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Role of intestinal inflammation as an early event in obesity and insulin resistance

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Abstract

Purpose of review—To highlight recent evidence supporting a concept that intestinal inflammation is a mediator or contributor to development of obesity and insulin resistance.

Recent findings—Current views suggest that obesity-associated systemic and adipose tissue inflammation promote insulin resistance, which underlies many obesity-linked health risks. Diet-induced changes in gut microbiota also contribute to obesity. Recent findings support a concept that high fat diet and bacteria interact to promote early inflammatory changes in the small intestine that contribute to development of or susceptibility to obesity and insulin resistance. This review summarizes the evidence supporting a role of intestinal inflammation in diet-induced obesity and insulin resistance and discusses mechanisms.

Summary—The role of diet-induced intestinal inflammation as an early biomarker and mediator of obesity, and insulin resistance warrants further study.

Keywords

Intestinal inflammation; cytokines; diet-induced obesity; high fat diet; insulin resistance

Introduction

Obesity has reached pandemic proportions affecting millions of individuals in developing as well as developed countries (1, 2). Obesity is associated with low-grade systemic inflammation, which is considered a major mechanism driving insulin resistance in obese individuals (3–5). Insulin resistance describes a condition in which elevated levels of plasma insulin are required to maintain normal fasting or postprandial glucose levels (5). Insulin resistance is considered a key initiating factor in the deleterious effects of obesity on health, including glucose intolerance, dyslipidemia and increased risk of non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, atherosclerosis, hypertension, ischemic heart disease and cancer (6, 7). Defining the sources, causes and mechanisms underlying the development of inflammation and insulin resistance during progressive increases in body weight and adiposity, is therefore central to the development of strategies and therapies to prevent or limit the adverse effects of obesity on health. To date, a majority of studies have focused on adipose tissue, particularly visceral adipose tissue, as the source of inflammation and proinflammatory cytokines in obese humans or animal models as described in a recent comprehensive review (7). This review will summarize recent evidence that diet-induced inflammation in the intestine, particularly the small intestine, may represent an early event that precedes and predisposes to obesity and insulin resistance. Evidence that intestinal

microbiota interact with diet to mediate intestinal inflammation and the mechanisms by which these interactions may promote obesity or insulin resistance is also reviewed.

Obesity, adipocyte inflammation and insulin resistance

Current concepts (7) suggest that during obesity, hypertrophic or hypoxic adipocytes are sources of proinflammatory cytokines including TNF α , IL-6 and monocyte chemoattractant protein-1 (MCP-1). MCP-1 further exacerbates inflammation by recruiting monocytes from the circulation and activating them to an M1 proinflammatory macrophage phenotype characterized by secretion of TNF α , IL-1 β , and IL-6. Proinflammatory cytokines compromise insulin signaling by multiple mechanisms (Fig. 1). Cytokines induce suppressors of cytokine signaling (SOCS) that bind the insulin receptor and limit its ability to bind, and tyrosine phosphorylate insulin receptor substrates (IRS-1 or IRS-2), which are critical to downstream signaling (8). Proinflammatory pathways activated by cytokines, including NF κ B, Jun-Kinase and I κ B kinase (IKK), also induce serine phosphorylation of IRS-1 and IRS-2 which limit the ability of IRS proteins to activate downstream pathways (5). While adipocytes are unquestionably sources of inflammation in obesity, increasing evidence suggests that obesogenic diets may stimulate inflammation in other organs (9, 10).

Intestinal inflammation in diet-induced obesity

Until recently, the potential role of intestinal inflammation as a mediator or contributor to obesity has received relatively little attention. This is because chronic inflammatory bowel diseases (IBD), such as Crohn's disease or ulcerative colitis, are associated with damage to the intestinal epithelium, malabsorption and weight loss. However, it is important to emphasize that the systemic and local tissue inflammation associated with diet-induced obesity is less severe than in chronic IBD.

