reversed upon administration of synthetic EGFR inhibitors or sustained epidermal growth factor (35). In an associated mechanism, treatment of Caco2 cells with supra-physiologic, but not physiologic, hydrophobic BA concentrations enhanced IEC generation of reactive oxygen species (ROS) resulting in oxidative stress (OS)-mediated phosphoinositide 3-kinase (PI3K) stimulation (Figure 3) (34). In this setting, PI3K activation promotes intestinal permeability through increased intercellular translocation of the regulatory p85 subunit, enabling PI3K-mediated tyrosine phosphorylation of ZO1 and $\beta$ catenin, inhibiting structural interactions with OCLN and E-cadherin isomers, respectively (37, 38). Last, the oxidation product of a linoleic acid (18:2, n–6), 13-hydroxyoctadecadienoic acid, the most abundant PUFA in a Western-style diet, is at its highest concentration in the intestinal lumen after a fat-rich meal and may promote intestinal permeability similarly to LCA as a result of close structural identity (39).

In contrast, recent evidence suggests that supplementation with hydrophilic BAs, such as ursodeoxycholic acid, which are thought to act in an opposite manner to hydrophobic BAs, improves the intestinal epithelium barrier integrity in murine models through a variety of mechanisms, including reducing OS (40–43). These results indicate that dietary fat–induced shifts in BA quantity and quality negatively impact intestinal permeability and may be a promising therapeutic route in treating intestinal diseases characterized by enhanced colonic bile output, such as bile acid malabsorption diarrhea, commonly associated with Crohn's ileitis (44).

## Dietary Fat–Associated Intestinal Inflammation Enhances Intestinal Permeability

It has long been known that the integrity of the intestinal barrier is exquisitely sensitive to the inflammatory state of the gut. For example, the intestinal hyperpermeability observed in Crohn's disease (CD) is a direct result of pathologic changes in IEC signaling, viability, and cohesiveness induced by proinflammatory mediators such as IL1B, IL6, IFN$\gamma$, and TNF$\alpha$, to name a few. Part of the IBD spectrum, CD is an autoimmune condition characterized by intestinal transmural inflammation, noncaseating granulomas, abdominal pain, and remitting diarrhea. CD may occur anywhere along the gastrointestinal (GI) tract, but primarily localizes to the terminal ileum. Specifically, the CD-associated $T_1H$ inflammatory response is directly responsible for the pathologic degeneration of the intestinal barrier through cytokine signaling to immune cells and IECs (**Table 1**) (45–74). Moreover, these cytokines have been prime targets for therapy as inflammation, in addition to intestinal permeability parameters, return to normal when pharmacologically inhibited (75–77).

Interestingly, the same cytokine state encountered in the intestines of CD patients is also present during HFD feeding, an idea supported by studies linking increased dietary fat intake with enhanced risk of CD development and increased flare-up number and severity. (For a review on how dietary fats regulate the immune system and how cytokines influence gut barrier integrity, please see references 78 and 79). In concordance with enhanced immune-cell infiltration of the lamina propria (LP) in CD, direct exposure of rat duodenum to olive oil activates leukocyte homing via stimulation of adhesion protein expression, primarily intercellular adhesion molecule 1, on postcapillary venules of Peyer's patches (80). Likewise, dietary fat enhances the expression of endothelial mucosal vascular addressin cell adhesion molecule 1 and vascular cell adhesion molecule 1, which enhances LP-homing of circulating immune cells during feeding (80–82). Mechanistically, Kawano et al. (45) showed that the enhanced infiltration of C-X-C motif chemokine receptor 3 (CXCR3+) macrophages of the murine LP observed during HFD feeding was due to stimulation of chemokine (C-C motif) ligand 2, the cognate chemokine of CXCR3, expression

