

# Obesity Affects the Liver – The Link between Adipocytes and Hepatocytes

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## Key Words

Adipocyte · Lipoapoptosis · Nonalcoholic fatty liver disease · Obesity

## Abstract

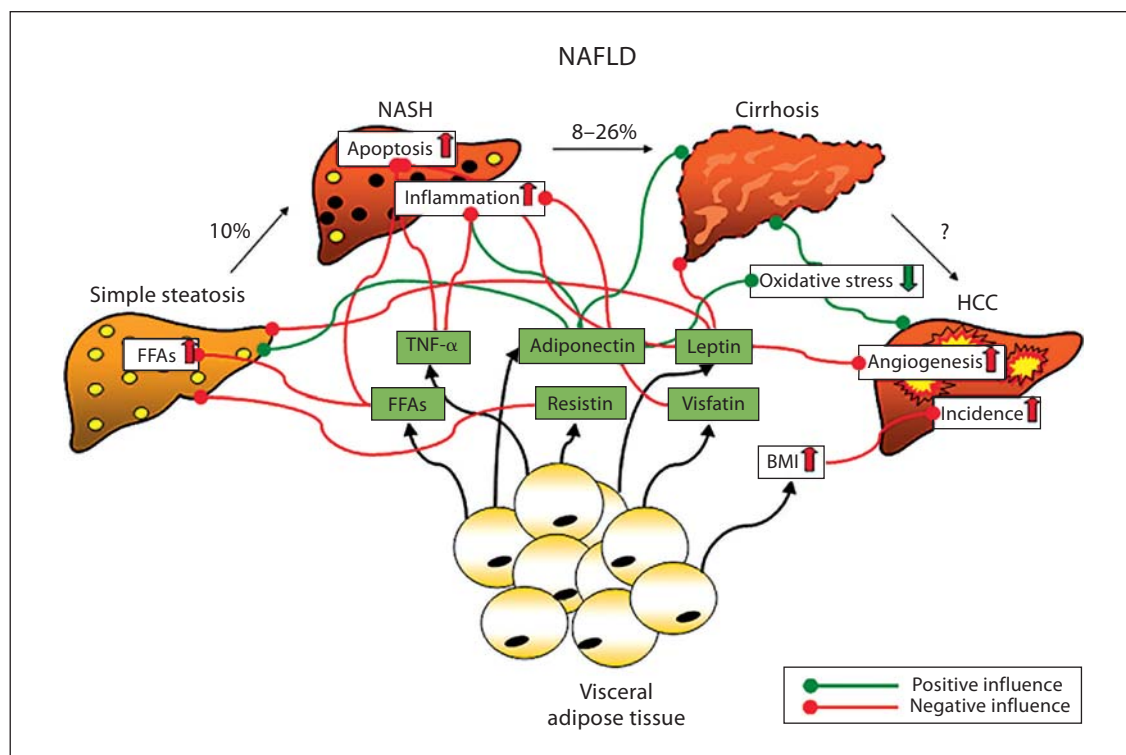
The incidence of obesity has dramatically increased in recent years. Consequently, obesity and associated disorders such as nonalcoholic fatty liver disease (NAFLD) constitute a serious threat. Therefore, the contribution of visceral adipose tissue to metabolic homeostasis has become a focus of interest. Visceral adipose tissue secretes free fatty acids (FFAs) and hormones, known as adipokines, and thus seems to play a major role in the development of NAFLD. Apoptotic cell death is a prominent feature in nonalcoholic steatohepatitis (NASH). Indeed, toxic FFAs can activate the intrinsic apoptosis pathway in hepatocytes via c-Jun N-terminal kinase (JNK). JNK activates the proapoptotic protein Bim, resulting in Bax activation and enhanced apoptosis, termed 'lipoapoptosis'. Reduced adiponectin levels may establish a proinflammatory milieu, thus increasing vulnerability to lipotoxicity, which promotes progression from simple steatosis to NASH and even advanced hepatic fibrosis. Moreover, obesity seems to be a risk factor for hepatocellular carcinoma, the most frequent liver cancer subtype. Even in acute liver failure, a high body mass index is associated with poor out-

come, and recent data suggest a major role of obesity in the progression of chronic hepatitis C and B. This review summarizes current knowledge – highlighting the inflammatory and cytokine view – of the intimate relationship between adipose and liver tissue.

