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Effect of Alcohol on Gut-Liver Axis and Adipose Tissue

Dhara Patel and Palash Mandal

Abstract

Adipose tissue comprises of large volumes of biologically functioning fat globule, which employs substantial systemic effect. Adipocytes and adipokines play an active role in autocrine, paracrine, or endocrine metabolic functions. Recent studies demonstrated that the hormonal role of adipocyte and adipose tissue dysfunction contributes to the pathogenesis of alcoholic liver disease (ALD) by the activation of CYP2E1. The gut microbiome and adipose tissue response play a pivotal role in the pathogenesis of ALD. Enteric dysbiosis increases plasma levels of metabolites that activate Kupffer cells. Recent literature suggested that chronic alcohol consumption is also correlated with oxidative stress in adipose tissue, inflammation, and adipocyte cell death, decrease in adiponectin, increase level of leptin and resistin, adipose tissue mass, and insulin resistance that acts on the muscle and liver. Dysbiosis combined with non-nutritional diet has an effect on the luminal metabolism causing immunological changes in the gut that might also contribute to pathogenesis of nonalcoholic fatty liver disease (NAFLD). Understanding the interaction between the altered gut microbiota, diet, environmental factors, and their effects on the gut-liver axis can provide an insight toward the pathogenesis of liver-associated disease.

Keywords: alcoholic liver disease, adipose tissue, adipokines, gut microbiota, nonalcoholic fatty liver disease

1. Introduction

Alcohol is considered the fifth leading risk factor for premature death and various disorders universally. It is psychoactive substance that leads to overuse of alcohol or alcoholism abuse. Alcohol related liver diseases are the primary cause of every third person undergoing liver transplants worldwide. Worldwide, alcohol liver disease (ALD) causes 14.5 million disability-reduced life years and approximately 500,000 deaths in 2010 [1]. Depending on behavior, genetics, and comorbidities, individuals who consume alcohol develop hepatic steatosis, an early stage of alcoholic hepatitis [2]. Although ALD is a disease that requires an intention for consumption of alcohol, there are various other factors, including genetic host system characteristics involved in the development and progression. The amount of pure alcohol consumption and duration is directly linked to cirrhosis.

Adipose tissue comprises of large volumes of biologically functioning fat globule, which employs considered to be submissive [3]. Researchers have established a remarkable understanding of adipocytes being an acute component of metabolic pathways and functioning of endocrine organs. Recent studies have given an insight on the hormonal role of adipocytes. Adipose tissue is identified to secrete proteins that are termed as

adipokines, which play an active role in autocrine, paracrine, or endocrine metabolic functions. Adiponectin, leptin, and resistin are the most affected functional adipokines.

The body as a whole is affected on the consumption of alcohol. It has been demonstrated that mainly enteric dysbiosis plays a significant role in the development of ALD. Due to an increased intestinal gut permeability of microbes like *Clostridiales*, *Ruminococcaceae*, and *Bifidobacterium* spp., this leads to an elevated plasma levels of metabolites like lipopolysaccharide (LPS), Toll like receptors (TLR-4, TLR-2), cell surface receptor and differentiation marker 14 (CD-14), NADPH oxidase homolog 4 (Nox-4), glucose transporter-4 (GLUT4), and short-chain fatty acid (SCFA) which activates Kupffer cells along with the consequent effects of inflammation, necrosis, and oxidative stress. The activation of cytochrome P450 2E1 (CYP2E1) mediated by ethanol breakdown leads to adipokine dysfunction. Adiponectin acts as an anti-inflammatory cytokine while leptin and resistin act as pro-inflammatory cytokines that trigger adenosine monophosphate-activated protein kinase (AMPK) pathway which activates fatty acid oxidation and decreased hepatic lipid influx and de novo lipogenesis. Studies have reported that chronic alcohol consumption leads to reduce levels of adiponectin and an increase in leptin secretion and macrophage migration inhibitory factor (MIF) leading to reduction in adipose tissue mass and increase in fatty acid uptake by hepatocytes [3, 4]. Compounds like rosiglitazone, a PPAR-ϒ agonist that targets the adipocytes exogenously, have shown to attenuate alcohol-induced fatty liver [5, 6]. Inflammation due to bacterial translocation is the main contributor to the development of alcoholic liver disease. Cytokines like tumor necrosis factor alpha (TNF-α), interleukins (IL-1β, IL6, IL8), induced nitric oxide synthase (iNOS), reactive oxygen species (ROS), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and heme oxygenase (HO-1) increase adipocyte lipolysis and systemic insulin resistance by stimulating the release of free fatty acids from adipose tissue into the blood stream, which acts on the muscle and liver [4].

