The Gut-Adipose-Liver Axis in the Metabolic Syndrome

Obesity is associated with altered gut microbiota composition and impaired gut barrier function. These changes, together with interrelated mesenteric adipose tissue inflammation, result in increased release of pro-inflammatory cytokines, bacteria-derived factors, and lipids into the portal circulation, promoting the development of (hepatic) insulin resistance. Herein, the potential impact of obesity-related changes in gut and visceral adipose tissue biology on the development of insulin resistance and Type 2 diabetes is reviewed.

Obesity is a major risk factor for insulin resistance and Type 2 diabetes. In the development of obesity-associated metabolic abnormalities, the liver plays a central role, given its importance in whole body glucose metabolism. Insulin curbs hepatic glucose production via inhibition of glycogenolysis and gluconeogenesis. Accordingly, the development of hepatic insulin resistance gives rise to increased glucose production and also enhanced lipogenesis, resulting in hyperglycemia, hyperinsulinemia, and hypertriglyceridemia (64). However, not all obese individuals are insulin resistant and diabetic (53). Fat distribution may influence the predisposition to the development of metabolic abnormalities, as was first noticed by Jean Vague (115). In particular, individuals with central obesity accumulating fat mainly in intra-abdominal and upper thoracic deposits are more susceptible for metabolic complications (17, 87, 93). Nevertheless, the causal relationship of central obesity and (hepatic) insulin resistance is only poorly understood, and the impact of different fat depots on the development of metabolic complications is still open to controversy (41, 78). In particular, it is unclear whether the different biological nature of visceral fat (e.g., mesenteric and omental fat depots) is driving the apparent stronger association between visceral fat and morbidity or whether it is the mere drainage to the liver, as suggested by the “portal theory.” Besides draining blood from visceral adipose tissue, the portal blood also collects nutrients and factors released by the gut and its microbiota. As a consequence, liver metabolism (e.g., insulin sensitivity) is directly affected by the secretory profile of the gut and the visceral fat, since it receives most of its blood via the portal vein. In obese patients, release of endotoxins from the gut as well as of pro-inflammatory cytokines and free fatty acids (FFA) from the visceral fat depots into the portal vein may increase (47). Consequently, such factors may negatively impact hepatic insulin sensitivity and thereby contribute to the development of (obesity-associated) insulin resistance and Type 2 diabetes (known as the portal theory). Herein, we aim to discuss how obesity-associated changes in gut and visceral adipose tissue biology may contribute to the development of hepatic insulin resistance and, hence, the metabolic syndrome.

Gut Microbiota and Inflammation

The human gut microbiota (the microbial community of the gut) contains up to 1,000 different species such as bacteria and archaea with \( \sim 10^{14} \) organisms and a biomass of \( \gt 1.5 \) kg (37, 131). Whereas exposure to pathogenic bacteria in the gut is rare and rather transient, most of the microbial bacteria are commensal and harbor many genes that are not present in the human genome (76). Accordingly, the microbiota may serve its host by protecting it against pathogens or by breaking down otherwise indigestible components of the consumed diet, thereby contributing to caloric harvesting (37, 80). Most of the microbial bacteria of humans and rodents belong to either the phylum Bacteroidetes or the Firmicutes (31, 67, 68, 84). Importantly, the gut microbiota is highly modifiable, since changes in diet may alter its composition within days (22). In particular, diets rich in fat or low in fiber (e.g., Western diet) were found to increase the relative abundance of Firmicutes (110, 112). In addition, there is increasing evidence that the composition of the microbial community of the gut is altered in obesity with a reduced relative abundance of Bacteroidetes but increased levels of Firmicutes in both men and mice (67, 68, 88, 112). Consequently, the capacity to extract energy out of consumed diet may increase (113). However, the finding of an increased abundance of Firmicutes in the microbiota of obese subjects is inconsistent (30, 100), and, hence, the question whether there is a causal relation between obesity and gut bacteria...
Responses. Commensal gut bacteria are able to modulate intestinal immune processes, since changes in gut microbiota composition may be an important determinant for body weight regulation comes from studies in patients undergoing bariatric surgery. The latter includes a variety of procedures resulting in a substantial and sustained weight loss in morbidly obese subjects commonly associated with improved metabolic function, such as recovery from diabetes. Very recent data provide evidence that bariatric surgery may alter composition of gut microbiota in humans (34, 55, 136). Of note, variations in bacterial composition correlated with changes in both clinical phenotype and adipose tissue mass. In mice, alterations of gut microbiota after bariatric surgery were independent of weight change and caloric restriction (70). Moreover, transfer of gut microbiota from operated mice to nonoperated, germ-free mice resulted in weight loss and decreased fat mass in recipient mice relative to recipients of microbiota from sham-operated mice. Hence, these studies support the notion that changes in the gut microbiota contribute to reduced host weight and adiposity after bariatric surgery. Furthermore, it underlines the impact of gut microbiota composition on body weight regulation.

