Adiponectin: A multitasking player in the field of liver diseases

T.E. Silva *, G. Colombo, L.L. Schiavon

Abstract

Adiponectin is the most abundant adipokine synthesized by adipose tissue and has been shown to be a key component in the relationship between adiposity, insulin resistance and inflammation. It circulates in plasma at physiological concentrations that represent 0.05% of all plasma proteins. Adiponectin has trimeric, hexameric and multimeric forms that bind to receptors AdipoR1, AdipoR2 and T-cadherin especially in liver, muscle and endothelial cells. Adiponectin is considered a potent modulator of lipid and glucose metabolism with antidiabetic, antiatherogenic and anti-inflammatory properties, and plays an important role in the pathogenesis of metabolic diseases. The hepatoprotective effects of adiponectin, especially in non-alcoholic fatty liver disease (NAFLD), have been widely investigated, and its antisteatotic, anti-inflammatory and antifibrogenic effects have already been described. Adiponectin levels are reduced in individuals with fatty liver disease independently of body mass index, insulin resistance and other adipokines, and are inversely related to the severity of steatosis and necroinflammation, suggesting an important role in the relationship between adipose tissue, the liver and insulin sensitivity. Adiponectin has also been found to be reduced in cases of hepatitis B and C infection, and in cholestatic and autoimmune diseases, but is increased in patients with cirrhosis of different aetiologies. In addition, an important role for the liver in the regulation of adiponectin secretion by adipocytes, mediated by bile acids, has recently been proposed. The present report describes the importance of adiponectin in hepatic diseases as well as some future perspectives of the role of adiponectin as a biomarker and therapeutic target in liver diseases.

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1. Introduction

Liver diseases are among the 10 main causes of mortality worldwide and the fifth most common cause of death in the UK, after heart disease, stroke, respiratory diseases and cancer [1]. Viral hepatitis is the main cause of liver disease, with an estimated 180 million individuals infected by hepatitis C virus (HCV) [2] and 350 million infected by hepatitis B virus (HBV) worldwide [3]. In addition, as a result of increasing rates of obesity in populations all over the world, non-alcoholic steatohepatitis (NASH) due to non-alcoholic fatty liver disease (NAFLD) is becoming a major public-health problem [1]. Together with abusive alcohol consumption, these diseases are important risk factors for the development of cirrhosis and hepatocellular carcinoma (HCC) [1].

The progression of liver diseases and fibrogenetic processes is caused by the excess accumulation of extracellular matrix products in the liver, the result of persistent activation of inflammation and tissue-repair mechanisms [4]. Among the features of liver fibrogenesis, the importance of metabolic factors, especially those related to obesity, is becoming increasingly accepted. Adipose tissue is not only a deposit for lipids, but also a recognized and important source of hormones that influence body adiposity, glucose homeostasis, inflammation and cardiovascular disease [5]. Adipocytes secrete several types of adipokines, including leptin [6], adiponectin [7], adipin [8], resistin [9], visfatin [10], tumour necrosis factor-alpha (TNF-α) [11] and plasminogen activator inhibitor type 1 (PAI-1) [12].

Since its discovery, adiponectin has proved to be a key component in the relationship between adiposity and insulin resistance (IR) [5]. The hepatoprotective effects of adiponectin in NAFLD have been widely investigated, and several recent studies evaluating the relationship between adiponectin levels and other liver diseases, such as chronic viral hepatitis, liver cirrhosis and autoimmune liver diseases, have also been published. In addition
to its influence in the progression of those diseases, the evidence also suggests an important role of the liver and bile acids in the regulation of adiponectin synthesis and release by adipocytes. The physiological actions of adiponectin and its role in chronic liver diseases are discussed here.

2. Biological actions of adiponectin

Adiponectin, identified by four independent groups in 1995 and initially called apM1, ACRP30, AdipoQ and GBP28 [7,13–15], is a 28-kDa protein composed of 274 amino acids [13] and encoded by the ADIPOQ gene, located on the long arm of human chromosome 3, locus 3q27 [16]. It comprises an amino-terminal signal sequence, a variable region, a collagen-like domain (cAd) and a carboxyl-terminal globular domain (gAd) [13]. Adiponectin in the circulation has two isoforms: full-length adiponectin (fAd); and a globular fragment (a proteolytically cleaved fragment consisting of gAd) [17,18]. The globular fragment is present in small amounts in plasma and increases free fatty acid oxidation in muscle tissue, an important mechanism for the control of energy homoeostasis [17], while fAd has the capacity to group globular domains into three isoforms: trimeric (low molecular weight); hexameric (middle molecular weight); and multimeric (high-molecular-weight) [18,19]. Each oligomeric form has distinct biological properties and activates different cellular signalling pathways in several tissues [19]. The monomeric (30-kDa) form appears to be confined to adipocytes and has not been observed in circulation [20], while only the trimeric form activates adenosine monophosphate-activated kinase protein (AMPK) in skeletal muscle, reduces interleukin (IL)-6 secretion and stimulates IL-10 secretion [18,19]. Surprisingly, the hexameric and multimeric isoforms both activate the nuclear factor-kappa B (NF-κB) pathway, which mediates IL-6 induction [21,22]. Although IL-6 is usually associated with IR, some reports have paradoxically suggested that IL-6 contributes to improved insulin sensitivity [22,23]. One of the proposed mechanisms is a transient rise in IL-6 levels, leading to insulin receptor substrate (IRS)-2 upregulation and enhanced insulin signalling in the liver, possibly by an as yet unidentified adiponectin receptor [22]. Multimeric adiponectin is the active form of the protein in the mediation of several of its activities, especially insulin sensitivity [24]. Central nervous system (CNS) activities of adiponectin are attributed to the trimeric and hexameric forms [25].