**TABLE 1** Compilation of studies showing which cytokines are changed during HFD feeding and how they mechanistically alter the integrity of the gut barrier system[1]

| Cytokine | Effects of HFD (reference[2]) | Permeability effects | Mechanism of action(s) on barrier integrity | Reference(s) |
|---|---|---|---|---|
| IL1B | ↑ (45) | ↑ | Reduction of *OCLN* expression | (46) |
| | | | MAPKKK-mediated NF$\kappa$B activation → MLCK-induced PAR contraction | (47–49) |
| IL4/IL13 | ↑ (50) | ↑ | PI3K-mediated actin reorganization | (51) |
| | | | STAT6–unknown | (52) |
| IL6 | ↑ (53) | ↑ | Reduction of *TJP1* expression | (54) |
| | | | Claudin switching—↑ pore-forming claudins[3] | (55) |
| IL10 | ↓ (56) | ↓ | Reduction in proinflammatory cytokine signaling—specifically IFN$\gamma$ | (57) |
| | | | p38 MAPK–mediated increase in cadherin levels | (58) |
| IL12 | ↑ (59) | ↑ | Unknown | |
| IL17/IL23 | ↓ then ↑ (60) | ↓ | Act1-mediated OCLN association with F-actin | (61) |
| IL18 | ↑ (45) | ↑ | Unknown | |
| IL22 | ↓ then ↑ (62) | ↓ | Increased IEC proliferation and migration | (63) |
| | | | Reduction in enterocyte ER stress | |
| | | | Replenishment of mucus layer by GCs | (64) |
| IFN$\gamma$ | ↑ (65) | ↑ | Internalization of TJ proteins via macropinocytosis | (66) |
| | | | PI3K-mediated NF$\kappa$B activation → MLCK-induced PAR contraction | (67) |
| TNF$\alpha$ | ↑ (68) | ↑ | ↑ IEC apoptosis | (69) |
| | | | Internalization of TJ components | (67) |
| | | | MLCK-dependent contraction of PAR | (70, 71) |
| | | | Claudin switching—↑ pore-forming claudins | (72) |
| Perforin | ↑ (73) | ↑ | Unknown | |
| Granzyme B | ↑ (73) | ↑ | Cleave TJ and AJ components | (74) |

[1] AJ, adherens junction; ER, endoplasmic reticulum; GC, goblet cell; HFD, high-fat diet; IEC, intestinal epithelial cell; MLCK, myosin light chain kinase; OCLN, occludin; PAR, peri-actinomyosin ring; TJ, tight junction; *TJP1*, zona-occludens 1 (*ZO1*) gene.
[2] These references address research into how HFD alters permeability generally. Right column references address research into specific mechanisms.
[3] Claudin switching refers to a change in expression of barrier-forming claudins (1, 3–6) to pore-forming claudins (2, 7, 10, 15, 17).

and secretion by IECs. This finding corroborates previous studies which show enhanced macrophage infiltration and exacerbation of pre-existing inflammation and tissue damage by HFD feeding in both chemically-induced (dextran-sulfate sodium and 2,4,6-trinitrobenzenesulfonic acid) and genetic ($Mdr1a^{-/-}$ and $Muc2^{-/-}$-$Tnf^{\Delta ARE}$) murine models of IBD (3, 4, 83, 84).

The prevailing theory behind how an HFD promotes intestinal inflammation is as follows: HFD induces preliminary intestinal hyperpermeability, transient gut microbiota dysbiosis (explained later), and enhanced recruitment of proinflammatory leukocytes to the LP. These changes may ultimately increase the risk of developing intestinal inflammation and exacerbates pre-existing inflammation such as in IBD. When inflammation is present, local cytokine signaling facilitates greater recruitment of proinflammatory leukocytes and induces strong pathologic degeneration of the intestinal barrier, furthering the cycle. In addition to what has been mentioned, dietary free fatty acids also participate in the inflammatory response by directly stimulating inflammatory signaling, which further potentiates the intestinal hyperpermeability. The different mechanisms in which dietary fats modulate the immune response in the context of modulating permeability are explored below.

## HFD promotes LPS-induced gut barrier dysfunction

One of the first studies to link dietary fats with intestinal immunity was from Miura et al. (85), who demonstrated that feeding mice a lard-based diet resulted in mesenteric lymph node leukocyte proliferation, presumably due to enhanced lymphatic chylomicronemia. Although the exact mechanism was unknown at the time, it is now thought that this response is due to increased intestinal permeation of LPS, which is directly incorporated into chylomicrons and delivered to the circulatory system (86). A major component of the outer cell membranes of gram-negative bacteria, LPS consists of an O-antigen, core polysaccharide, and immunogenic lipid A. Specifically, lipid A is composed of branched chain SFAs and is the primary component recognized by the proinflammatory Toll-like receptor 4 (TLR4)–CD14 system in immune cells and intestinal epithelial cells.