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## Introduction

Obesity is a major issue worldwide and has increased dramatically during recent decades. Consequently, obesity and associated disorders now constitute a serious threat to the current and future health of all populations on earth. The World Health Organization (WHO) estimates that more than 1 billion adults worldwide are overweight, 300 million of whom are clinically obese – defined as having a body mass index (BMI) equal to or greater than 30 kg/m<sup>2</sup> [1]. Particularly alarming is the equally marked increase in obesity among children [2]. Obesity is associated with an array of additional health problems, including increased risk of insulin resistance (IR), type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), atherosclerosis, degenerative disorders, including dementia, airway diseases, and even some cancers [3]. The clustering of abdominal obesity, IR, dyslip-



**Fig. 1.** Influence of visceral adipose tissue on NAFLD. Visceral adipose tissue secretes a variety of proteins, known as adipokines, which can influence the liver. FFAs play a major role in the development of simple steatosis. With the influence of adipokines like TNF- $\alpha$ , simple steatosis can progress to NASH by induction of

apoptosis and inflammation. Apart from adiponectin, which can prevent the development of NASH, cirrhosis and even HCC, most adipokines exert a negative influence on liver diseases. An elevated BMI may increase the incidence of many cancers, including HCC.

idemia, and elevated blood pressure is known as the metabolic syndrome. Its components reflect overnutrition, sedentary life-styles, and resultant excess adiposity, which is associated with a chronic proinflammatory state. Unlike the hepatitis C virus (HCV) epidemic, which is estimated to peak in 2010, the obesity/metabolic syndrome epidemic shows no signs of abating [4].

The adipocyte and visceral adipose tissue have begun to fascinate researchers as a result of rapidly accumulating new knowledge of their function and contribution to whole-body metabolic homeostasis [5]. Three major functions of visceral adipose tissue have been characterized so far: (1) adipocytes have a large capacity to store energy in form of lipids; (2) lipids stored in adipocytes can be metabolized rapidly and either released as fatty acids (FAs) or used to increase thermogenesis by uncoupling substrate oxidation from ATP generation [6, 7], and (3) adipocytes communicate with other tissues by secreting hormones, commonly referred to as adipokines, in either an endocrine or a paracrine fashion [8].

The adipocyte secretome ranges from molecules of direct metabolic relevance to those with effects unrelated to metabolism. These include the adipocyte-specific proteins adiponectin and leptin, the inflammatory chemokine tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and an array of interleukins, angiogenic, and vasoactive molecules such as vascular endothelial growth factor and angiotensinogen. Thus, visceral adipose tissue seems to play a major role by secreting free FAs (FFAs), hormones and adipokines, in the development of NAFLD and particularly in nonalcoholic steatohepatitis (NASH) (fig. 1). This article gives an overview of the current knowledge of the influence of obesity in liver diseases.

### Relation between the Liver and Adipose Tissue

The intimate relationship between visceral adipose tissue and the liver reflects their common origins. Key metabolic and immune functions in higher organisms

have evolved from common ancestral structures. One such structure is the *Drosophila* fat body, which incorporates the mammalian homologues of the liver and the hematopoietic and immune systems [9, 10]. Interestingly, this site is also recognized as the equivalent of mammalian adipose tissue, sharing similar developmental and functional pathways [11, 12]. The fly's fat body exerts a crucial function in sensing energy and nutrient availability and coordinates the appropriate metabolic and survival responses [9]. In higher organisms, the adipose tissue, the liver and the hematopoietic system have specialized into distinct functional units or organs. However, these organs have maintained their developmental heritage, which was shared in earlier organisms. Therefore, it is possible to imagine a situation in which common or overlapping pathways regulate both metabolic and immune functions through common key regulatory molecules and signaling systems.