High fat diet and intestinal inflammation in animal models

The gastrointestinal tract is the first organ to be exposed to dietary components, such as diets high in saturated fat, that promote obesity. In a recent study C57BL6 mice were exposed to high-fat or low-fat diets (HFD and LFD), and expression of multiple proinflammatory cytokines was assessed in small intestine and colon. Of many cytokines assayed, only TNF α was up-regulated by HFD, and this occurred specifically in the ileum and within 2 to 6 weeks of HFD, preceding diet-induced weight gain and increased fat mass (9). Importantly, the increases in ileal TNF α mRNA showed strong and significant correlations with the degree of weight gain, increases in fat mass, and increases in plasma glucose or insulin (9). In this study, there were no detectable increases in plasma TNF α or other cytokines, suggesting that local up-regulation of ileal TNF α was a more sensitive measure of diet-induced inflammation than circulating cytokine levels at least in this animal model (9). An NF κ BRE^{EGFP} reporter mouse expressing a transgene composed of NF κ B response elements (RE) driving enhanced green fluorescent protein (EGFP) was used as an independent model to assess intestinal inflammation. Use of this model detected activation of NF κ B-driven transcription in ileum and to a lesser extent colon of mice fed HFD (9). Intriguingly, NF κ B activation was localized to multiple cell types, including intestinal epithelial cells, CD3+ or CD45+ immune cells, endocrine cells and endothelial cells, but not resident F4/80 positive intestinal macrophages (9). This study strongly suggests that intestinal inflammation and proinflammatory signaling in multiple cell types is an early response to HFD and correlates with subsequent development of obesity and insulin resistance. Two other recent studies have demonstrated that high fat diet induces intestinal inflammation. de La Serre et. al. (11) compared obesity-prone (DIO-P) or resistant (DIO-R) Sprague Dawley rats and found that HFD up-regulated myeloperoxidase activity, a marker of inflammation, in ileum of only the DIO-P animals. This is a significant observation linking intestinal inflammation specifically

to HFD-induced obesity and not HFD alone. de Wit and colleagues performed gene microarray on proximal, mid and distal small intestine of C57BL6 mice fed HFD and found induction of macrophage migration inhibitory factor (MIF), which has been associated with obesity and insulin resistance as well as enrichment of inflammation and interferon- γ -induced gene subsets in ileum of mice fed HFD (12).

Evidence for and against intestinal inflammation in obese humans

Recent evidence demonstrates intestinal inflammation in obese humans. Spagnuolo et. al. (13) examined a small cohort of severely obese children. Using fecal calprotectin and rectal nitric acid as biomarkers of inflammation, they found that approximately 50% of obese and glucose-tolerant children had elevated fecal calprotectin, while more than 80% of obese and glucose-intolerant children had elevated rectal nitric oxide. This study indicates that intestinal inflammation occurs in obese humans and suggests that relatively non-invasive calprotectin or nitric oxide assays may be used to monitor obesity-associated intestinal inflammation. The study was however limited to a small sample size and severely obese children. Pendyala et. al. (14) examined proinflammatory cytokines and gene expression profiles in colon mucosal biopsies from a small cohort of obese women before and after a very low calorie diet to induce a loss of 10% body weight. They found that weight loss was associated with significant reductions in mucosal TNF α , IL-1 β , and IL-8 and dramatic down-regulation of gene networks linked to proinflammatory signaling (15). Together, these animal and human studies strongly support a concept that intestinal inflammation is linked to obesity and insulin resistance.

Counterbalancing these studies are recent findings of Brignardello (16), who found no evidence of colonic inflammation in obese compared to lean adults based on assays of fecal calprotectin and leptin. However, the obese individuals in this study had signs of systemic inflammation based on elevated plasma C-reactive protein but had fasting glucose levels within the normal range. Thus, systemic inflammation and obesity in the absence of detectable colonic inflammation was not associated with insulin resistance. Tiisonen et. al. also found no increase in fecal calprotectin, TNF α , or IgA in obese vs. lean individuals despite systemic inflammation and elevated plasma insulin (17). However, the lack of inflammation detected in these latter human studies may indicate that the fecal biomarkers do not have optimal sensitivity for detecting intestinal inflammation. Furthermore, in animal models, HFD-induced inflammation is particularly evident in small intestine compared with colon. Additional studies that specifically evaluate small bowel inflammation are therefore required to definitively establish the impact of diet or obesity on intestinal inflammation in humans.

Role of intestinal microbiota in obesity-associated intestinal inflammation

Compelling evidence supports a role of gut microbiota in diet-induced obesity (reviewed in Musso 2011 (18). Although mechanisms are still to be defined, findings that germ-free (GF) mice do not develop obesity or insulin resistance when placed on a HFD (19), provide definitive evidence that gut microbiota must be present for deposition of excess dietary energy intake into adipose tissue. Furthermore, colonization of germ-free mice with microbiota from obese vs. lean animals resulted in increased total fat mass, demonstrating a causal role of microbiota in diet-induced obesity (20). Recent findings demonstrate that microbiota are also necessary for development of intestinal inflammation associated with HFD and obesity. This evidence is based on our findings that GF mice fed HFD, as well as being resistant to obesity, do not exhibit up-regulation of ileal or colonic TNF α (9). Thus interactions between HFD and microbiota are required for HFD to induce intestinal inflammation. de La Serre et. al. also found that HFD results in activation of ileal toll-like

receptor 4 (TLR4) only in obesity-prone but not obesity-resistant rats (11). Since TLR4 is a primary receptor mediating the proinflammatory effects of lipopolysaccharide (LPS) derived from gram negative bacteria, this provides important evidence to link bacteria-induced proinflammatory signaling in the intestine to the development of diet-induced obesity. Intriguingly, HFD was associated with reduced levels of small intestinal alkaline phosphatase (IAP), an enzyme that detoxifies LPS (11). Recent findings in IAP knockout mice suggest that this enzyme is essential to preserve normal gut microbial homeostasis and to protect against pathogenic bacteria (21). Thus HFD-induced decreases in IAP may be important determinants of diet:microbe interactions that promote intestinal inflammation.