In the gut, LPS is derived from the regular turnover of microflora-derived gram-negative bacteria and, depending on the intestinal permeability and dietary fat content, becomes incorporated into chylomicrons via its lipid A tail (86). Intestinal permeability facilitates passive translocation of luminal LPS or LPS-containing bacteria into the LP, promoting greater translocation of LPS into blood (termed endotoxemia) independent of diet. This relationship may

partially explain the elevated serum LPS observed in patients with IBD and other intestinal pathologies such as necrotizing enterocolitis (87, 88). In fact, serum LPS is now an accepted surrogate marker for assessing in vivo intestinal permeability (89).

Similarly, dietary fat can enhance serum LPS levels independent of permeability status, mainly through luminal micellar incorporation and stimulation of lipid raft-mediated endocytosis (90). Cani et al. (91) was the first to demonstrate that serum LPS levels varied in the fast compared with the fed state and that an HFD was responsible for 3-fold greater serum LPS in mice. In addition, Cani et al. showed that HFD feeding significantly enriched the gut microflora with LPS-containing bacteria. Concerning the components of an HFD, the elevation of serum LPS was solely dependent on the dietary content of SFAs, but not PUFAs, presumably due to lipid rafts (90). These results may explain the original findings that humans consuming an LFD have serum LPS levels ranging from 0 to 0.2 ng/mL while those consuming diets high in fat may have levels up to 2 ng/mL (92). This mechanism also confirms findings that consuming diets high in calorie content (fats) is associated with elevated serum LPS in healthy men (93). Interestingly, a popular theory explaining insulin resistance observed in metabolic syndrome is that it may be a result of low-grade inflammation due to metabolic endotoxemia in the obese state, which could be a combinatorial effect of resting intestinal hyperpermeability and diet-induced LPS translocation (94–96).

Indeed, LPS is best known for stimulating a TLR4-CD14–dependent proinflammatory response that directly alters the intestinal barrier. In addition, LPS has been found to directly modulate TJ organization and enhance permeability of Caco2 (as measured by decreased transepithelial electrical resistance) monolayers via TLR4-CD14–mediated activation of NF$\kappa$B (97). Furthermore, LPS directly induces rapid IEC shedding without compensatory TJ-resealing (98). Last, LPS may promote IEC OS, mitophagy, and overall mitochondrial failure resulting in enhanced intestinal permeability (99). These results provide an indirect mechanism by which an HFD promotes intestinal hyperpermeability; HFD-feeding enhances local and serum LPS levels which *1*) promote intestinal inflammation, *2*) modulate TJ organization through signaling cascades, and *3*) induce IEC dysfunction, ultimately resulting in hyperpermeability.

### SFAs directly promote an LPS-like inflammatory response

It has been proposed that the structural similarity between dietary SFAs and the lipid A component of LPS may permit SFA-TLR4 interactions, which would provide a direct link between HFD consumption and intestinal inflammation (100). Indeed, it was initially found that SFAs, specifically lauric acid, but not PUFAs, activated NF$\kappa$B-signaling in a TLR4-dependent manner, which was later attributed to TLR4-homodimerization via lipid-raft incorporation (101, 102). Interestingly though, it was also discovered that SFAs can promote TLR4-independent inflammation through stimulation of TLR2 heterodimerization with TLR1 or TLR6 (an activating signal) via lipid-raft incorporation (103, 104). However, although only a limited number of SFAs have been found to promote TLR activation, there is still active research on other mechanisms by which dietary fats promote inflammation, and therefore, intestinal permeability.

### Dietary fats inhibit probarrier signaling between immune cells and IECs

There is increasing evidence that the gut immune system coordinates with IECs to promote gut barrier maintenance (Table 1), and that this cross-talk is dysregulated during acute HFD-feeding (105). For example, intestines of mice fed an HFD showed markedly reduced IL17, a cytokine that promotes gut barrier TJ organization via Act1-mediated association of OCLN with F-actin (61). Similarly, rats fed an HFD showed drastic reduction of intestinal IL10 as soon as within 1 wk of starting the diet (57, 58). IL10 is the principle anti-inflammatory cytokine that helps maintain the intestinal barrier through inhibiting proinflammatory cytokine signaling (57, 58). Importantly, HFD feeding depletes the LP of T-regulatory cells, the primary source of IL10, through a yet unknown mechanism and may be a contributing factor behind the unfavorable cytokine environment and intestinal permeability status observed with this diet (65). Lastly, mice fed an HFD demonstrated reduced IL22 (source yet to be identified), another gut barrier–promoting cytokine, in the acute period, followed by dramatic elevation in the chronic phase due to compensatory forces (62). Mechanistically, IL22 is thought to enhance gut barrier function through PI3K-mediated IEC proliferation, enhancing the wound-healing response, and reduce fatty acid–induced ER stress (63, 64).