The effects of adiponectin are mediated by membrane receptors/proteins called AdipoR1, which is abundantly expressed in skeletal muscle, and AdipoR2, which is predominantly expressed in the liver [26]. AdipoR1 has a high affinity for globular fragments and a low affinity for fAd, whereas AdipoR2 has an intermediate affinity for both fAd and gAd [26]. Adiponectin also binds to T-cadherin, a receptor for hexameric and high-molecular-weight forms of adiponectin expressed in endothelial and smooth muscle cells [27], and the underlying factor for some of the antiatherogenic and vasoprotective actions of adiponectin [5].

Adiponectin circulates through plasma at physiological concentrations that represent 0.05% of total serum protein [13]. Despite its abundant presence in plasma, adiponectin is cleared rapidly with a half-life of around 75 min [28]. It interacts with an adaptor protein containing a pleckstrin homology domain (APPL1) [29], and provokes activation of AMPK and peroxisome proliferator-activated receptor-alpha (PPAR-α). Adiponectin also provokes several signalling molecules in most tissues, including skeletal muscle, liver, heart, endothelium, adipocytes and brain [18,30–33], thereby increasing glucose uptake in muscle, decreasing hepatic glucose production (gluco-neogenesis), and increasing fatty acid oxidation in muscles and the liver [30,34]. This leads to lowered IR as a result of decreased triglycerides in muscles and liver [35]. Adiponectin also inhibits endothelial NF-κB signalling and proinflammatory cytokines such as IL-6 and TNF-α, while stimulating anti-inflammatory cytokines such as IL-10 [19,21,36]. Thus, adiponectin is considered a powerful metabolic modulator of glucose and lipids with antiatherogenic, anti-diabetic and anti-inflammatory properties, and plays a role in the regulation of glucose and lipid homoeostasis (Fig. 1). This means it is important in the pathogenesis of metabolic diseases [37].

Adiponectin secretion varies with circadian rhythm [38] and is influenced by hormones such as prolactin [39], growth hormone [39], testosterone [40] and osteocalcin [41] as well as by beta-adrenergic agonists [42] and glucocorticoid treatments [43]. Women have higher levels of adiponectin than men possibly because of the effects of sex hormones, their greater subcutaneous fat accumulation and higher percentage of body fat. This leads to increased sensitivity to insulin and lipogenesis [44]. Testosterone selectively reduces the high-molecular-weight form of adiponectin by inhibiting its secretion by adipocytes [45].

Adiponectin secretion is inversely correlated with body mass index (BMI) [46], with higher adiponectin levels in non-obese than obese people [46,47]. Elevated levels were observed in patients with anorexia nervosa [48]. Adiponectin is thought to have protective effects against the metabolic syndromes and type 2 diabetes mellitus (DM2) [49,50]. Increased adiponectin levels after bariatric surgery suggest that its expression is subject to feedback inhibition in obesity [51,52]. As obese individuals have more body fat, adipocyte hypertrophy and macrophage infiltration of adipose tissue activates proinflammatory cytokines (TNF-α, IL-6, IL-10) and nitric oxide [53,54]. These alterations can lead to a reduction in the expression of adiponectin mRNA and adiponectin release from adipocytes [46]. Adiponectin and TNF-α are mutually inhibited, and the expression of adiponectin is suppressed by IL-6 [36,55]. The latter is characterized by a decrease in insulin-sensitizing and anti-inflammatory adipocytokines such as adiponectin, with an increase in proinflammatory adipocytokines such as TNF-α, IL and resistin [56]. This may explain why obese people have lower circulating levels of adiponectin despite the fact that adipose tissue is responsible for its synthesis [46]. Adipocytokine dysregulation plays a crucial role in metabolic syndromes [57].

The association between high adiponectin levels and low DM2 risk was confirmed in a meta-analysis by Li et al. [58]. Adiponectin levels are significantly reduced in patients with DM2 and increased after treatment with insulin-sensitizing
agents (thiazolidinediones). These agents stimulate synthesis of adiponectin by activating the synthesizing peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist, thus boosting insulin sensitivity [59]. Recently, the importance of the fibroblast growth factor (FGF) 21–adiponectin–ceramide axis in the control of energy expenditure and insulin action was highlighted [60]. So too has the role of sphingolipids such as ceramides and glucosylceramides as an important class of bioactive lipids, the accumulation of which has been implicated in a multitude of metabolic processes such as atherosclerosis, IR and diabetes [61], and as an important player in NAFLD and its progression to NASH [62]. Adiponectin is a potent stimulator of ceramidase activity and enhances ceramide catabolism [63].