It is remarkable to note that both visceral adipose tissue and the liver share similarities in which metabolic cells (adipocytes or hepatocytes) are in close proximity to e.g. immune cells (NK and NKT cells), Kupffer cells, hepatic stellate cells, and endothelial cells or macrophages, and both having immediate access to a vast network of blood vessels. With this configuration, both tissues form a suitable environment for continuous and dynamic interactions between immune and metabolic responses [13]. In fact, this interface might contribute to the emerging importance of these two organs in the initiation and development of metabolic diseases, particularly in the context of obesity and type 2 diabetes [14, 15].

### **Obesity Is Highly Associated with NAFLD**

NAFLD is becoming the most common liver disease worldwide with approximately 30% of the population affected in industrialized, western countries. NAFLD is characterized by hepatic steatosis in the absence of a history of significant alcohol use or other known liver diseases. Alcohol intake as low as 20 g daily in women and 30 g daily in men may be sufficient to cause alcohol-induced liver disease [16]. In the general population of the Dionysos study, fatty liver at ultrasound examination was documented in 10–15% of normal individuals and in up to 76% of obese subjects not drinking alcohol in toxic amounts [17]. Compared with healthy controls, risk for steatosis was 4.6-fold increased in obese subjects and only 5.8-fold higher in subjects who were obese and drank heavily.

Depending on etiologic factors, two different types of NAFLD can be distinguished – primary and secondary NAFLD [18]. Primary NAFLD emerges due to the metabolic syndrome. Secondary NAFLD is due to infections, medication intake, parenteral feeding, and rare metabolic and congenital diseases. Histopathologically, NAFLD can appear as simple steatosis (nonalcoholic fatty liver), or with inflammatory reaction defined as NASH with or without portal fibrosis that may lead to fatty liver-associated cirrhosis (NASH-induced cirrhosis). Approximately 10% of patients with NAFLD develop NASH and about 8–26% of individuals with NASH progress to cirrhosis [19]. These patients are at risk of developing hepatocellular cancer (HCC), portal hypertension with gastroesophageal bleeding, ascites and liver failure. Indeed, recent data implicate de novo HCC in NAFLD patients [20]. The pathogenesis of NAFLD and especially NASH is currently in the focus of many studies.

### **FA Transport Proteins and the Development of Simple Steatosis (NAFL)**

FFAs play a pivotal role in the development of simple hepatic steatosis. The oral intake of fat and the subsequent lipolysis in visceral adipose tissue lead to an increased level of FFAs in the serum. Donnelly et al. [21] investigated the origin of FFAs and found that visceral adipose tissue was contributing 82% of the FFA pool in the fasting condition and 62% in the feeding condition. The lipid metabolism in the liver has 3 different aspects: (1) de novo synthesis and active uptake of FFAs; (2) processing via  $\beta$ -oxidation and/or de novo synthesis of triglycerides, and (3) export of FFAs as triglycerides and very low-density lipoproteins [22]. Several plasma membrane protein transporters are involved in the FA uptake process. The main translocation process across the plasma membrane involves members of the FA transporter protein (FATP) family. Indeed, when expressed, they facilitate the uptake of long-chain FA (C12–C20). FATPs are highly expressed in hepatocytes and adipocytes that reveal high-level FA uptake for both metabolism and storage. So far, six members of this protein family (FATP1–6) have been identified. Their isoforms show distinct organ-specific distribution patterns in human beings [23, 24]. For example, FATP1 is found in visceral adipose tissue and in the heart. In contrast, FATP2 and FATP5 are expressed in the liver, while FATP4 is expressed in the intestine [25, 26]. Indeed, overexpression of FATP5 in cultured cells has been shown to increase

FFA uptake [23]. Recently, it has been shown that FATP5-knockout mice exhibit less fat accumulation [23]. Thus, FATP5 is an important membrane protein involved in FA accumulation by the liver [23, 25]. Indeed, we recently found a correlation between excess serum FFAs, hepatocyte apoptosis and fibrosis in patients with NAFLD. Moreover we showed that FATPs, in particular CD36/FAT and FATP5, play an important role in the progression towards liver damage and failure in NASH [27].