## Dietary Fat Disrupts the Intestinal Epithelial Shedding–Proliferation Axis

The intestinal tract bears the tremendous responsibility of absorbing different nutrients from the diet while protecting the body from ingested toxins, bacteria, and other foreign substances. For this reason, IECs are constantly shed and replaced by new enterocytes every 2–6 d, guided by an active proliferating layer at the base of the crypts of Lieberkühn guided by Wnt signaling (106, 107). It has been estimated that approximately $10^{11}$ IECs are lost daily and that this number requires a regenerative supply, making the intestines one of the sites of the fastest fixed-cell turnover rate in the human body (108). The balance between proliferation and shedding is controlled by a complex process of superficial enterocyte apoptosis, extrusion with rapid resealing of AJCs, and basal cell proliferation with upward movement and differentiation. This process is highly coordinated and tightly regulated and thus is susceptible to a myriad of stimuli, one of which is diet-induced OS [for an extensive review on this subject see (108)].

### Effects of oxidative stress on the enterocyte shedding–proliferation axis

It has been proposed that the pathogenesis of multiple HFD-associated diseases, such as obesity, diabetes, and metabolic syndrome, involves self-propagating inflammation secondary to OS (109). OS involves an intracellular redox balance shift from a reducing environment to an oxidizing one and is caused by dysfunction or depletion of antioxidant molecules such as vitamin E, ascorbic acid, and glutathione by pro-oxidant electrophiles generated from cellular respiration or exogenous toxins. HFDs are rich in PUFAs, which contain double bonds that are susceptible to oxidation via exogenous or endogenous sources (110). Previous studies have shown that oxidation of PUFAs may be caused by different premeal preparation techniques, such as thermophilic-oxidative conversion or frying, or endogenous oxidation via transit through oxidative environments of the GI tract, such as the stomach (111–114). These PUFAs are delivered to the intestines, where they are prepared for absorption by IECs via interaction between bile salts, pancreatic lipases, and brush border enzymes. It has been proposed that their oxidized counterparts passively diffuse across the apical membrane and induce intracellular oxidative stress. Additionally, it is suggested that oxidized PUFAs peroxidize plasma membrane phospholipid components from the luminal compartment. Both mechanisms result in free-radical initiation, propagation, and OS (115). Studies have shown that OS predisposes the intestines to chronic diseases such as IBD primarily through disruption of the gut barrier function via alteration in the enterocyte shedding-proliferation axis, disruption of the OCLN-ZO1 pathway, and induction of inflammation (116).

The importance of maintaining the proliferation-shedding axis is exemplified by studies which show that conditions favoring enterocyte apoptosis, such as endotoxemia or systemic inflammation, induce basement membrane damage and the formation of numerous mucosal "gaps," thereby increasing intestinal paracellular permeability (117, 118). By the same measure, other studies have linked chronic enterocyte OS with dysregulation of the enterocyte shedding-proliferation axis, either through depressed proliferation, disruption of AJC resealing, or enhanced apoptosis, particularly through HFD-derived oxidized PUFAs (119). For example, treatment of Caco2 cells with lipid peroxides (LOOHs), which can be found at detectable concentrations in a typical Western-style diet, not only induced pronounced oxidative stress (decreased reduced glutathione:oxidized glutathione ratio), but also depressed G0/G1 cell transition and cyclin D/cyclin-dependent kinase 4 expression, while enhancing DNA oxidation in a concentration-dependent manner (120, 121). In addition, LOOH-induced apoptosis of Caco2 cells was uninhibited by redox homeostasis restoration, suggesting that chronic HFD-induced oxidative stress results in permanent IEC damage (115). Moreover, intestinal absorption of 4-hydroxy-2-hexenal, a natural decomposition product of oxidized PUFAs, not only elicited site specific (duodenal) OS and inflammation, but also markedly enhanced IEC apoptosis both in vitro and in vivo (110). However, although none of these groups directly studied the effect of enterocyte turnover on intestinal permeability, some have speculated that HFD-related intestinal oxidative stress may be the initiating factor underlying the gut barrier dysfunction and endotoxemia observed in type 2 diabetes and various other intestinal and extraintestinal diseases (89–91). More studies are needed to solidify the connection between dietary fats and intestinal OS, and how these factors influence intestinal permeability and risk of enteric pathology.