Individuals with higher concentrations of adiponectin also present with lower cardiovascular risk [64,65]. Low plasma adiponectin levels are associated with progression of subclinical coronary atherosclerosis in type 1 diabetic and non-diabetic subjects independently of other cardiovascular risk factors [65].
whereas mutations of the adiponectin gene related to low hormone levels have been identified and associated with DM2 [66] and NAFLD [67].

3. Adiponectin levels in selected liver diseases

Several studies have reported that the disruption of adipocytokines affects liver disease. Indeed, leptin and TNF-α levels are significantly higher, while adiponectin and ghrelin levels are lower, in patients with NASH compared with controls [68]. Other studies have shown obesity to be an independent risk factor for fibrosis in chronic liver diseases such as NASH [69], alcoholic liver disease [70] and chronic HCV infection [71]. Despite low levels of adiponectin being related to several hepatic diseases, mainly NAFLD [72,73], cirrhosis patients of any aetiology paradoxically have high levels of this adipokine [74,75], suggesting an independent mechanism by which the liver exerts a regulatory effect on the release and/or degradation of circulating adiponectin.

While the liver is most likely not a relevant source of circulating adiponectin, it is nonetheless a major target organ for many adiponectin effects, including regulation of steatosis, IR, inflammation and fibrosis [76]. The role of adiponectin in liver disease was first studied in animal models, which showed that adiponectin improved hepatomegaly, steatosis and aminotransferases in mice with NAFLD [77] and liver fibrosis induced by carbon tetrachloride [78]. Adiponectin liver-protective properties, as described in several clinical and animal studies, include antisteatotic [77], anti-inflammatory [79] and antifibrotic [78] effects (Table 1).

The antisteatotic effect results partly from the ability of adiponectin to increase carnitine palmitoyltransferase-1 (CPT1) activity and enhance hepatic fatty acid oxidation, while reducing the activities of two key enzymes involved in fatty acid synthesis—namely, acetyl-CoA carboxylase and fatty acid synthase [77]. It also suppresses the expression of sterol regulatory element-binding protein (SREBP)-1c, the master regulator that controls and upregulates enzymes involved in fatty acid synthesis [80]. The anti-inflammatory effect of adiponectin is associated with inhibition of the synthesis and/or release of TNF-α (so preventing lipopolysaccharide-induced liver injury) [81] and induction of IL-10 [84]. Adiponectin also exhibits antifibrotic properties by suppressing the proliferation and migration of stellate cells through attenuation of the expression of transforming growth factor beta 1 (TGF-β1), a regulator of extracellular matrix synthesis [78,87,88].

In healthy people, adiponectin levels were negatively correlated with alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) levels before and after adjusting for gender, age, BMI and IR, which suggests a contribution of adiponectin to the maintenance of liver integrity through regulation of both insulin sensitivity and/or inflammatory responses [89]. Indeed, studies in healthy subjects show a positive correlation between visceral fat and liver enzymes in both men and women [90], and a significant negative correlation between adiponectin and liver enzymes in men, suggesting that visceral obesity and hypoadiponectinaemia are significant determinants of hepatic dysfunction in asymptomatic people [90,91]. In women, a negative correlation between adiponectin and GGT was observed [91,92] as well as a positive correlation between GGT and homeostasis model assessment-estimated insulin resistance (HOMA-IR) [92].

Thus, the liver represents an important target wherein adiponectin participates in the control of various events such as metabolism, inflammation and fibrosis. The adipokine also appears to exert distinctive effects in different liver diseases and appears to be significantly influenced by liver function. The following is a discussion of the relevance of adiponectin in the most important liver diseases, and its future possibilities as a biomarker and therapeutic target.

3.1. NAFLD

This common cause of chronic liver disease in many countries comprises a wide spectrum of liver damage, including simple steatosis and NASH, with the possibility of progression to cirrhosis and HCC [93,94]. NAFLD is present in 17–40% of various populations and NASH may be found in one-third of all NAFLD cases. The rate of cirrhosis development in cases of NASH are reported to range from 5% to 20% over a period of 10 years and, once cirrhosis is established, the mortality rate is between 12% and 25% over a period of 7–10 years [95]. Currently, NASH is the third most common indication for liver transplantation in the USA, with rates that have risen from 1.2% of the total number of transplants in 2001 to 9.7% in 2009 [96].

Table 2 summarizes the main clinical studies investigating the relationship between adiponectin and NAFLD. In a meta-analysis of 27 studies and a total of 2243 subjects, Polyzos et al. [107] revealed that serum adiponectin was higher in controls than in NAFLD or NASH patients and higher in NAFLD compared with NASH patients. However, adiponectin levels were similar between controls and simple steatosis patients when only controls subjected to liver biopsy were analyzed. These findings suggest an important pathophysiological role of hypoadiponectinaemia in the progression from NAFLD to NASH, although the role of this adipokokine in the development of NAFLD (simple steatosis) remains unclear [107].