Changes in gut microbiota composition may affect the function of the immune system, since microbial bacteria modulate intestinal immune responses. Commensal gut bacteria are able to shed microbial-associated molecular patterns (MAMPs) (20). MAMPs [also known as pathogen-associated molecular patterns (PAMPs)] like bacterial lipoproteins or lipopolysaccharides (LPS) are recognized and bound by pattern recognition receptors (PRRs) present on epithelial or immune cells of the gut (5, 84, 98). Activation of PRRs, such as Toll-like receptors (TLRs) and Nod-like receptors (NLRs), can initiate a host defense via induction of signaling cascades involving nuclear factor-κB (NF-κB) and mitogen-activated protein kinases (MAPK) (19, 84). Do changes in the composition of gut microbiota (as outlined above) impact on local inflammation in the gut? The fact that a high-fat diet (HFD) cannot only decrease the relative abundance of Bacteroidetes but also increase LPS-containing microbiota in the gut suggests that this might be the case (15, 112). Increased LPS binding to its receptor TLR4 may trigger an inflammatory response (12). Moreover, obesity-associated reduced abundance of Bacteroidetes may negatively affect gut immune response in rodents, since Bacteroides fragilis (phylum Bacteroidetes) were shown to suppress gut immune responses via modulation of regulatory T-cells and reduction of invariant natural killer T cells (6, 95). However, studies showing an effect of gut microbiota on gut immune response are so far lacking in humans. In agreement with the hypothesis that diet-associated changes in gut microbiota impact on intestinal inflammation, it was recently shown that high fat feeding induced ileal expression of tumor necrosis factor alpha (TNF-α) and activation of NF-κB in control but not in germ-free mice and that gut inflammation preceded fat accumulation and insulin resistance (27). In addition, HFD-fed rats showed expected changes in gut microbiota, but only rats that developed gut inflammation (i.e., increased TLR4 activation in the gut wall) were prone to accumulate fat mass (23). Of note, besides affecting gut inflammation via modulation of microbiota composition, increasing amounts of fatty acids present in Western diets may directly act on intestinal cells. In mice, high fat feeding elevated TNF-α expression in intestinal macrophages, whereas treatment of intestinal epithelial cells with fatty acids increased the release of interleukin-6 (IL-6) (33, 133). To what extent different mechanisms (direct effect of fatty acids on intestinal cells vs. changes in gut microbiota composition) contribute to local inflammatory processes in the gut and how they are possibly interconnected is less clear and may be the subject of future studies. Physiologically, local gut inflammation may be an acute adaptation to modulate gut barrier function and facilitate chylomicron transport to cope with increased dietary lipid intake (48, 65). Chronically elevated intake of fatty
acids or altered microbiota composition, however, may trigger a persistent inflammatory response in the gut, thereby contributing to the development of the metabolic syndrome.

**Gut Barrier Function and Lymphatic System**

The intestinal epithelium ensures an important physiological barrier, since it prevents harmful mediators such as microorganisms and related endotoxins to enter the circulation (39). At the same time, it allows the translocation of water and ingested nutrients, such as lipids. Most dietary lipids are taken up by intestinal enterocytes, packed in chylomicrons, and transported via the lymphatic system to systemic circulation (45). Consistently, long-chain fatty acids enter the lymphatic system after reesterification into triglycerides (TG) and incorporation into chylomicrons. In contrast to long-chain fatty acids, short- and medium-chain fatty acids are directly absorbed into the blood circulation (portal vein) (28, 114, 117, 134). Consequently, dietary lipids absorbed from the gut are mainly transported in the form of short- and medium-chain FFA in the portal vein, whereas TG are transported via lymphatic system and, hence, reach the systemic circulation and peripheral organs (60, 134).