The gut microbiome and adipose tissue responses play an essential role in the pathogenesis of alcohol liver disease. The mechanism between adipose tissue and alcohol consumption is yet to be answered.

2. Adipose tissue

An obese person can have up to 80 L volume of adipose tissue, which contains about 24 L volume of biologically active adipose tissue [7, 8]. The factors that affect the distribution and volume of adipose tissue mainly vary by gender and location. For example, body fat is found more in women than in men. Similarly people from southeast Asia have less body fat compared to white people of identical body mass index (BMI) [9].

Depending upon the anatomy, adipose tissue is classified as follows:

- Visceral adipose tissue (VAT)

- Subcutaneous adipose tissue (SAT)

Visceral adipose tissue corresponds with insulin resistance and diabetes mellitus [10].

2.1 What does adipose tissue composed of?

Adipocytes are considered to be the building blocks of adipose tissue. Adipocyte stores energy from non-esterified fatty acids (NEFA) and esterification of triglyceride [11]. Lipotoxicity refers to as uptake of circulating lipids, which prevents accumulation

of NEFA in the organs [12]. There are various processes that take place in adipose tissue which are controlled by hormonal pathways and are useful for metabolic demand [13]:

- Hydrolysis of triglycerides (lipolysis) takes place during fasting or exercise.

- Synthesis of triglyceride (lipogenesis) takes place during fed state.

2.2 Which cytokines are released by adipocytes?

Adipose tissue secretes adipokines that play a central role in metabolism of energy. The secretion of adipokines can be altered due to obesity and insulin resistance. Out of several adipokines, leptin, adiponectin, and resistin are the primary ones that are responsible for insulin resistance as well as in ALD [14].

2.3 Different kind of adipokines:

2.3.1 Leptin

Leptin receptor is located in numerous tissues, which controls expenditure of energy, food consumption, lipolysis, fatty acid oxidation, lipogenesis, and insulin sensitivity signifying as a paracrine and autocrine hormonal function [15]. It also helps in enhancing the release of a TNF-α by Kupffer cells [16].

2.3.2 Adiponectin

Adiponectin has a significant role in insulin sensitizing by altering the signaling pathway of AMPK and metabolism of glucose and fatty acid oxidation in tissues. It is also responsible for adiopogenesis, prevention of ectopic fat storage and decline in Kupffer cell activation [14, 16]. The onset of chronic exposure to ethanol can lead to the disruption of adiponectin which is proven to contribute toward the imbalance of pro-inflammatory pathways [3]. A preventive study was performed on the mice along with the treatment of adiponectin and chronic ethanol exposure and signifies the prevention of the liver injury indicating the decrease in both steatosis and TNF-α expression in the liver [17]. Though the mechanism of the therapeutic adiponectin is not well understood, the hypothesis suggests the vital role of a adiponectin in decreasing steatosis which is related to glucose and lipid homeostasis [3].

2.3.3 Resistin

Resistin can acquire insulin resistance and regulates food intake, thus acting as an antagonist to adiponectin [18]. Resistin, a 12.5-kDa polypeptide, is secreted by white adipose tissue in female [19]. In human, resistin gene is mainly found in the bone marrow and lung with untraceable levels in adipose tissue [20]. Resistin gene expression was provoked during adipocyte differentiation [21]. Thus, serum resistin can act as a powerful diagnostic marker to access the severity of liver disease and patient with clinical complications [22].

2.3.4 Omentin

Omentin secretion increases insulin sensitivity in adipocytes [16]. It is mainly secreted from the stromal vascular fraction of adipose tissue which enhances glucose uptake mainly activated by insulin [23]. The concentration of omentin was increased in portal vein which is a consistent marker for ALD [24].

2.3.5 Chemerin

Chemerin helps pre-adipocyte differentiation and contributes to immune cell trafficking. It is also proven to increase the sensitivity of insulin as well as provides anti-inflammatory effects on endothelium immune cell [25].

2.4 The role of non-adipocytes

Non-adipocyte cells are present in a considerable amount of overall cellularity of the adipose tissue. They include cells from perivascular, endothelium, immune, and stem cells. These clusters of cells are known as stromal vascular fraction (SVF) [14].

2.4.1 Macrophages as inflammatory mediators

Macrophages make up the majority of the resident immune cells in the adipose tissue [26]. The systemic insulin resistance and inflammation are linked with increased macrophage infiltration into the adipose tissue indicating M1 pro-inflammatory state [27]. "Crown-like structure" is formed where macrophages present in adipose tissue encircle dying adipocytes [28]. Adiponectin suppresses macrophage activity using several ways; one of them is to prevent proliferation of myelomonocytic progenitor cells. This reduces the upregulation of endothelial adhesion molecules in response to cytokine production by macrophages [3].