Levels of adiponectin and AdipoR2 mRNA expression were significantly reduced in liver biopsies from patients with NASH compared with patients with simple steatosis [101]. Furthermore, hypoadiponectinaemia was associated with NASH independently of BMI, IR and other adipokines such as TNF-α [68,73,100]. Some studies have found an association between adiponectin levels and histological severity, with an inverse relationship between adiponectinaemia and intensity of steatosis and necroinflammatory activity in patients with NASH [72,73,100]. The relationship between low levels of adiponectin and fibrosis in patients with NASH, however, remains controversial [72,73,100,108]. These findings are supportive of a role for low circulating adiponectin in the pathogenesis of NAFLD, and confirm the strong association among reduced adiponectin production by adipose tissue, NAFLD and IR, together with the hypothesis that an imbalance between proinflammatory and
anti-inflammatory cytokines may have a pathogenetic role in the development of liver damage in NAFLD [99].

Given the importance of adiponectin in the pathophysiology of NAFLD, some studies have assessed the relevance of these adipokine levels for the identification of NASH in NAFLD patients. The association between adipokines and the presence of NASH was assessed using non-invasive diagnosis by the so-called NASH test. The most important predictors of borderline NASH were adiponectin and high-density lipoprotein (HDL) as protective factors and, as risk factors, leptin, abdominal obesity, triglycerides and glycosylated haemoglobin. The area under the receiver operating characteristic (AUROC) curve for predicting NASH was 0.75 for leptin [confidence interval (CI): 0.7–0.8] and 0.74 for adiponectin (CI: 0.68–0.80). Taken together, adiponectin and leptin exhibited an AUROC of 0.81 (CI: 0.76–0.86), demonstrating that the combination of these two adipokines had predictive value for early-stage NASH [109]. Another study evaluating liver histology in morbidly obese individuals found that adiponectin levels < 23 ng/mL were associated with a 12-fold greater risk of NASH [104]. However, adiponectin exhibited an AUROC of only 0.654 with high specificity (95.8%), but low sensitivity (36.4%), for predicting NASH. A formula combining adiponectin, leptin and ghrelin showed good accuracy for NASH with an AUROC of 0.789, a specificity of 76.1% and a sensitivity of 81.8% [104]. Shimada et al. [110] observed that the combination of adiponectin, HOMA–IR and serum type IV collagen presented with high sensitivity and specificity for a steatohepatitis diagnosis (94% and 74%, respectively).

Recent studies have demonstrated an association between NASH and increased bile acids [111,112]. Bechmann et al. [106] noted that, in obese patients with NAFLD, bile acid synthesis and serum bile acid levels directly correlated with disease severity, while an inverse correlation was found with adiponectin. In their study, adiponectin levels < 29.16 ng/mL were associated with histological severity, higher bile acid levels, lower expression of bile acid metabolism-related genes and increases in the cytochrome P450 7A1 (CYP7A1) enzyme responsible for bile

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Subjects</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu et al. [77]</td>
<td>2003</td>
<td>Animals</td>
<td>Antisteatotic: Increases CPT1 activity, enhances hepatic fatty acid oxidation, decreases activity of two enzymes involved in fatty acid synthesis: acetyl-CoA carboxylase and fatty acid synthetase</td>
</tr>
<tr>
<td>Awazawa et al. [80]</td>
<td>2009</td>
<td>Animals</td>
<td>Anti-inflamatory: Suppresses expression of SREBP-1c, which controls and upregulates enzymes involved in fatty acid synthesis</td>
</tr>
<tr>
<td>Xu et al. [77]</td>
<td>2003</td>
<td>Animals</td>
<td>Suppresses hepatic production and plasma concentrations of TNF-α</td>
</tr>
<tr>
<td>Masaki et al. [81]</td>
<td>2004</td>
<td>Animals</td>
<td>Prevents lipopolysaccharide (LPS)-induced hepatic injury by inhibiting synthesis and/or release of TNF-α in KK-Ay obese mice</td>
</tr>
<tr>
<td>Matsumoto et al. [82]</td>
<td>2006</td>
<td>Animals</td>
<td>Suppresses TNF-α production and induces IL-10 production by Kupffer cells in response to LPS stimulation; lack of adiponectin enhances LPS-induced liver injury</td>
</tr>
<tr>
<td>Wolf et al. [83]</td>
<td>2006</td>
<td>Animals</td>
<td>Uregulated Ad expression in concavealain A-mediated acute liver failure, so may play a role in control/limitation of liver inflammation, suggesting a role in Ad-mediated IL-10 induction</td>
</tr>
<tr>
<td>Mandal et al. [84]</td>
<td>2010</td>
<td>Animals</td>
<td>gAd prevents LPS-stimulated TNF-α expression in Kupffer cells via activation of IL-10/STAT3/HO-1 pathway</td>
</tr>
<tr>
<td>Nepal et al. [85]</td>
<td>2012</td>
<td>Animals</td>
<td>gAd prevents ethanol-induced apoptosis in human hepatoma (HepG2) cell lines via HO-1 induction, revealing a novel biological gAd liver-protective response against alcohol abuse</td>
</tr>
<tr>
<td>Ouchi et al. [36]</td>
<td>2000</td>
<td>Humans</td>
<td>Modulates inflammatory response of endothelial cells via crosstalk between cAMP–PKA and NF-κB pathways</td>
</tr>
<tr>
<td>Ouchi et al. [79]</td>
<td>2001</td>
<td>Humans</td>
<td>Suppresses macrophage-to-firm cell transformation, so may act as a modulator</td>
</tr>
<tr>
<td>Kamada et al. [78]</td>
<td>2003</td>
<td>Animals</td>
<td>Anti-fibrotic: Attenuates liver fibrosis induced by carbon tetrachloride through reduction of TGF-β1 effects in hepatic stellate cells (HSC)</td>
</tr>
<tr>
<td>Ding et al. [86]</td>
<td>2005</td>
<td>Animals</td>
<td>May reverse HSC activation, maintain HSC quiescence and, significantly, have important therapeutic implications for liver fibrosis</td>
</tr>
<tr>
<td>Adachi et al. [87]</td>
<td>2008</td>
<td>Humans</td>
<td>Ad and AMPK inhibit HSC proliferation and hepatic fibrosis via multiple molecular mechanisms</td>
</tr>
<tr>
<td>Shafiei et al. [88]</td>
<td>2011</td>
<td>Animals</td>
<td>PPAR-γ effect on HSC activation and fibrogenetic cascade may be Ad-dependent, but Ad inhibition of HSC activation is not dependent on PPAR-γ, suggesting PPAR-γ-dependent and -independent pathways in HSC</td>
</tr>
</tbody>
</table>