Diet-induced changes in the gut may favor the translocation of inflammatory factors through gut epithelium, thereby contributing to the development of the metabolic syndrome. Although bacteria do not translocate through the gut barrier in regular chow-fed mice (10), they do so under fat-enriched diets. In HFD-fed mice, gut barrier function may be reduced due to decreased transmucosal permeability or due to enhanced bacterial mucosal adherence and consequent facilitated translocation of bacteria through the epithelium (5, 16, 58). Bacteria that cross the mucosal barrier of the gut are either phagocytosed, translocate to surrounding tissue (such as mesenteric fat), or reach mesenteric lymph nodes (5, 24, 74, 91, 98). Once arrived in mesenteric lymph nodes, commensal bacteria may be prevented from entering the systemic circulation (98). Nevertheless, bacterial DNA from commensal intestinal bacteria is detected in the blood of both lean and obese mice (5). Besides bacteria, other inflammatory factors such as LPS may pass the gut barrier under certain circumstances. LPS are large glycolipids derived from the outer membrane of gram-negative bacteria (75). They are taken up from the gut into the systemic circulation predominantly by passive transcellular diffusion, and its absorption is regulated by the gut barrier system (29). Of note, the intestinal endocannabinoid (eCB) system may regulate gut barrier function and, hence, circulating LPS levels (81). Interestingly, the eCB may also modulate adipogenesis of white adipose tissue LPS-dependently (9, 81), and dys-regulation of the adipose eCB system was linked to human visceral obesity (13). In support of increased LPS translocation in obesity, elevated systemic plasma LPS levels were recently reported in genetic-related and HFD-induced obese mice (15, 16) as well as in humans consuming a fat-enriched diet (4, 62). But how does LPS reach the systemic circulation? In fact, LPS may primarily leave the gut via the lymphatic system rather than via the portal circulation (25). Hence, it enters systemic blood circulation at the subclavian vein (via the thoracic duct), circumventing the liver in the first passage (24). Once in systemic circulation, LPS may affect insulin sensitivity by triggering a CD95-mediated inflammatory response in myeloid cells (125). In addition, circulating LPS [either bound to LPS binding protein (LBP) or to lipoproteins] reach peripheral organs and tissues such as liver, skeletal muscle, or white adipose tissue (WAT) (75, 118, 123), where they induce inflammatory processes impairing insulin sensitivity (15, 71).

As outlined above, the lymphatic system contributes to metabolic processes and energy storage as it transports most dietary lipids. Recent evidence suggests that inflammation may impair the function of the lymphatic system. In particular, inflammation of the gut mucosa correlated with impaired contractile function of mesenteric lymphatic vessels in rodents (124). Moreover, acute inflammation may impair barrier function of endothelial cells in initial lymphatics (microvessels lacking smooth muscle that merge into collecting lymphatics), leading to reduced clearance of fluid and inflammatory mediators from the affected rodent tissue (28, 72). Therefore, impaired function of mesenteric lymphatic vessels may directly affect tissue of the mesenterium, such as WAT surrounding mesenteric lymph and blood vessels. In support of such notion, impaired lymphatic vasculature (promoted by haploinsufficiency of Prox1, a master gene for the development of the lymphatic system) increased adipose tissue accumulation around mesenteric lymph vessels in mice (42). Accordingly, Prox1 expression was decreased in adipose tissue of patients with familial combined hyperlipidaemia (FCHL), a form of genetic dyslipidemia associated with insulin resistance and abdominal obesity (44). In summary, the close proximity to the gut may lead to elevated levels of gut-derived inflammatory factors in mesenteric fat compared with peripheral organs and tissues.
Drainage of Mesenteric Adipose Tissue