There are other immune cells like B cells, T cells, and dendritic cells which contribute to the obesity-related inflammation. Dendritic cell in particular promotes CD4$^+$ T helper cells to activate macrophage recruitment [29]. Neutrophils are seen in lean and obese individuals, which are primary defense cells in a high-fructose diet mice model [30]. Thus, cytokine expression in adipose tissue is predominately from SVF, while in case of obese individuals, there is an increased expression of cytokines [31, 32]. Studies suggested the important link between the adiponectin and IL-10, the two main critical anti-inflammatory mediators. For instance, adiponectin stimulates IL-10 mRNA and protein expression in RAW264.7 macrophages. In the same cells, gAcrp-mediated desensitization to LPS is prevented due to the immunoneutralization of IL-10 [3]. HO-1 shows antiproliferative, anti-inflammatory, and anti-apoptotic properties. HO-1 is considered as a vital downstream mediator of the anti-inflammatory effects of IL-10 in macrophages [33].

3. What is gut microbiota comprised of?

The human gut contains more than 400 different species, comprising of four major bacterial families that play important roles like defining the physiology of the host [34]. The majority of mammalian gut microbiota belongs to the two bacterial phyla, the gram-negative *Bacteroidetes* and the gram-positive *Firmicutes*, which play a major role in the maintenance of normal health condition, metabolism, and disease. Mainly four major families play an important role, an dthey are comprised of:

• *Bacteroidetes*

• *Firmicutes*

• *Actinobacteria*

• *Proteobacteria*

Proximal two thirds of the small intestine and stomach contain less number of microbes in the range of 10^0–10^4 cfu/ml due to acidic pH. The ileum contains more diverse microflora and higher bacterial strains from 10^7 to 10^8 cfu/ml. Most amounts of species of obligate anaerobe reside in the colon due to a low oxidation-reduction potential of the colon. Thus, a subsequent increase in microbes from the stomach to colon has been observed, as the human gastrointestinal tract pH has shown an increase from the stomach (pH 2.0) to duodenum, jejunum, ileum, and colon (pH 5.0–7.0) [35].

Bacteroidetes contain variety of enzymes like hydrolase, dehydrogenase, and dehydroxylase that play a major role in the biotransformation of bile acids. *Firmicutes* play an important role in the energy extraction from undigested carbohydrates in the form of production of short-chain fatty acids [36]. Far from being a static ecosystem, the content of this phylum radially shifts in the response to change in host adiposity and nutrient uptake [37].

Changes in the intake of diet clearly affect composition of an individual's gut microbiota and its body physiology [38]. Complex carbohydrates are metabolized by the colonic microorganism. *Bifidobacteria* convert complex carbohydrates into oligosaccharides and monosaccharide, further fermenting into the short-chain fatty acid end products like acetate, propionate, and butyrate. Colon absorbs SCFA, where butyrate provides energy for colonic epithelial cells; acetate and propionate migrate to the liver and other peripheral organs, where they act as substrates for gluconeogenesis and lipogenesis [39].

3.1 Gut microflora in well-being, metabolism, and disease

3.1.1 How does gut microflora gets affected in nonalcoholic fatty liver disease?

Nonalcoholic fatty liver disease is the liver disorder whose pathogenesis is not well understood due to the portal system interaction with the intestinal lumen and liver. Therefore, it is considered that gut microbiome plays an important role in the pathogenesis of NAFLD. Also, diet has a potential to modify the gut microbiome and several metabolic pathways. Thus, the combination of diet, gut, and liver associates directly with the progression of NAFLD or T2D. Most of the diabetic patients are diagnosed with high blood glucose levels in context with insulin resistance and insulin deficiency.

Westernized diet and pattern of eating are the main driving forces for the increased prevalence of insulin resistance and increased obesity. Studies have suggested that the diet rich in saturated fats are directly proportional to weight gain, insulin resistance, and hyperlipidemia in humans and animal models [40]. In addition, diet specifically high in sugars like fructose and sucrose has contributed to the metabolic alterations in animal models resulting in weight gain hyperlipidemia and hypertension [41]. An overconsumption of fructose hampers glycolysis and glucose uptake pathways in the liver. This leads to an enhanced rate of de novo lipogenesis and triacylglycerol synthesis leading to insulin resistance through fructose catabolism.

Increased activity of the inflammatory pathways is a very important mechanism for insulin resistance. An increase in the activity of the nuclear factor kB (NF-kB) pathway and the maintenance of a subacute inflammatory state are associated with obesity. These cytokines and chemokine activate intracellular pathways which promote the development of T2D [42]. Pattern recognition receptors (PRRs) play an important role for identification of commensals versus pathogenic microbes, which reside in the gastrointestinal tract. TLR recognize extracellular patterns, whereas NOD-like receptors (NLRs) recognize intracellular (cytosolic) pathogen Associated molecular patterns (PAMPs) [43].