## Dietary Fats Alter Intestinal Mucus Properties

In addition to the numerous TJs that inhibit permeation of luminal contents, the intestinal barrier consists of a superficial unstirred mucus layer (SUML) which coats IECs with a protective milieu of bicarbonate, antimicrobials, IgA, glycoproteins, and lubricant. Research into the SUML has revealed its importance in maintaining intestinal homeostasis mainly by filtering out bacteria, luminal toxins, and insoluble material, thereby preventing damage to bathed enterocytes (122, 123). Indeed, the SUML was shown to be integral to gut health as mice deficient in mucin 2 (MUC2), a glycoprotein which forms the bulk of the mucus, spontaneously developed colitis, with a presentation similar to dextran sulfate-sodium–induced colitis (124). Recent evidence points to the ability of dietary fats to modulate the composition and function of the SUML, which is primarily produced by goblet cells (GCs) and becomes more numerous moving distally through the intestinal system. For example, mice fed an HFD stimulated the GC unfolded protein response (UPR) pathway via localized generation of OS, resulting in enhanced misfolding of MUC2 and a degeneration of the SUML morphology (Figure 3) (64). In this setting, the destruction of the mucus layer correlated directly to gut barrier dysfunction, assessed by enhanced endotoxemia, either as a result of diminished TJ protein expression, increased TJ protein misfolding, or inflammation (64, 125). Moreover, HFD feeding repressed the expression of the cystic fibrosis transmembrane receptor (*Cftr*) gene in mouse ileal enterocytes via activation of peroxisome-proliferating factor gamma. The CFTR enhances chloride secretion, which hydrates the SUML and promotes its fluidity and robustness. In contrast, reduced CFTR levels decrease the viscosity and density of the SUML, promoting the loss of intestinal barrier integrity (126).

Other studies have subsequently parsed out the role other contents of the SUML play on maintaining intestinal barrier integrity. For example, the SUML contains a reservoir of antioxidants which actively protect the intestinal mucosa from luminal pro-oxidative molecules like oxidized PUFAs (127). Indeed, one study showed that mucus derived from inflamed pancreases, which is rich in oxidative compounds (modified via the inflammatory environment), depletes the antioxidant capacity of the SUML (as measured by

enhanced nitrosylation and carbonylation of mucus proteins) and increases intestinal permeability (127). Likewise, studies have linked HFD with increased OS, and it is possible that oxidized FAs may deplete the antioxidant capacity of the mucus and increase intestinal permeability (64, 128).

In another possible connection between dietary fats and intestinal mucus–associated changes, GC fatty acid synthase (FAS), is responsible for the palmitoylation of the N-terminus, and therefore proper secretion, of MUC2 and therefore may play a role in intestinal barrier functionality (129). For example, knockout of *FAS* in GCs resulted in significantly diminished mucus MUC2 content and increased intestinal permeability. As FAS is a metabolic keystone enzyme, it is subjected to heavy regulation. HFD feeding diminishes FAS activity in hepatocytes, thus leaving open the possibility that a similar regulatory process may occur in GCs or even IECs, although no studies to date exist (130, 131). Interestingly, because FAS is an insulin-sensitive enzyme, FAS downregulation in the setting of HFD-induced insulin resistance (diabetes or metabolic syndrome) may provide additional insight into the pathophysiology of enhanced intestinal permeability and associated endotoxemia seen in these patients (95, 132, 133). Although research into the dietary modulation of the intestinal mucus layer is still in its infancy, the effects of HFD on intestinal permeability may be explained partly by disruption of the SUML. However, more research is needed to fully describe these interactions.