CPT1: carnitine palmitoyltransferase-1; SREBP-1c: sterol regulatory element-binding protein 1c; gAd: globular adiponectin; STAT3/HO-1: signal transducer and activator of transcription 3/heme oxygenase 1; cAMP–PKA: cyclic adenosine monophosphate–protein kinase A; NF-κB: nuclear factor-kappaB; TGF-β1: transforming growth factor beta 1; AMPK: adenosine monophosphate-activated kinase protein; PPAR-γ: peroxisome proliferator-activated receptor-gamma.
Table 2
Clinical studies of adiponectin (Ad) in non-alcoholic fatty liver disease (NAFLD).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Disease</th>
<th>Subjects (n)</th>
<th>Primary findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hui et al. [73]</td>
<td>2004</td>
<td>NAFLD</td>
<td>191: 80 with NASH, 29 with simple steatosis, 82 controls</td>
<td>Hypoadiponectinaemia is a feature of NASH independent of IR; reduced Ad levels are associated with more extensive necroinflammation and may contribute to necroinflammatory forms of NAFLD</td>
</tr>
<tr>
<td>Targher et al. [97]</td>
<td>2004</td>
<td>NAFLD</td>
<td>68 obese: 43 with steatosis, 25 without steatosis, by ultrasonography</td>
<td>Decreased plasma Ad levels are closely correlated with NASH in healthy obese individuals</td>
</tr>
<tr>
<td>Bugianesi et al. [98]</td>
<td>2005</td>
<td>NAFLD</td>
<td>216: 174 with NAFLD, 42 controls</td>
<td>Hypoadiponectinaemia in NAFLD is part of a metabolic disturbance characterized by ectopic fat accumulation in the central compartment</td>
</tr>
<tr>
<td>Pagano et al. [99]</td>
<td>2005</td>
<td>NAFLD</td>
<td>37: 9 with steatosis, 8 with NASH, 20 controls</td>
<td>Low circulating Ad in pathogenesis of NAFLD; confirmation of close association between reduced Ad production by adipose tissue, NAFLD and IR</td>
</tr>
<tr>
<td>Musso et al. [100]</td>
<td>2005</td>
<td>NASH</td>
<td>65: 20 with NASH, 30 insulin-sensitive controls, 15 insulin-resistant controls</td>
<td>Hypoadiponectinaemia is a feature of NASH and may have pathogenetic role in beta-cell dysfunction, hepatic necroinflammation and fibrosis independent of IR, visceral fat accumulation, TNF-α axis activity and dietary habits</td>
</tr>
<tr>
<td>Kaser et al. [101]</td>
<td>2005</td>
<td>NASH after bariatric surgery</td>
<td>22: 13 with NASH, 9 with steatosis</td>
<td>Reduced hepatic expression of Ad and adipor82 may have pathophysiological relevance in NAFLD</td>
</tr>
<tr>
<td>Kim et al. [102]</td>
<td>2005</td>
<td>NAFLD</td>
<td>213: 75 with NAFLD by ultrasonography, 138 controls</td>
<td>Serum Ad level and baPWV are significantly associated with NAFLD and various liver enzymes, especially in women</td>
</tr>
<tr>
<td>Targher et al. [72]</td>
<td>2006</td>
<td>NAFLD</td>
<td>120: 50 with NASH, 10 with steatosis, 60 controls</td>
<td>Low Ad levels are strongly associated with severity of liver histology, further supporting the hypothesis that Ad may be involved in the development of NAFLD</td>
</tr>
<tr>
<td>Yalniz et al. [68]</td>
<td>2006</td>
<td>NASH</td>
<td>62: 37 with NASH, 25 controls</td>
<td>Ad and ghrelin levels are lower in NASH than in controls; significant relationship between NASH, adipokines and ghrelin independent of BMI and glucose metabolic status</td>
</tr>
<tr>
<td>Hamano et al. [103]</td>
<td>2012</td>
<td>NAFLD</td>
<td>5588 healthy Japanese men</td>
<td>Hypoadiponectinaemia is a significant determinant of steatotic dysfunction at all levels of alcohol consumption</td>
</tr>
<tr>
<td>Machado et al. [104]</td>
<td>2012</td>
<td>NAFLD</td>
<td>82 morbidly obese, biopsy-proven NAFLD: 11 with NASH, 71 without NASH</td>
<td>Imbalance between Ad, leptin and ghrelin may be associated with more severe NAFLD</td>
</tr>
<tr>
<td>van der Poorten et al. [105]</td>
<td>2013</td>
<td>NASH</td>
<td>119: 65 with biopsy-proven advanced NASH (fibrosis stage 3/4), 54 with mild NASH (fibrosis stage 0/1)</td>
<td>Relationship between Ad, bile acids and adipocyte FXR activation seen in vivo and in vitro, suggesting hepatocyte–adipocyte crosstalk; serum Ad levels in advanced NASH are independently associated with hepatic fat loss; Ad may be partly responsible for ‘burnt-out’ NASH</td>
</tr>
<tr>
<td>Bechmann et al. [106]</td>
<td>2013</td>
<td>NAFLD</td>
<td>98 morbidly obese: 59 with NASH, 39 with steatosis, 10 controls</td>
<td>Bile acid synthesis and serum bile acid levels correlate with disease severity in NAFLD; Ad levels are inversely correlated with NAFLD disease severity; bile acid accumulation in NASH induces hepatocyte cell death; late FXR activation fails to prevent hepatocyte injury due to decreased Ad; early treatment with FXR ligands and/or Ad-receptor agonists might prevent NASH</td>
</tr>
</tbody>
</table>