TLRs, extracellular (innate) pattern recognition receptors, are expressed nearly on all the cell types. In total, 13 different TLRs are present in human genome, which remain specific for unique class of PAMPs. Among the TLRs, TLR2 and TLR4 are considered to be vital for the pathogenesis of insulin resistance and diabetes in both clinical and experimental conditions. TLR2 specifically binds to peptidoglycan (gram-positive bacteria), and TLR4 binds to lipopolysaccharide (gram-negative bacteria) [43]. High-fat or high carbohydrate food intake increases the concentration of plasma LPS levels and LPS binding protein, which increases the expression of TLR2 and TLR4 at mRNA and protein level [44]. The study has also shown that the absence of TLR4 protects against the detrimental effects of obesity and lipids on the insulin resistance [44]. A study on TLR4 null mice demonstrated a reduced adiposity and hepatic steatosis compared with the wild-type control when fed on high fat diet (HFD) [45].

NLRs are intracellular or cytoplasmic pattern recognition receptors, which exhibit specificity toward one or more PAMPs. In gastrointestinal epithelial cells, nucleotide-binding oligomerization domain (NOD) is mainly characterized by NLRs. Caspase activation and recruitment domain (CARD) is unique for each NOD protein.

- NOD1 (CARD 4): senses peptidoglycan contents in gram-negative bacteria specifically meso-diaminopimelic acid (meso-DAP)

- NOD2 (CARD 15): senses muramyl dipeptide, the common molecular motif both in gram-positive and gram-negative bacteria.

NOD1 and NOD2 are essential since they were the first NLRs reported as potential sensors of bacterial components. It has been reported that NOD1 and NOD2 are also involved in high fat diet induced-inflammation and insulin intolerance [46]. NOD1 agonist causes inflammation and insulin resistance in a primary hepatocytes of the wild-type mice, but this effect was absent in NOD1 knockout mice [47].

The downstream pathway that follows after the engagement of NLRs and TLRs with their respective ligands leads to the activation of NF-kB-mediated inflammatory pathways through adaptor protein MyD88 and secretes the major pro-inflammatory cytokines like TNF-α and IL-6. Pro-inflammatory cytokines phosphorylate the serine/threonine residue of insulin and downregulate the insulin signaling pathway, which finally leads to the insulin resistance and occurrence of T2D [48]. In vivo studies in mice have shown that the gut tight junction between the cells loosens up when the population of *Bifidobacteria* is decreased. These loose junctions increase the gut permeability and allow lipopolysaccharide present in microbes to pass through the gut epithelial resulting into metabolic endotoxemia causing a low-grade inflammation which is responsible to induce a metabolic disorder including the insulin resistance [49].

Increased body weight with other metabolic phenotypes was observed in the germ-free mice who were fed with either low-fat mouse chow or with different levels of saturated fat and fruits along with vegetables in different groups [50]. In another study, group of mice developed hyperglycemia and high plasma concentration of pro-inflammatory cytokines when HFD was induced. Hyperglycemia resulted in hepatic macro-vesicular steatosis, elevated hepatic triglycerides, and de novo lipogenesis [51].

When an adult germ-free C57BL/6 mouse was orally fed with normal microbiota harvested from the distal intestine of any normal animals, they developed 60% increase in body fat content with insulin resistance. Fasting-induced adipocyte factor (FIAF), a circulating protein of angiopoietin, is essential for the microbiota-induced deposition of triglycerides in adipocytes [52]. Deficiency of choline is usually liked with NAFLD and nonalcoholic steatohepatitis (NASH) [53].

The above-mentioned examples show the significance of the environment and genetic factors in correlation with the liver diseases.

3.1.2 How does a whole body responds to alcoholic liver disease?

The liver is a vital organ of the body, as it metabolizes alcohol in three different ways as follows:

- By the use of an enzyme alcohol dehydrogenase (ADH)

- By the use of CYP2E1

- By the use of mitochondrial catalase

ADH and CYP2E1 are two significant ways through which alcohol gets converted into acetaldehyde; ADH is used when the consumption of alcohol is limited, while on the consumption of an excess alcohol, CYP2E1 metabolism plays a role [54]. ADH is not only present in the liver but, it also is expressed in the gastric mucosa. It is an assumption that people with lower gastric ADH are more prone to the alcoholic liver disease [55].