### **Adipokines Are Involved in the Development of NASH**

The combination of lipid accumulation in hepatocytes and apoptosis of hepatocytes is known as lipoapoptosis, which is a pivotal mechanism in NASH [28, 29]. In hepatocytes, saturated FFAs (like palmitol or stearin acid) can induce a time- and dose-dependent lipoapoptosis [30]. These two toxic FFAs can activate the intrinsic pathway of apoptosis via c-Jun N-terminal kinase (JNK). JNK activates the proapoptotic member of the Bcl-2 family Bim, resulting in activation of Bax and increased apoptosis. In line with this observation, a study by Schattenberg et al. [31] demonstrated that induction of JNK type 1 promotes the development of NASH.

Visceral adipose tissue may affect the development of NASH by secreting TNF- $\alpha$ , which is highly expressed in the metabolic syndrome [13]. Clinically enhanced TNF- $\alpha$  expression was shown in patients with NASH compared with patients exhibiting simple steatosis [32]. Experimental data described that FFAs induced TNF- $\alpha$  production through promoting hepatic lipotoxicity [33]. In turn, TNF- $\alpha$  activates nuclear factor  $\kappa$ B via TNF-receptor 1 (TNF-R1) as a central transcription factor for many proinflammatory cytokines [33]. TNF- $\alpha$  further induces de novo lipogenesis in hepatocytes, leading to lipid accumulation. In case of TNF- $\alpha$  signal-chain interruption – either pharmacologic or genetic –, reduced lipid accumulation can be documented [34, 35]. Taken together, these findings indicate that TNF- $\alpha$  is one of the critical factors for occurrence and progression of NAFLD/NASH.

While results from controlled animal experiments seemed quite clear, circulating levels of leptin in patients with NAFLD provided rather ambiguous data. With advancing stages of liver disease, higher levels of circulating leptin were found although the concentration was independent of BMI in NASH patients [36]. On the other hand, serum leptin was correlated with severity of steato-

sis but not with inflammation or liver fibrosis [37]. In contrast to this, some studies revealed no significant differences in leptin serum concentration of NASH patients compared with healthy controls [16, 38]. Strong evidence was provided that leptin acts as a fibrogenic agent in animal models, but complementary data in patients are ambiguous or missing. Further studies may clarify the role of leptin in humans, especially regarding its influence on liver tissue.

Adiponectin is thought to counteract IR and to have protective effects. Despite this, NASH patients exhibit reduced adiponectin levels compared with matched controls or patients with simple steatosis, seemingly without any relation to IR or the waist-hip ratio [39]. While low adiponectin was associated only with increased steatosis and necroinflammation, IR additionally predicted severe hepatic fibrosis. Other studies demonstrated a correlation between adiponectin levels and suppression of endogenous glucose, as well as an inverse association of adiponectin with intrahepatic fat. Adiponectin levels also predicted the presence of the metabolic syndrome but not inflammation or fibrosis [40]. The correlation of adiponectin with hepatic fat content, IR and altered lipid metabolism has been described in other studies investigating nondiabetic subjects [41, 42]. Taking all data together, adiponectin levels generally predict steatosis and severity of liver disease although to what extent this is a direct effect or related to the presence of more severe IR remains to be addressed. Nevertheless, reduced levels of adiponectin in obesity and IR establish a proinflammatory milieu and individual susceptibility to lipotoxicity could determine which subjects ultimately progress from simple steatosis to NASH and develop advanced hepatic fibrosis. Indeed, Xu et al. [43] demonstrated that adiponectin administration significantly improved fatty liver in mice. Moreover, in adiponectin knockout mice, liver injury and fibrosis were increased [44].