Blood and lymphatic vessels draining the gut are embedded in mesenteric WAT. Compared with other adipose depots, blood flow as well as the amount of blood vessels and lymph node weight is increased in mesenteric WAT of lean rodents (21, 52, 97), which constitutes together with the omental fat depot the visceral adipose tissue in humans. The blood of both pads is drained to the portal vein. Of note, mice and rats have a negligible omental fat depot (82) but instead show a very unique fat pad: the perigonadal adipose tissue (in male rodents, it is also called the epididymal adipose tissue). Often the term visceral fat is synonymous used with the term abdominal fat. However, as pointed out by many reports, different abdominal fat pads display unique features (e.g., different metabolic properties were reported for superficial vs. deep subcutaneous abdominal adipose tissue) (38). One of the features to distinguish between the different abdominal fat pads is their venous drainage. Whereas visceral adipose fat pads (i.e., the mesenteric and omental depots) are drained by the portal vein, blood of all other abdominal fat pads, including the perigonadal, is drained systemically, i.e., bypasses the liver (47). Consequently, whereas lymphatic flow of all different fat depots ends in the systemic circulation, the portal drainage of cytokines, adipokines, and FFA released from visceral adipose tissue directly to the liver may significantly impact metabolism. For example, fat transplantation studies in mice reported impaired glucose tolerance and the development of (hepatic) insulin resistance in mice receiving a portal vein-drained intra-abdominal fat transplant, whereas glucose tolerance was improved or not affected in mice receiving systemically drained intra-abdominal fat transplants (43, 56, 96, 108, 109). However, not all factors secreted from visceral depots are released into the portal vein, since those of higher molecular size are mainly released into lymphatic circulation (79).

Mesenteric Adipose Tissue Inflammation

In obesity, WAT is increasingly infiltrated by macrophages and other immune cells, resulting in pro-inflammatory immune response (32, 85, 121, 129, 135). Physiologically, such triggered response may serve to induce local insulin resistance to maintain tissue and whole body homeostasis in conditions of famine or infection (111). However, if such adaptive response persists, as observed during obesity, it may have deleterious effects contributing to obesity-associated metabolic dysfunction. With regard to adipose tissue inflammation, several studies reported a higher degree of inflammation in visceral/omental adipose tissue compared with fat tissue of other depots (8, 14). Moreover, visceral but not subcutaneous macrophage infiltration was reported to distinguish insulin-sensitive from insulin-resistant obese individuals (53, 106). Such findings may be explained by unique genuine properties of visceral adipose tissue, since depot-specific differences in the expression of genes during development were reported (36). On the other hand, the close proximity of visceral adipose tissue to the gut may provide an alternative explanation. Do gut-derived factors affect the inflammatory profile of the visceral adipose tissue? As mentioned above, chronically elevated intake of fatty acids or altered composition of gut microbiota in obesity may result in an increased release of gut-derived inflammatory factors into the portal as well as lymphatic circulation. Moreover, they may directly enter mesenteric WAT under certain conditions. In mice, HFD-feeding increases translocation of intestinal gram-negative bacteria (which can produce LPS) not only to mesenteric lymph nodes but also to mesenteric fat (5). Interestingly, a short exposure to a fat-enriched diet, which is associated with the development of hepatic insulin resistance as outlined below (57, 61), was sufficient to increase bacterial translocation to mesenteric WAT (5), suggesting that the latter may be an early event in the development of diet-induced metabolic dysregulation. Similarly, increased bacterial translocation to mesenteric WAT was also observed in patients with Crohn’s disease, a chronic inflammatory disease characterized by impaired barrier function and increased mesenteric fat accumulation (11, 91). Importantly, it was shown that several functional PRRs are expressed in adipocyte and in immune cells such as macrophages comprising WAT (99). Hence, increased infiltration of adipose tissue by bacteria and their fragments may be of (patho) physiological importance, since their MAMPs (such as LPS) may trigger inflammatory responses in mesenteric WAT. In support of such notion, LPS-mediated activation of TLR4 increases transcription of TNF-α and IL-6 in adipocytes (104), and the release of pro-inflammatory cytokines such as TNF-α, IL-6, interleukin-1β (IL-1β), and monocyte chemo-attractant protein-1 (MCP-1) in macrophages (73, 94). In addition, endothelial cells may be also involved, since there is evidence that targeting endothelial cell inflammation in visceral WAT prevents adipocyte alterations contributing to obesity comorbidities (90). In support of the hypothesis that gut-derived MAMPs may impact visceral adipose tissue inflammation, murine mesenteric WAT is characterized by a higher degree of obesity-induced expression of pro-inflammatory...
cytokines such as TNF-α, IL-6, and MCP-1 compared with other fat depots (2, 58, 135). Consistently, human omental fat [a part of the visceral fat, which also includes mesenteric WAT (102)] released higher amounts of TNF-α and IL-6 compared with subcutaneous WAT (59). A causal link between HFD-induced gut and mesenteric WAT inflammation is further supported by the fact that HFD-induced gut inflammation was associated with an inflammatory profile in mesenteric (i.e., increased expression of TNF-α, IL-6 and IL-1β) but not in subcutaneous or perigonadal WAT (58, 69). Thus the close relation of the mesenteric and omental adipose tissue to the gut makes them more vulnerable to obesity-associated changes in the gut. Since the visceral fat depot is interconnected between the gut and the liver, further biological characteristics of mesenteric/omentumal fat is outlined below.