Alcoholic liver disease includes various stages like alcoholic hepatitis, steatosis, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Alcohol consumption, diet, nutrition, and genetics determine the severity and prognosis of ALD. Morbidity and mortality remain higher in the liver cirrhosis than in benign liver disease (i.e., liver steatosis) [54]. Twenty percent of the patients with simple steatosis with continuous abuse can develop fibrosis within a period of 10 years [56]. In an absence of alcohol for a few weeks, simple steatosis is reversible, while a fibrogenic process of steatohepatitis can induce cirrhosis. Human trials on reversing the steatohepatitis for the treatment of chronic hepatitis C and NASH are well documented [57].

Oxidative stress mainly occurs due to CYP2E1 accompanied along with the shortage of antioxidants in the hepatocytes and an altered inflammatory cytokines [58]. It has been known that changes in the lipid metabolism and adipose tissue will also enhance the process of liver injury [59]. Genetics of an individual is also another factor that is taken into account for the susceptibility of alcoholism. Lately correlations between the genetic polymorphism of alcoholic metabolizing enzymes and ALD have shown a significant association [60]. Family studies in Asian population have shown association of the following two genes in particular with ALD [61, 62].

- Alcohol dehydrogenase ADH1B*1 allele: responsible for increase in alcohol dependence

- Alcohol dehydrogenase ADH2B*2 allele: responsible for decrease in alcohol dependence

Diet is also one of the significant factors affecting the structure and functionality of gut microbiota. Alcohol and its degradation products can contribute toward the gut dysbiosis [63]. Patients with ALD have shown decrease in commensal groups like *Roseburia*, *Faecalibacterium*, *Blautia*, and *Bacteroides*, while increase in *Proteobacteria* and *Bacilli* resulting in an increased gut permeability, tight junction barrier dysfunctioning, and inflammation [64, 65]. One of the proposed mechanisms is the direct interaction of gut and endotoxins from the liver via

hepatic artery, as well as mechanism of bile acids that contributes toward ALD [66], although the mechanism of the latter interaction is yet to be elucidated.

Due to an exposure of alcohol, intestinal microbiome is getting affected by causing bacterial (gram negative) overgrowth in animal models and humans. Particularly the genus *Lactobacillus* is on a lower side due to the onset of chronic alcohol consumption [67]. It has been recently demonstrated that supplementing saturated long-chain fatty acid with commensal *Lactobacilli* stabilizes the intestinal gut barrier and tight junction barrier in ethanol-induced liver disease in mice [68]. NOD2 is mainly responsible for increasing bacterial peritonitis and bacterascites in cirrhosis, which primarily affects the survival [69]. PAMPs or damage-associated molecular patterns (DAMPs) are recognized by inflammasomes and activate the pro-inflammatory cytokines such as pro-interleukin (IL-1, IL-18) [70]. Chemokine (C-C motif) ligand causes inflammation in colon due to intestinal dysbiosis [71]. TNF-receptor-1 (TNFR-1) present on the intestinal epithelial cells are crucial mediator for ALD and also cause an intestinal barrier dysbiosis [72]. Thus, inflammation can lead to intestinal permeability, which is associated with the translocation of microbial products to TLRs in the liver, which is related to aggravated hepatic steatosis.

4. Role of immune system in intestinal membrane

Maintaining the balance and symbiotic relation between the immune system and host intestinal microbiome is a very important aspect. This is because they maintain a balance of an immune system by restricting the overgrowth of pathogenic microbiota, as well as the bacteria that reaches the intestinal barriers, chemical barriers, and physical barriers [73]. Innate signaling by MyD88 in T cells directs IgA-mediated microbiota to promote the healthy gut. In IgA-deficient mice, it has been observed that TLR-5 and host protein programmed cell death 1 (PD1) regulate the modulation of IgA homeostasis by differentiating B cells into IgA producing antibodies [74, 75]. The importance of IgA in the microbiota composition in chronic liver disease is yet to be studied.

In liver cirrhosis patient, buccal origin microbes were found in intestine, taxonomically signifying the translocation or invasion from mouth to intestine. Simultaneously these patients also observed to have compromised innate immune system, reduced bile flow and impaired AMP production [76, 77]. The production of AMP is mainly regulated by the gut microbiota that includes defensins, C-type lectins (Reg3b and Reg3g), ribonucleases, and S100 proteins, which rapidly inactivate microbes [78]. In MYD88-deficient mice, NOD2 altered AMP production, which was closely marked [79, 80]. Chronic alcohol administration results in decreased expression of the intestinal C-type lectins in mice, and similar results were observed in the duodenum [81, 82].