Resistin – another adipokine – varied between different studies in NAFLD patients. On the one hand, raised mRNA expression of resistin in visceral adipose tissue and raised plasma levels of resistin were found in one group of patients with NAFLD and NASH compared with lean and obese control groups [45]. Other investigators reported decreased resistin concentrations in NAFLD patients. Low resistin was negatively correlated with intrahepatic fat content, although this did not reach statistical significance [46]. A third study demonstrated unaltered resistin expression in visceral adipose tissue of patients undergoing bariatric surgery while serum resistin was increased in NASH patients with IR [47]. Interestingly, re-

**Table 1.** Serum levels of different adipokines in liver diseases

|                  | Adiponectin             | FFAs              | TNF- $\alpha$      | Leptin                       | Resistin           | Visfatin           |
|------------------|-------------------------|-------------------|--------------------|------------------------------|--------------------|--------------------|
| Lean             | $\leftrightarrow$       | $\leftrightarrow$ | $\leftrightarrow$  | $\leftrightarrow$            | $\leftrightarrow$  | $\leftrightarrow$  |
| Obese            | $\downarrow$            | $\uparrow$        | $\uparrow$         | $\uparrow$                   | $\uparrow$         | $\uparrow$         |
| Simple steatosis | $\downarrow$            | $\uparrow$        | $\uparrow$         | $\leftrightarrow/\uparrow^*$ | $\uparrow$         | $\uparrow\uparrow$ |
| NASH             | $\downarrow\downarrow$  | $\uparrow$        | $\uparrow\uparrow$ | $\leftrightarrow/\uparrow^*$ | $\uparrow\uparrow$ | $\uparrow$         |
| ALF              | $\uparrow$              | 0                 | 0                  | 0                            | 0                  | 0                  |
| Liver cirrhosis  | $\downarrow$            | 0                 | 0                  | $\uparrow$                   | $\downarrow$       | $\downarrow$       |
| CHC              | $\uparrow/\downarrow^*$ | 0                 | 0                  | $\leftrightarrow/\uparrow^*$ | $\uparrow$         | 0                  |

\* = Conflicting data available; 0 = no data available;  $\leftrightarrow$  = normal;  $\downarrow$  = reduced;  $\downarrow\downarrow$  = strongly reduced;  $\uparrow$  = elevated;  $\uparrow\uparrow$  = strongly elevated; NASH = non-alcoholic steatohepatitis; ALF = acute liver failure; CHC = chronic hepatitis C virus infection.

sistin expression in liver tissue of patients suffering from alcohol-induced liver disease or NASH was increased and correlated with inflammatory cell infiltration [48].

Studies investigating other adipokines like visfatin with regard to NAFLD are rare. NASH patients exhibited lower visfatin levels than those with simple steatosis or obese controls although, compared with healthy controls, all groups of obese patients had increased visfatin [49]. Additionally, elevation of visfatin levels predicted portal inflammation [50].

Information of the biological basis of adipokine action in the context of liver diseases is given by an excellent review by Marra and Bertolani [51]. Information on other adipokines may be found in another recent review [52].

Though the role of some adipokines remains unclear and ambiguous, obesity and especially adipokines as crucial mediators directly influence hepatic steatosis, steatohepatitis, and NASH-induced cirrhosis (table 1).

### Obesity Is a Risk Factor for HCC

Obesity is a risk factor for several chronic diseases, most notably hypertension, type 2 diabetes, dyslipidemia, and chronic heart diseases. In addition, obesity has been shown to constitute a risk factor for colon cancer, postmenopausal breast cancer, endometrial cancer, renal cell cancer, as well as adenocarcinoma of the esophagus [53].