**Adipose Tissue Expandability**

The capacity of adipose tissue to expand is crucial to adapt to increasing storage demands during increased caloric intake. However, such capacity to store lipids is limited (116) and may differ between fat depots. Accordingly, expandability of subcutaneous adipose tissue, which may be further constrained by inflammation/pro-inflammatory cytokines such as IL-1β (86), is reduced and may lead to increased lipid accumulation in visceral fat depots such as mesenteric and omental adipose tissue (as well as in liver, skeletal muscle, and heart, rendering them prone to develop insulin resistance as suggested by the “ectopic fat/lipid overflow theory”) (3, 35, 77). Importantly, many studies reported a strong correlation between visceral fat mass and hepatic lipid accumulation. Moreover, changes in visceral adipose tissue mass was the only variable independently explaining changes in liver fat mass in twin studies (83). In the same study, discordance in the metabolic health status between twin pairs was dependent on liver fat accumulation, further supporting an important role for the portal theory in the pathogenesis of obesity-associated disturbances in (glucose) metabolism.

WAT may expand in two different ways, i.e., via an increase in cell size (hypertrophy) or an increase in cell number (hyperplasia). Interestingly, expansion of mesenteric WAT is predominantly hypertrophic, whereas it is rather hyperplastic in subcutaneous WAT (26, 50). However, it is still under debate whether intrinsic (e.g., developmental program or abundance of adipocyte progenitors) or extrinsic factors (e.g., the close proximity of the visceral fat to the gut) are responsible for the observed differences in the expansion pattern (50, 51, 107). How could the anatomical location of visceral fat impact on its expandability? Adipocyte hypertrophy may be the result of impaired adipocyte differentiation due to reduced activation of the peroxisome proliferator-activated receptor gamma (PPARγ) in preadipocytes (1, 46). Importantly, pro-inflammatory factors such as TNF-α and LPS were shown to reduce PPARγ expression in preadipocytes, thereby negatively affecting differentiation (18, 71, 92, 120, 130). Consequently, predisposition to hypertrophic WAT expansion in visceral fat may result from enhanced downregulation of PPARγ via an elevated pro-inflammatory profile. In support of such notion, PPARγ expression in preadipocytes of visceral compared with subcutaneous depots was decreased in obese humans (101, 107). But why does adipocyte size matter? Although small, hyperplastic adipocytes are able to store and retain FFA, and hypertrophic adipocytes may have an impaired capacity to deposit FFA, thereby contributing to elevated circulating FFA levels (66). Accordingly, hypertrophic adipocytes release higher amounts of FFA and pro-inflammatory cytokines compared with small adipocytes of the same adipose depot, suggesting an adverse metabolic profile of enlarged adipocytes (63, 103, 126).

Taken together, visceral adipose is a unique fat depot characterized by an altered pattern of expandability and an increased obesity-induced inflammatory profile compared with other fat depots. In addition, glucose and lipid metabolism is differently regulated in visceral compared with subcutaneous and perigonadal WAT as reported elsewhere (97, 127, 128, 132).