Mucin is secreted by the goblet cells which are glycosylated and accountable for the construction of the inner and outer layer of mucus. In mice and humans, mainly mucin-2 is responsible for the mucus layer formation. Upon interaction with the lectin, they are responsible for bacterial composition of the host that promotes formation of glycosidase and metabolic enzymes which are used as a source of energy [83]. Innate immune system is activated to maintain the intestinal homeostasis in the absence of mucin-2. An experiment in the mucin-2-deficient mice demonstrated higher expression of antimicrobial proteins and protected the intestinal barrier from bacterial overgrowth and dysbiosis. This interconnection between the different intestinal defense layers and microbiota helps in decreasing ALD [81].
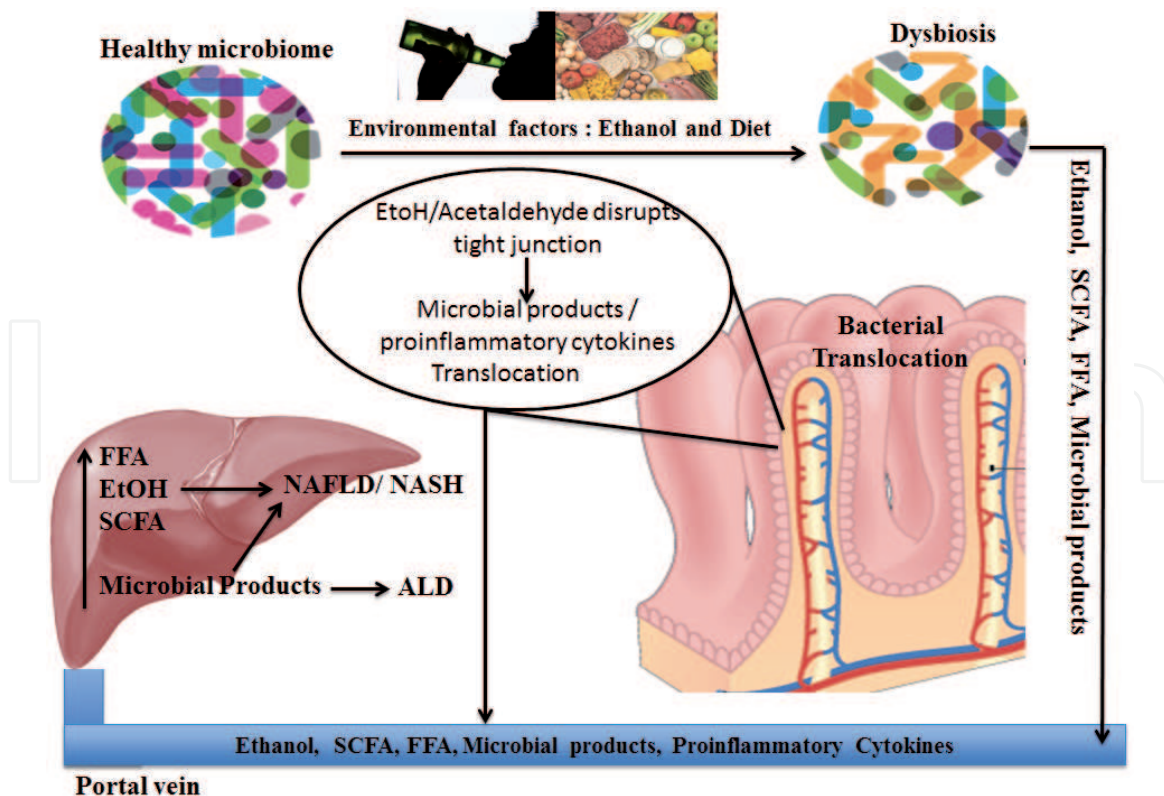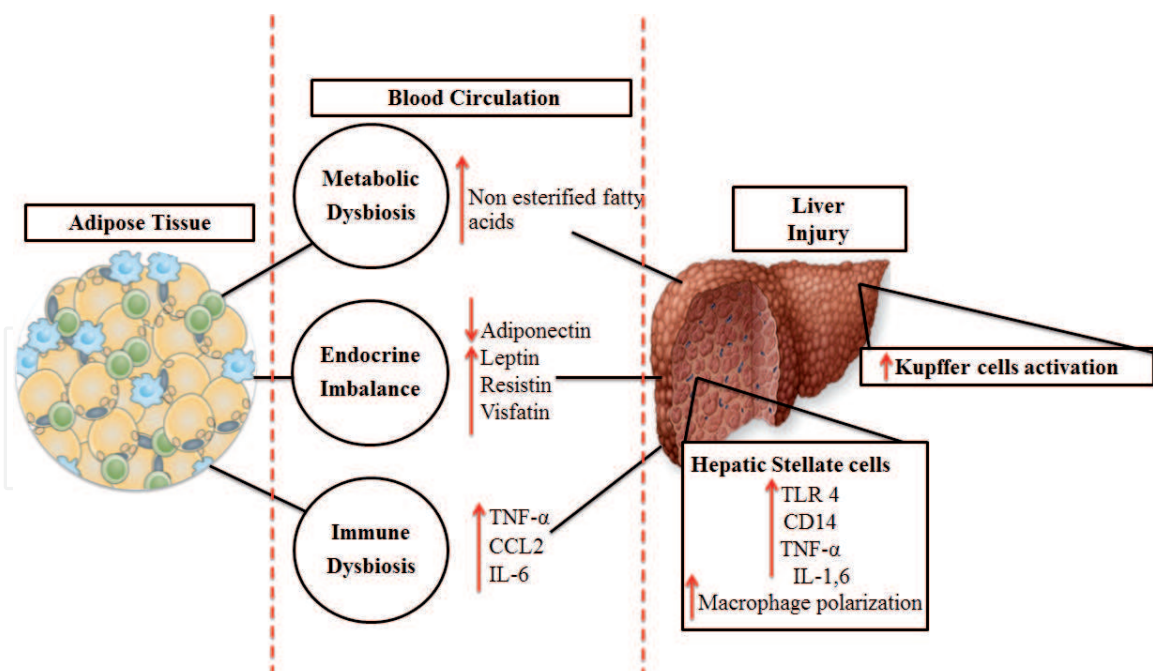
Figure 1.
Effect of microbiome dysbiosis on liver disease.