HCC is the most rapidly increasing cause of cancer death in the United States and Europe. From 1973 to 1980 intrahepatic liver cancers ranked as the 8th most common malignancy in the United States, accounting for 1 death per 100,000. In 1998, intrahepatic liver cancer ranked as the 6th most common malignancy, resulting in

a death rate of 3.5 per 100,000 [54]. Although many risk factors for HCC are well defined, including hepatitis B/C viruses and alcohol, most series have indicated that 5–30% of patients with HCC lack a readily identifiable risk factor for their cancer [55]. Obesity and type 2 diabetes are also likely to be risk factors for HCC, the most frequent subtype of liver cancer [56]. Interestingly, most cases of ‘cryptogenic’ HCC in the United States are attributed to NAFLD [57]. The main pathway by which obesity increases risk probability relates to the association between obesity and NAFLD [58]. Retrospective data suggest that after cirrhosis has developed, 4–27% of cases of NASH transform to HCC [59]. These figures lead to theoretical HCC incidence rates ranging from 0.6 to 210 per 100,000. Case reports have also described patients with NASH who developed HCC without underlying cirrhosis [60, 61]. Additionally, animal models have demonstrated a clear progression from NASH to cirrhosis and to cancer [62]. Although, in a smaller patient cohort, obesity significantly increased HCC [63], a larger study including 1,145 patients failed to reproduce these findings [64]. Large prospective studies are needed to further address both of these issues more definitively.

Comorbidities, such as coronary artery disease and/or worsened secondary effects of chemotherapy, in obese individuals may be responsible for an impaired outcome although the general relations remain ambiguous [65]. Another study found that visceral adipose tissue is able to secrete vascular endothelial growth factor and other adipokines, suggesting dysregulated angiogenesis as a possible connection between obesity and worsened clinical outcome [66]. In animal models, leptin has been shown to promote angiogenesis and thus could facilitate progression of NASH to HCC [67]. In addition, leptin is

able to activate multiple signal transduction pathways, such as JNK, protein kinase B, the AKT pathway, and the extracellular signal-regulated kinase pathway in HCC cells, all recognized to promote cancer progression [68].

Little information is available on the role of adiponectin in liver cancer although administration of a choline- and amino acid-deficient diet to adiponectin-knockout mice has recently resulted in an increased incidence of liver tumors [69]. These correlations suggest a possible association between the metabolic syndrome and worsened clinical outcomes that may be related to adipokines.

### **Obesity Is a Negative Prognostic Factor in the Treatment of Chronic Hepatitis C**

Obesity is recognized as a cofactor in liver injury induced by chronic hepatitis C (CHC) infection. Adipokines may be the link between increased BMI and disease progression in CHC. For example, CHC genotype 3 infection is likely to produce steatosis through a virus-mediated mechanism [70]. In subjects with genotype non-3 CHC infection, steatosis is generally considered as the effect of coexisting metabolic conditions [71], possibly exacerbated by viral infection [72]. The presence of obesity and obesity-associated IR and steatosis facilitates the development of diabetes in the precirrhotic stage, carries a higher risk of failure during interferon treatment [73] or higher recurrence after initial response [74], and increases fibrosis [75–77].

In a meta-analysis on data from 3,068 patients with histologically confirmed CHC recruited by 10 clinical centers in different ethnic settings, steatosis was independently associated with several variables, including higher BMI and predicted hepatic fibrosis [78]. On this basis, pretreatments of IR with insulin-sensitizing agents and/or weight loss by dietary intervention have been proposed as preinterferon strategies to increase sustained virological response [74]. In addition, adiponectin has recently been shown to protect against Fas-mediated hepatocyte death, with possible implications for patients with CHC [79].

Obesity, steatosis, and IR have a negative impact on disease progression and response to antiviral therapy in patients with CHC [80]. Treatment failure in obese patients might result from lower interferon concentrations and a milder biological response upon exposure to exogenous interferon- $\alpha$  in obese patients [81]. In turn, CHC is often associated with alterations in glucose metabolism, leading to hepatic steatosis, IR, and type 2 diabetes [82]. Fatty liver is generally more evident in patients infected

with HCV genotype 3, where virus-specific mechanisms play a pivotal role (so-called ‘viral steatosis’). In contrast, ‘metabolic steatosis’ is associated with HCV genotypes other than genotype 3, with host factors playing a major pathogenic role.