While much emphasis is currently placed on dysbiosis or altered microbial communities in obesity, it is important to distinguish general diet-induced changes in microbial communities from those specifically linked to obesity. For example, HFD altered gut microbial populations in both obesity-prone and obesity-resistant rats (11). Similarly, another report found that HFD led to comparable changes in microbiota in wild type mice that develop obesity and in RELM β knockout mice that are resistant to diet-induced obesity (22). These findings demonstrate the need for caution in interpreting diet-induced changes in microbial communities as causative factors in obesity. Dramatic increases in Enterobacteriales, a member of the minor proteobacteria phylum, have been associated specifically with development of intestinal inflammation and obesity in DIO-P rats fed HFD and were not increased in DIO-R rats (11). This is interesting since enterobacteriaceae have recently been linked to induction of spontaneous colitis in mouse models (23). Thus, the specific roles of these particular bacteria in intestinal inflammation associated with obesity warrants further study.

LPS as a key mediator of obesity or inflammation-associated insulin resistance

A body of work by Cani and colleagues in mouse models demonstrates key roles of increases in systemic LPS, a condition termed 'metabolic endotoxemia' in the development of obesity-associated insulin resistance (24–26). In a large study in healthy men, fat and energy intake were also found to be strongly correlated with increased plasma LPS concentrations (27). Another study in healthy humans showed that a high-fat/high-carbohydrate meal induced a significant postprandial endotoxemia, coupled with increased expression of TLR4, SOCS3, and NF- κ B in circulating mononuclear immune cells (28). In contrast, there were no increases in these proinflammatory mediators after meals rich in fiber and fruits (28). Deopurkar et. al. compared the effects of isocaloric meals rich in glucose, saturated fat, and orange juice on plasma LPS and inflammatory markers and found that only saturated fat intake was linked to plasma LPS and systemic inflammation markers, including NF κ B, SOCS3, TNF α , IL-1 β expression (29).

Current evidence suggests that diet-induced changes in intestinal permeability underlie the elevated circulating LPS in obesity. HFD has been shown to reduce intestinal permeability by affecting tight junction proteins, favoring increased translocation of LPS and potentially other proinflammatory markers into the systemic circulation (11, 26). Antibiotics, prebiotics or probiotic bacteria appear to ameliorate this effect and protect against weight gain, systemic inflammation and insulin resistance (26, 30). A recent study suggests that LPS may enter the lymph nodes and systemic circulation due to uptake into chylomicrons, which mediate absorption of dietary fat from enterocytes (31). Thus, current views would support a concept that inflammatory mediators absorbed from the gut due to diet:bacteria interactions promote systemic inflammation and associated insulin resistance.

Other mediators of intestinal inflammation due to diet:bacteria interactions

The complex and extensive interactions between host-dietary factors and microbiota (32) are beyond the scope of this review, and readers are referred to an excellent recent review (18). However it is important to recognize that many factors other than LPS may promote intestinal inflammation in response to HFD. Diet can alter the profiles of short chain fatty acids (SCFA) produced by bacterial fermentation of indigestible polysaccharides. Ratios of the SCFA butyrate, propionate and acetate depend on diet pH and microbiota (18). Butyrate has protective effects on intestinal epithelium by multiple mechanisms, including induction of alkaline phosphates and protection against intestinal inflammation (33). Butyrate also protects against HFD-induced obesity (34). Thus alterations in fecal SCFAs due to diet:microbial interactions may favor intestinal inflammation. Other bacterial metabolites such as secondary bile acids, lactate or phenolics, which have been associated with obesity or insulin resistance (17), and linoleic acid or choline which have protective effects (18), warrant further examination for roles in diet-associated intestinal inflammation.

TLR5 is protective against colitis and obesity

It is important to recognize that some bacteria-activated signaling pathways may be protective against intestinal inflammation or obesity. TLR5 is a receptor that recognizes bacterial flagellin, and when deleted in mouse models, a significant number of animals developed colitis (35). However, after rederiving TLR5 null mice with standard microbiota, the animals developed mild intestinal inflammation and by 20 weeks of age developed obesity, preferential increases in visceral fat, dyslipidemia and insulin resistance (36). The TLR5 null mice also had altered microbiota, which when transplanted to germ-free wild type mice induced obesity. While this study does not definitively link intestinal inflammation to obesity and insulin resistance, it emphasizes the key points that host receptors for bacterial ligands can impact gut microbial communities and can be protective against both intestinal inflammation and obesity.