NASH: non-alcoholic steatohepatitis; IR: insulin resistance; TNF-α: tumour necrosis factor-alpha; baPWV: brachial–ankle pulse wave velocity; BMI: body mass index; FXR: farnesoid X receptor.

acid synthesis. It was also demonstrated that, in NASH, bile acid accumulation induced hepatocyte cell death, while late farnesoid X receptor (FXR) activation failed to prevent hepatocyte injury due to decreased adiponectin levels, suggesting that early treatment with FXR ligands and/or adiponectin receptor agonists might prevent NASH [106]. This inverse relationship between adiponectin and bile acids reveals a potential direct effect of adiponectin on bile acid homoeostasis [106]. Nevertheless, the exact mechanism linking bile acid metabolism, hepatocellular death and adipocytokines is still not completely understood.

Based on the fact that adiponectin levels are elevated in patients with cirrhosis of variable aetiology, van der Poorten...
et al. [105] investigated the role of this adipokine in advanced NASH. The researchers concluded that the relatively high levels of adiponectin in compensated late-stage NASH were significantly related to hepatic fat loss independent of metabolic factors and liver dysfunction, and were likely responsible, at least in part, for the paradox of ‘burnt-out’ NASH [105]. The most probable cause of the increased adiponectin levels in advanced NASH is bile acid-mediated hepatocyte–adipocyte crosstalk [105,113]. This hypothesis was supported by an experiment wherein differentiated 3T3-L1 adipocytes were treated with bile acid receptor agonists (FXR agonist fexaramine and TGR5 agonist taurolithocholic acid), and demonstrated >10-fold increased adiponectin secretion, thereby suggesting that bile acids act directly to regulate adiponectin synthesis in adipocytes [105]. These data, albeit contradictory to some extent, provide clues to the relationship between the liver and adipose tissue, and serve as a basis for new therapeutic targets in NAFLD. It is possible that the type of bile acid may have influenced these results, as demonstrated by van der Poorten et al. [105], whose study showed that levels of deoxycholic acid (DCA) and glycine-conjugated DCA, but not cholic acid, chenodeoxycholic acid and ursodeoxycholic acid, paralleled the increases in adiponectin.

Given that hypoadiponectinaemia is an important risk factor for the progression of NAFLD, therapeutic strategies to increase these adipokine levels have been assessed. Clinical treatment with PPAR-γ agonists (thiazolidinediones) has shown promising results, while a study that included 47 patients with NASH showed that pioglitazone increased adiponectin levels by 2.3 times, improved IR and was associated with histological improvement of steatosis, inflammation and fibrosis [114]. Studies with rosiglitazone showed that it increased circulating adiponectin and improved steatohepatitis [115,116] by acting directly on the modulation of Adipor1 and Adipor2 receptors, and indirectly by decreasing serum TNF-α [115]. A mouse study showed that PPAR-γ has potent inhibitory effects on the growth of stellate cells and TGF-β1-induced connective tissue growth factor (CTGF) expression, suggesting a potential antifibrotic effect of thiazolidinediones [117]. In a randomized controlled study comparing the efficacy of vitamin E and pioglitazone vs placebo, the group receiving pioglitazone showed reduced steatosis and lobular inflammation compared with the placebo group. However, the drug was not superior to vitamin E and failed to reach the predetermined primary study endpoint [118]. This suggests that adiponectin may be an important therapeutic target in NAFLD. However, further studies of such therapeutic strategies at different stages of disease are necessary.