Regarding IR, steatosis, and liver injury in CHC, impact and regulation of leptin is as ambiguous as in NAFLD. Leptin was shown to be increased in CHC-infected patients compared with healthy controls [83]. In contrast, other studies found similar or even lower concentrations of leptin in such patients [36, 84, 85]. Likewise, some groups observed a positive correlation between leptin and the severity of fibrosis [86, 87] while other groups did not [84, 88]. If leptin has an impact on CHC-induced steatosis this has to be further elucidated since leptin levels were associated with steatosis [88] or correlated with steatosis in patients infected with genotype 1 but not with genotype 3 [89]. Conversely, other studies could not show any alteration of serum leptin levels in the context of steatosis [84, 86].

In contrast to NAFLD, serum adiponectin levels in CHC patients were not consistently different from those of healthy subjects, even after matching for age, gender, and BMI [90–92]. Whereas one study associated high viral load and genotype 2 infection with decreased serum adiponectin [90], another group did not find any relation between histological features and concentrations of adiponectin, leptin or IL-6 levels in serum [93]. Thus, virus-related effects, independent of adipokines may lead to the more severe IR observed in patients with CHC. While one study demonstrated hepatic steatosis to be associated with decreased adiponectin levels [94], a different group found this relation only in males [95]. Additionally, CHC patients exhibit an interrelation between hypoadiponectinemia and the grade of hepatic steatosis in CHC, suggesting a pathogenetic mechanism involving dysregulation of adiponectin and TNF- $\alpha$  levels [96]. Independently of steatosis, lower adiponectin levels were detected in patients with genotype 3 [96, 97], which increased after successful antiviral treatment, implying a direct effect of the virus on adiponectin [98]. This is also supported by nonresponders to antiviral therapy showing low adiponectin levels [98]. Combined CHC infection and steatosis increase hepatocyte expression of CD95/Fas, making the cells more susceptible to apoptotic stimuli, which again amplifies inflammation and fibrosis [79].

In contrast to NAFLD, no other adipokines have been scrutinized in CHC. Serum resistin, for example, is increased in CHC compared with NASH patients, but was inversely related to fibrosis stage [99].

## Obesity Is Associated with Poor Outcome in Acute Liver Failure

Acute liver failure (ALF) is a devastating clinical syndrome associated with high mortality [100]. Annually, approximately 8% of all current liver transplantations in Europe are required as a result of ALF. Several studies have recently demonstrated that a high BMI is associated with a preexisting liver damage. Such damage can manifest as steatosis and obviously corresponds to an increasingly poor outcome in patients with ALF [101, 102]. These results must be viewed as preliminary as both studies were conducted for limited periods of time and on small numbers of patients only. An attempt to obtain prospective data over a longer period of time and from a larger cohort of patients therefore promises to provide more reliable information about conditions associated with the onset and outcome of ALF.

Multivariate analyses in patients without preexisting liver damage (for example NAFLD) did not identify BMI as an independent predictor [103]. Preexisting liver damage due to obesity renders subjects more susceptible to a 'second hit' (such as by drug toxicity or viral hepatitis), which results in acute-on-chronic liver failure [101, 102, 104]; this is in line with findings from overweight rodents. Therefore, obesity should be considered as a relevant prognostic factor in patients with ALF [103].

## Conclusion

Obesity and visceral adipose tissue affect the liver and hepatocytes. The liver disease influenced most by obesity is NAFLD. It is well established that the development of NAFLD is closely linked to an excess flow of FFAs arising from visceral adipose tissue. Chronic lipid supply exceeding the metabolic ability of the liver may induce hepatocellular injury. Multiple mechanisms including proinflammatory cytokines and pathways have been implicated in the pathogenesis of NAFLD. Understanding the role of obesity and lipotoxicity in patients with liver disease as part of a broader metabolic disorder is likely to improve the management of these challenging diseases. In CHC, studies have shown that HCV core proteins can directly inhibit insulin signaling, leading to poor outcomes. However, the mechanisms by which obesity and visceral adipose tissue affect cancer development remain to be elucidated.

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