**The Portal Theory**

Blood from the portal vein drains to the liver and, thus, the liver is exposed to relatively high concentrations of different mediators released by the gut, the spleen, and the visceral (mesenteric and omental) adipose tissue. As discussed above, obesity induces fundamental changes in the gut as well as in the mesenteric adipose tissue. The resulting increase in bacteria-derived factors such as endotoxins, pro-inflammatory cytokines, and FFA (and/or the change in their composition) negatively impact hepatic insulin sensitivity, as suggested by the concept of the portal theory and reviewed elsewhere (47). The development of hepatic insulin resistance is an early event in the development of HFD-induced impairment of glucose metabolism. For example, 3–4 days of high fat feeding is sufficient to induce hepatic insulin resistance (57, 61) but did not significantly impact skeletal muscle insulin sensitivity in rodents (57, 122). Even though the development of hepatic insulin resistance was
associated with mesenteric adipose tissue inflammation (40, 122), it remains arguable whether short-term HFD-initiated hepatic insulin resistance is mediated by adipose tissue inflammation or is the result of acute lipid overload, even though we recently provided clear evidence that adipose tissue inflammation is at least partly involved (49, 122). In addition, it remains currently unclear whether it is related to changes in gut microbiota composition, albeit such changes were reported as early as 1 wk after initiation of HFD (89).

Although hepatic insulin resistance and steatosis are closely associated in obesity, a causal link between the two is currently under debate (105). Potentially, hepatic steatosis induced by increased portal delivery of FFAs may inhibit insulin signaling through the formation of lipid metabolites. On the other hand, increased release of pro-inflammatory cytokines from the gut and visceral fat may induce liver insulin resistance and subsequently hepatic steatosis. Irrespective of the underlying cause, portal delivery of fatty acids, pro-inflammatory cytokines and/or bacteria-derived factors to the liver would be compatible with both hypotheses. Of interest, even though alleviated mesenteric adipose tissue inflammation was associated with a reduction in short-term HFD-induced hepatic insulin resistance, it did not impact hepatic steatosis (122), indicating that the latter may be the result of an acute lipid overload rather than a dysfunctional adipose tissue-liver cross talk at an early stage of HFD.

In conclusion, obesity-associated changes in the gut microbiota composition as well as in gut and/or visceral WAT properties/biology (whereby the latter are at least partly interconnected to each other) may contribute to the development of hepatic insulin resistance, hepatic steatosis, as well as the metabolic syndrome. Herein, the direct exposure of the liver to increasing amounts of bacteria-derived factors, such as endotoxins, pro-inflammatory cytokines, and lipids seems to be critical (FIGURE 1). However, further studies are needed for a better and comprehensive understanding of the apparent causal link between obesity-related changes in gut as well as visceral adipose tissue biology and the development of insulin resistance and Type 2 diabetes.

**FIGURE 1.** Pathophysiological processes in the gut-adipose-liver axis that potentially contribute to the development of the metabolic syndrome

1: increased intake of fat-enriched diet (Western diet) and/or elevated release of bacteria-derived factors such as LPS due to altered gut microbiota composition in obesity led to increased production of pro-inflammatory cytokines in the gut. 2: such pro-inflammatory cytokines as well as diet-derived FFA and LPS are partly drained into the portal circulation. 3: obesity-/diet-induced impairment of the gut barrier function led to (elevated) translocation of bacterial particles and endotoxins into mesenteric white adipose tissue (WAT). In mesenteric WAT, translocated factors stimulate adipocytes and resident immune cells to release pro-inflammatory cytokines. Subsequently, these cytokines may be released into the portal circulation and/or favor the development of hypertrophic adipocytes that secrete higher levels of FFA and/or pro-inflammatory cytokines (4). 5: the evolving pro-inflammatory milieu along the gut-visceral WAT region in situations of high dietary fat intake and/or obesity impairs lymphatic function, thereby leading to reduced clearance of inflammatory mediators from the mesenteric WAT. Altogether, pathophysiological changes in the gut-visceral WAT region led to increased delivery of LPS, FFA, and pro-inflammatory cytokines into the portal circulation, thereby negatively affecting liver metabolism. Please see main text for details.
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