Mechanisms by which gut inflammation itself may affect obesity or insulin resistance

A key unanswered question is whether diet-induced intestinal inflammation itself, in absence of systemic inflammation, is sufficient to initiate or promote insulin resistance or obesity. Evidence in the literature points to several potential mechanisms. Vagal afferent neurons (VAN) within the intestinal wall mediate satiety by a cholecystokinin/ CCK₁R pathway acting on the central nervous system feeding centers (37). HFD impairs sensitivity of this pathway and promotes hyperphagia. Intestinal inflammation itself could act locally on VAN to alter their sensitivity, although this remains to be formally tested. HFD and bacteria and associated inflammation may also impact enteroendocrine cells which impact feeding, metabolic pathways linked to obesity or insulin synthesis and secretion. Recent studies demonstrate that a Western HFD increases serotonin availability by increasing serotonin-synthesizing enterochromaffin cells, serotonin-synthesis genes and by decreasing transporters for serotonin reuptake (38). While this has not yet been linked to diet-associated intestinal inflammation, it is known that inflammation in other settings increases in enterochromaffin cells. Serotonin reduces gut motility (38), and therefore HFD-induced increases in serotonin and reduced motility may favor more efficient processing of ingested nutrients or fat, or could mediate diet-induced alterations in specific microbiota. Glucagon-like peptides (GLP) are synthesized in intestinal L cells and are derived from a common intestinal proglucagon precursor. GLP-1 promotes insulin synthesis and secretion (39, 40). GLP-2 promotes intestinal growth, has anti-inflammatory effects and improves gut permeability (41–43). Both GLP-1 and GLP-2 are implicated as mediators of the beneficial

effects of prebiotics to protect against weight gain, insulin resistance and diet-induced increases in intestinal permeability (39, 40, 43, 44). Further studies are required to define whether interactions between diet and endogenous bacteria, or their proinflammatory effects on intestinal epithelium, affect L cells, GLP-1 or GLP-2 secretion or action.

Conclusions

Mounting evidence links HFD and diet-induced obesity to low-grade intestinal inflammation. As indicated in the model in Fig. 2, we propose that diet interacts with intestinal microbiota to promote early inflammatory changes in the intestine, particularly the small intestine, which favor obesity and insulin resistance. Much remains to be done to define precisely how mild intestinal inflammation favors obesity and insulin resistance, but mechanisms likely include altered epithelial permeability, translocation of bacterial products, up-regulation of proinflammatory cytokines, hormones produced from gut endocrine cells and modulation of neural signaling between gut and brain that impacts appetite or satiety. Future studies should dissect the temporal course and specific roles of intestinal inflammation and associated functional effects in mediating obesity and insulin resistance compared with those related to systemic and adipose inflammation.

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and that intestinal inflammation is an early event that correlates with the development of diet-induced obesity and insulin resistance.

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Key points

- Emerging evidence in animal models suggests that high fat diet and microbes interact to promote low-grade inflammation in small intestine and to a lesser extent colon
- Intestinal inflammation precedes and strongly correlates with diet-induced obesity and insulin resistance
- Some but not all studies in humans link obesity and insulin resistance to inflammation in the colon
- Better non-invasive biomarkers of diet:microbe-induced small intestinal inflammation in humans are needed
- Intestinal inflammation may promote obesity and insulin resistance by multiple mechanisms
- Future studies need to address the specific contributions of intestinal inflammation vs. systemic or adipose inflammation to initiation and progression of obesity and insulin resistance

Figure 1. Mechanisms of insulin resistance linked to proinflammatory cytokines

Insulin activation of insulin receptor (IR) normally promotes tyrosine phosphorylation of IRS-1 (or IRS-2) to mediate downstream signaling. Proinflammatory cytokines block insulin/insulin receptor action by inducing suppressors of cytokine signaling (SOCS), which prevent IRS-1 binding to IR and by promoting serine phosphorylation and inactivation of IRS-1 via proinflammatory Jun-Kinase or NF κ B pathways.

Figure 2. Proposed roles of intestinal inflammation in obesity and insulin resistance

Top: current views of diet-associated obesity linking diet and gut microbes to development of obesity, and subsequent systemic or adipose inflammation promoting insulin resistance.

Bottom: proposed, although not mutually exclusive, model of mechanism by which diet interactions with gut microbes or metabolites induces early proinflammatory changes in the intestine which, by the multiple mechanisms indicated, promote or increase susceptibility to obesity and insulin resistance.