3.2. Other liver diseases

Table 3 summarizes the main clinical studies investigating the relationship between adiponectin and different liver diseases.

3.2.1. Viral hepatitis

HCV infection is another disease in which adipokines may represent the link between IR and viral infection, emphasizing the important role of adiposity in regulating immune responses in such infections [121,126]. Steatosis has been reported in around 50% of liver biopsies of patients with chronic HCV infection [134] and is especially associated with HCV genotype 3 [120,135]. Unlike other genotypes in which BMI was an important pathogenic factor of steatosis [136], steatosis is more pronounced in genotype 3 and significantly correlated with intrahepatic HCV RNA levels. Furthermore, the steatosis in patients with HCV genotype 3 disappears after treatment achieving a sustained virological response, suggesting that, in these cases, steatosis is the morphological expression of viral cytopathology [135].

In chronic HCV infection, levels of adiponectin are reduced [119,127,132] and significantly lower in patients with vs without steatosis [119], and inversely correlated to grade of steatosis, histological activity index and stage of fibrosis [132]. These findings suggest that hypoadiponectinaemia may be contributing to hepatic steatosis and liver injury progression in these patients, an outcome most likely related to the effect of adiponectin on lipid metabolism [119]. A recent study found hypoadiponectinaemia in non-obese mice with HCV-induced hepatic steatosis as well as improvement in steatosis after treatment with adiponectin [137]. Also, studies by Liu et al. [121] and Jonsson et al. [120] found reductions in the expression of hepatic receptors of adiponectin in patients with chronic HCV infection. In addition, Corbetta et al. [133] suggested that adiponectin resistance may be induced by IR and may be contributing to the progression of liver fibrosis in those infected by HCV.

Despite studies demonstrating that adiponectin is not related to histological parameters in hepatitis C, low levels of the adipokine have been associated with high viral loads and HCV genotypes 2 [121] and 3 [127]. In addition, weight loss in overweight HCV-infected patients has been associated with an increase in serum levels of adiponectin, improvement in fibrosis, and reductions in steatosis and abnormal liver enzymes, despite persistence of the virus [51,138]. This highlights the importance of obesity and adiponectin in the modulation of immune responses in chronic HCV infection [126]. Low levels of adiponectin have also been identified as independent predictors of liver steatosis and failing to achieve a sustained virological response at the end of antiviral therapy in chronic hepatitis C [127].