Interestingly, there is no single assigned bacterial species that marks the beginning or development of the liver disease. It is always marked by an increased percentage of gram-negative bacteria especially *Proteobacteria* which is known for accelerating cholestatic liver fibrosis [84]. To study the importance of the intestinal microbiota for chronic liver disease, liver fibrosis was induced into the germ-free mice model via the administration of thioacetamide in the drinking water. As a result in comparison to conventional mice, germ-free mice showed elevated liver fibrosis [85].

Ethanol consumptions lead to the elevation of lipopolysaccharide and endotoxin in the portal blood circulation that sensitizes Kupffer cells to activate the inflammatory mediators like TNF-α, IL6, and ROS. Another factor that facilitates the liver disease is the loss of anti-inflammatory mediators. A study has shown IL-10 deficient mice to be more sensitive to ethanol liver injury [3]. The alterations in the intestinal microbiota composition are significant for the pathogenesis of chronic liver disease which is demonstrated and briefed in **Figure 1**.

5. Effect of alcohol on liver and adipose tissue

The energy value of alcohol is equal to those of other nutrients, so when the alcohol consumption is increased, the overall calorie intake excessed the expenditure of energy, which leads to adiposity [86]. It has been established that chronic cirrhosis patient shifts toward the lipid oxidation instead of carbohydrate as fuel to meet the energy requirements which in turn reduces the overall fat mass in an individual [87]. Thus, malnutrition with low adipose skeletal muscle mass is a symptom for an advancement of the liver disease [88]. Alterations in the body mass may also depend on the type of drinking pattern; for instance, a person drinking beer or spirits gains more body mass than wine consumption [89]. Thus, excess alcohol

Figure 2.
Association of adipose tissue in alcoholism due to metabolic, endocrine, and immune dysbiosis.

intake increases the amount of visceral adipose tissue as compared to the changes observed in case of obesity [90].

In vivo mice experimental alcoholic model has shown the significant increase in the number of adipocyte death in white adipose tissue. The mechanism for death of adipocytes involves interaction between CYP2E1, BH3-an interaction domain agonist for death (BID) and C1Q complement pathway. As sequence, these interaction lead to adipose tissue inflammation, insulin resistance, lipolysis, NEFA and release of proinflammatory cytokines [91]. Hence, increase in uptake of fatty acids in the adipose tissue will lead to an increase in hypertrophy, hypoxia, and inflammation ultimately leading to the cell death [92]. However, alcohol uptake in the moderation has been associated with insulin sensitivity [93]. Thus, acute or chronic alcohol consumption is associated with metabolic, endocrine, and immune dysbiosis as shown in **Figure 2**.