## Dietary Fat–Associated Gut Dysbiosis Alters Intestinal Permeability

It is now well established that diet modulates the gut microbial composition, maintaining intestinal homeostasis in the normal individual. It is estimated that trillions of microbes colonize the gut ($\sim 10^{11}$–$10^{14}$ bacteria per g of colon weight) and have a multitude of functions which include, but are not limited to, metabolism, inflammation, and maintenance of gut barrier integrity (91, 134–138). These microbes colonize the gut early at birth and differentially develop up until adulthood with a composition primarily reflecting the dominant diet (Figure 2) (139). This is one of the primary reasons why colonic bacterial composition is similar within a geographical region and drastically different between regions (140, 141). However, although established at an early age, the microbiome diversity is both dynamic and malleable as sustained, but not short-term, changes in diet can directly alter microbiome richness and composition (142). In addition, 16s ribosomal RNA "fingerprinting" of colonic bacteria has revealed dominant bacterial species are associated with certain diets such as *Prevotella* (carbohydrates and fiber) and *Bacteroides* (meat and fats) (143, 144). Gut microbial diet–associated patterns can be explained by the fact that colonic microbes inhabit the same luminal space and directly compete for undigested nutrients supplied by the diet. Thus, microbiome balance is in part dependent on nutritional balance, and thus dietary imbalances in quantity or quality are reflected as microbial imbalances, or dysbiosis (Figure 3). Moreover, gut dysbiosis has been implicated in numerous disease processes, most notably diet-induced obesity, and has direct effects on gut permeability.

Obesity-mediated dysbiosis has been directly linked to dietary excess of fats and manifests in a reduced overall microbial load, a shift in species abundance, and an overall increase in intestinal permeability (136, 145). This concept was exemplified in a landmark study by Bäckhed et al. (146), in which gut microbiota transplanted from HFD-induced obese mice into sterilized mice colons resulted in the development of a metabolic syndrome phenotype with epithelial barrier dysfunction independent of recipient diet. In addition, as previously mentioned, several studies have shown that obesity, as well as high-fat intake, was associated with enhanced gut-derived endotoxemia as a direct result of barrier dysfunction and enhanced paracellular permeation of luminal LPS in both mice and humans (91, 135, 147–149). Some have argued that this endotoxemia is partly responsible for the low-grade inflammatory state seen in obesity. For example, one group showed that germ-free mice fed an HFD did not develop systemic inflammatory markers associated with obesity (150). This same group also revealed that transplantation of bacteria from HFD mice to germ-free mice resulted in elevated intestinal *Nfkb1* expression, indicating that the presence of diet-induced dysbiosis alone is sufficient for inflammation (150). Furthermore, the dominant bacterial species distributed in an HFD gut support the general notion that there exists a link between dietary fats, colonic microflora composition, and inflammation, which greatly influences gut permeability.

Research into diet-induced colonic dysbiosis has provided insights into possible mechanisms explaining the inverse correlation between fat intake and gut barrier function. Numerous studies have probed dietary fat–induced alterations in gut microflora species and related them to changes in gut permeability (**Table 2**) (151–159). The results of these studies reveal that HFDs transiently reduce gut barrier–promoting microbes, such as *Lactobacillus* spp., *Bifidobacterium* spp., *Bacteriodetes* spp., *Clostridiales* spp., and *Akkermansia muciniphilia*, while augmenting microbes involved in decreasing barrier integrity, such as *Oscillibacter* spp., and *Desulfovibrio* spp. Although the exact mechanism of how these specific microbial species modulate intestinal permeability is still highly debated, it is speculated that they exert their effects either directly through secreted products, or indirectly through immune system provocation. For example, HFD increases levels of *Desulfovibrio* spp., specifically *Bilophila wadsworthia*, which produces genotoxic hydrogen sulfide ($H_2S$) gas, causing IEC hypoplasia and hyperpermeability (156, 160–162). Specifically, *B. wadsworthia* uniquely utilizes taurocholic acid (TCA)-derived sulfur as a reducing equivalent in its electron transport chain system for survival and proliferation in the gut (157). The link between HFD, *B. wadsworthia*, and enhanced intestinal permeability is hypothesized to be a result of physiologic elevation of taurine-containing luminal bile salt levels in