5.1 Influence of alcohol on metabolic dysbiosis

Metabolically, an increase of NEFA is seen in ALD patients [94]. Increase in NEFA depends on the increase in expression of adipose triglyceride lipase (ATGL) but is independent of lipase [95]. Lipolysis is particularly marked by acute alcoholic hepatitis (AAH), but it may decrease during the advanced cirrhosis. The molecular mechanism that leads to lipolysis with excess ethanol consumption is not clearly understood; the possible primary factor may be the ethanol-mediated insulin resistance. Contradicting effect is seen with the use of catecholamine, which may reduce lipolysis or remain unchanged [96]. Consequently, higher level of circulating NEFA shows reduced capacity of the adipose tissue to esterify alcohol and store up free fatty acid [97]. Further these unsaturated fatty acids are delivered to the liver which contributes to hepatic steatosis as they get converted to triglyceride [98]. c-Jun N-terminal kinase (JNK) pathway triggers the hepatocyte apoptosis by increase in number of saturated fatty acids with enhanced hepatotoxic effect [99]. Hepatic de novo lipogenesis increases due to the transcription of sterol regulatory

Adipokine	In vivo model (mouse and human)	Acute alcoholic model	Chronic alcoholic model	Reference
Leptin	In both models	↓	↓	[102]
Adiponectin[*] (high fat diet and alcohol)	In human model	↑	↑	[103]
	In mouse model	↑	↑	[104]
Visfatin	In both models	↑	↑	[105]
Omentin	In human model	↑	↑	[24]
Chemerin	In human model	↑	↑ Chronic alcoholic patient	[106]
			↓ Cirrhosis patient	[107]

[*]*Adiponectin data are in contrast with the observation in individual with obesity and metabolic syndrome due to changes in liver function while affecting the bile obstruction.*

Table 1.
The changes in adipokines in mouse and human models with severity of alcohol abuse.

element-binding protein 1 (*Srebf1*) [100]. The mechanism that follows in hepatocytes on increase in NEFA activates the hepatic stellate cells (HSCs) which lead to the deposition of collagen and fibrosis, which in turn exerts the inflammatory pathway through stimulation of NF-κB and the activation of Kupffer cells and myeloid cells stimulating cytokine release [101].

5.2 Endocrine imbalance due to consumption of alcohol

Acute or chronic alcohol intake has an important difference in both animal and human models with respect to the endocrine aspect as shown in **Table 1**.

Due to the change in an endocrine function, the liver fibrosis takes place by promoting HSC activation [108]. Leptin contributes to the activation of TNF-alpha and the Kupffer cells, thereby causing hepatic inflammation by stimulating CCL2 release from HSCs [109]. The administration of adiponectin and recombinant adiponectin in ethanol-fed mice reduced the circulating NEFA level as well as decreased weight loss, steatosis, and hepatic inflammation due to the inhibition of Kupffer cell sensitivity toward LPS [67].

5.3 Immune dysbiosis due to alcohol intake

Oxidative stress due to the consumption of alcohol leads to adipose tissue hypoxia which in turn increases the expression of TNF-α, CCL2, IL-6, infiltration of macrophages, and expression of CD4^{+} T cells and dendritic cells in the adipose tissue [110]. The secretion of pro-inflammatory cytokines alters the hepatic immunology via hepatic inflammation affecting the role of parenchymal and non-parenchymal liver cells. TNF-α activation triggers ALD pathogenesis, which induces apoptosis through the activation of JNK and NFκB pathways [111]. A protective mechanism of the hepatocytes is exerted by IL-6 through promoting the hepatic survival, proliferation, and improved hepatic steatosis [112]. Nevertheless, an excessive exposure of IL-6 can lead to the liver carcinogenesis [113]. In CCL2 knockout mice, there is a reduced level of hepatic inflammation, proving CCL2 to not play any protective role in hepatic inflammation [114]. The role of CCL2 is much more clear as an inflammatory factor through an insulin signaling in NASH, but its role in ALD is yet to be determined [115].

5.4 Role of microRNA

Exosomes that contain small biologically active but noncoding RNA, i.e., microRNA (miRNA), are released by adipocytes which regulate various intracellular processes. These miRNAs are able to temper the distant tissues and organs representing the alteration between adipose tissue and liver function as well as immune responses [116]. In an animal model, miRNA-122 and miRNA-192 expressions are elevated in the ALD, while miRNA-155 expression is increased in the adipose tissues in particular, which contributes to the hepatic steatosis and fibrosis [117].

6. Conclusion

Chronic alcohol consumption not only disturbs the metabolism of whole body but also has a prominent effect on the function of gut microbiota and adipose tissue. These alterations have direct as well as indirect effects on the liver functions, which contribute to the advancement of ALD. Cessation of alcohol intake can quickly reverse inflammatory reaction in the adipose tissue and halt the progression of ALD. In addition to that, pharmacological treatment can also help to improve ALD. There is a significant overlapping in an alteration of the adipose tissue between obesity, NAFLD, and ALD mechanism. The physicians who are dealing with patients of ALD should keep an eye on the adipose tissue dysfunction and its effect on the liver and consider the therapeutic treatment accordingly. Understanding the fundamental mechanism of the alcohol and metabolic syndrome in the pathogenesis of liver disease will help in pursuing an effective treatment for liver diseases.

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