**TABLE 2** Compilation of data from different studies looking at the effects of high-fat feeding on gut microbiota composition and their effects on intestinal barrier integrity[1]

| GI microbe phylum | GI microbe subclass | Effects of HFD | Permeability effects | Potential function(s) | Reference(s) |
|---|---|---|---|---|---|
| Actinobacteria | *Bifidobacterium* spp. | ↓ | ↓ | Short-chain fatty acid production increases gut barrier integrity | (91, 142, 151) |
| Bacteriodetes | *Bacteriodiodes* spp. | ↑ | ↓ or ↑ | Decreases gut colonization of *Enterobacteriaceae* | (143, 144) |
| | *Prevotella* spp. | ↓ | ↓ | Unknown | (152) |
| Firmicutes | *Clostridium* spp. | ↑ | ↓ | Acetate, propionate, and toxin production | (153, 154) |
| | *Lactobacillus* spp. | ↓ | ↓ | Increases expression of *OCLN* and *TJP1* | (155) |
| | *Oscillobacter* spp. | ↑ | ↑ | Decreases expression of *TJP1* | (156) |
| Proteobacteria | *Desulfovibio* spp. | ↑ | ↑ | $H_2S$ production from TCA | (157) |
| Verrucomicrobia | *Akkermansia* spp. | ↓ | ↓ | Increases GC mucus and IEC TJ protein synthesis | (158, 159) |

[1] GC, goblet cell; GI, gastrointestinal; HFD, high-fat diet; IEC, intestinal epithelial cell; *OCLN*, occludin gene; TCA, taurocholic acid; TJ, tight junction; *TJP1*, zona-occludens 1 (*ZO1*) gene.

response to dietary fat, as discussed previously (Figure 3). TCA is then used as a reducing equivalent, thereby enhancing intracellular energy production, proliferative capacity, and $H_2S$ gas production, resulting in inhibition of butyrate oxidation, a step required for maintenance of both gut permeability and enterocyte energy balance (157). Indeed, increased colonic levels of TCA select for *Bilophila* spp., ultimately resulting in a nutritional advantage and increased representation in the gut flora. Moreover, HFD enhanced intestinal levels and the nutritional advantage of *Oscillibacter* spp., directly correlating with depressed IEC expression of *Tjp1* and gut barrier dysfunction (163).

In contrast, *Bifidobacterium* spp. and *Lactobacillus* spp., which are decreased in HFD, are associated with enhanced gut barrier function (163, 164). These microbial species act on the intestine through unknown mechanisms to stimulate enterocyte gene expression of the TJ proteins cingulin, *OCLN*, *TJP1*, and *TJP2* (165–168). Similarly, *Akkermansia muciniphila*, which accounts for approximately 1–3% of total gut microflora, induces *Tjp1* and *Ocln* gene expression in addition to counteracting HFD-induced thinning of the SUML, thus preventing increased permeation of luminal substrates and pathogens (158, 159). At this point, it is still unknown how the gut microbiome specifically modulates the zonulin pathway or leads to intestinal barrier dysfunction by other means, and thus more research is needed to elucidate mechanisms associated with gut–microbial cross-talk and its implications in diseases associated with enhanced intestinal permeability, such as IBD.

In addition to all that was described previously, there are many other ways by which HFD-associated changes in gut microbiota impact gut barrier functionality, and this field is still evolving. More research is continuously conducted on this topic and hopefully we will see microbe-targeted therapeutics for eliminating strains that negatively impact barrier function while preserving those species with positive impacts. This may be therapeutically relevant as it is possible that these treatments can be used in conjunction with what is already available to produce the best outcome in those with diseases of the gut.

## Conclusions

The intestines serve as the first line of defense against toxins and antigens from ingested food. Although the intestinal tract employs a multilayered barrier system, consisting of a superficial mucus layer, an epithelial monolayer, the adherens-junctional complex system, an immune system, and gut microflora (Figure 2), these components may be disrupted by the diet, thus predisposing the host to various intestinal diseases. Here, we discuss how dietary fats disrupts every aspect of the intestinal barrier system and how this may manifest clinically (Figure 3).

## Take-Home Message

As interest in the field of nutrition grows, there is heightened awareness in what we consume and how that affects intestinal health. Although the consequences of consuming a Western-style HFD are readily understood, such as obesity, diabetes, cardiovascular disease, and atherosclerosis, less is known about the effects of this diet on the GI tract. Bringing together data from a vast array of studies, it is clear that an HFD negatively impacts intestinal health by disrupting the intestinal barrier system through a variety of mechanisms. Thus, this review should bring greater awareness of the impacts of diet on intestinal physiology and how this may contribute to the etiology of diseases in addition to potentially providing an alternative/supplement to treating existing GI pathologies.

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