Few studies have evaluated the role of adiponectin in chronic HBV infection. In these patients, levels of adiponectin are lower [123] or similar [139] to those of patients with HCV. The higher levels of adiponectin in HCV carriers may be partly responsible for the slower progression of chronic hepatitis C [123]. However, in HBV patients, a fourfold increase in serum adiponectin was detected in those with more advanced stages of fibrosis [125]. Furthermore, adiponectin appears to have a direct effect on fibrosis progression, with a marked decline in its levels after antiviral therapy being associated with reduced fibrosis [125]. However, another study including HBV patients showed an association between hepatic necroinflammation and TNF-α and IL-6 only, and not adiponectin, which was decreased in patients with IR and hepatic steatosis [130]. The investigators concluded that adiponectin protects against IR and hepatic steatosis, but has no effect on liver lesions related to HBV. This suggests that
Table 3
Clinical studies of adiponectin (Ad) in different liver diseases.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Disease</th>
<th>Subjects (n)</th>
<th>Primary findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tietge et al. [74]</td>
<td>2004</td>
<td>Cirrhosis</td>
<td>20 cirrhotic: 6 alcoholic, 6 with HBV &amp; HCV, 6 with biliary disease, 2 cryptogenic, 20 controls</td>
<td>Liver is a major source of Ad; Ad plasma levels are significantly elevated and not correlated with parameters of body composition or metabolism, but correlate exclusively with reduced liver function and altered hepatic haemodynamics</td>
</tr>
<tr>
<td>Petit et al. [119]</td>
<td>2005</td>
<td>HCV</td>
<td>71: 42 with steatosis, 29 without steatosis</td>
<td>Hypoadiponectinaemia is significantly associated with liver steatosis; plasma levels of Ad are inversely correlated with steatosis, suggesting that hypoadiponectinaemia may contribute to hepatic steatosis progression and liver injury in HCV</td>
</tr>
<tr>
<td>Jonsson et al. [120]</td>
<td>2005</td>
<td>HCV</td>
<td>194 with HCV</td>
<td>Adiponectinaemia is associated with steatosis only in men and paradoxically increases with inflammation</td>
</tr>
<tr>
<td>Liu et al. [121]</td>
<td>2005</td>
<td>HCV</td>
<td>95 with HCV</td>
<td>Low levels of Ad are significantly associated with male gender, IR, large HCV load and genotype 2, suggesting a correlation between Ad and HCV factors in serum and liver tissue</td>
</tr>
<tr>
<td>Tacke et al. [122]</td>
<td>2005</td>
<td>Chronic liver diseases</td>
<td>111: 18 without cirrhosis, 35 Child A, 44 Child B, 14 Child C, 226 healthy controls</td>
<td>Ad is elevated and correlates with inflammation and liver damage; high Ad levels after bile duct ligation in mice and in human bile in cholestasis suggest that biliary secretion is involved in Ad clearance; Ad could serve as a novel marker for cholestasis in liver cirrhosis</td>
</tr>
<tr>
<td>Siagris et al. [123]</td>
<td>2007</td>
<td>HCV, HBV</td>
<td>145: 72 with HCV, 73 with HBV</td>
<td>Higher levels of serum Ad in HCV vs HBV may be related to slower disease progression of chronic HCV; no clear positive association between Ad and hepatic necroinflammation found</td>
</tr>
<tr>
<td>Cua et al. [124]</td>
<td>2007</td>
<td>HCV</td>
<td>315: 240 with HCV (not treated), 154 with fibrosis stage 0–2, 75 healthy controls</td>
<td>Adipocytokines leptin and Ad were not associated with histological features of chronic HCV; HCV-associated IR is most likely an adipocytokine-independent effect of HCV on modulation of insulin sensitivity</td>
</tr>
<tr>
<td>Hui et al. [125]</td>
<td>2007</td>
<td>HBV</td>
<td>100: 66 without liver cirrhosis, 34 with cirrhosis</td>
<td>Serum Ad may affect fibrosis progression; marked decline in serum Ad after antiviral therapy is associated with fibrosis reduction</td>
</tr>
<tr>
<td>Palmer et al. [126]</td>
<td>2008</td>
<td>HCV, cirrhosis</td>
<td>35: 15 treatment responders, 20 non-responders</td>
<td>Reciprocal association between BMI, Ad and anti-HCV immune responses in chronic HCV emphasizes the importance of adiposity in regulating immune responses in HCV infection</td>
</tr>
<tr>
<td>Zógrafos et al. [127]</td>
<td>2008</td>
<td>HCV, HBV</td>
<td>142: 83 HCV, 59 HBV, 43 controls</td>
<td>HCV genotype 3 may directly affect Ad; further supported by significant increase of Ad after treatment only in HCV genotype 3 patients; serum Ad at baseline may be an independent predictor of liver steatosis and end-of-treatment virological responses</td>
</tr>
<tr>
<td>Fioreani et al. [128]</td>
<td>2008</td>
<td>PBC</td>
<td>304: 137 PBC, 30 with NAFLD, 137 controls</td>
<td>Ad levels are higher in PBC than in either NASH or controls and associated with histological progression of PBC; high Ad levels may be a possible protective factor against atherosclerosis</td>
</tr>
<tr>
<td>Durazzo et al. [129]</td>
<td>2009</td>
<td>AIH</td>
<td>115: 42 with AIH, 31 with NASH, 42 controls</td>
<td>Significantly higher Ad levels in AIH vs controls despite higher HOMA–IR values; significant correlation between Ad and serological features of cholestasis suggest a role in biliary function; Ad may be a marker of AIH disease progression</td>
</tr>
<tr>
<td>Wong et al. [130]</td>
<td>2010</td>
<td>HBV</td>
<td>266: 68 with cirrhosis</td>
<td>Ad protects against IR and hepatic steatosis, but has no effect on liver injury</td>
</tr>
<tr>
<td>Balmer et al. [75]</td>
<td>2010</td>
<td>Chronic liver diseases</td>
<td>232: 45 with cirrhosis, 64 with NAFLD, 71 with viral hepatitis, 18 with autoimmune disease, 3 with alcohol-induced liver disease, 31 with elevated liver enzymes of unknown origin, 20 controls</td>
<td>Circulating Ad levels are significantly lower in NAFLD vs other chronic liver diseases; Ad is significantly higher in patients with vs without cirrhosis; Ad levels correlate positively with surrogate markers of hepatic fibrosis (transient elastography, fasting serum bile acids and hyaluronate)</td>
</tr>
<tr>
<td>Salman et al. [131]</td>
<td>2010</td>
<td>Cirrhosis, cholestasis</td>
<td>90: 40 with cirrhosis, 30 with cirrhosis &amp; cholestasis, 20 controls</td>
<td>Ad is elevated in cirrhosis and correlates with degree of hepatocellular injury and cholestasis, but not with parameters of body composition or metabolic activity; exclusively correlates with reduced liver function</td>
</tr>
<tr>
<td>Latif et al. [132]</td>
<td>2011</td>
<td>HCV, cirrhosis</td>
<td>60: 30 with steatosis, 30 without steatosis</td>
<td>Serum Ad levels are inversely correlated with grade of steatosis, histological activity index and stage of fibrosis</td>
</tr>
<tr>
<td>Corbeta et al. [133]</td>
<td>2011</td>
<td>HCV</td>
<td>108: 54 with HCV, 54 controls</td>
<td>Fibrosis is associated with hyperadiponectinaemia; hepatocytes in chronic HCV show reduced Adipor1 expression, suggesting Ad resistance</td>
</tr>
</tbody>
</table>

HBV: hepatitis B virus; HCV: hepatitis C virus; BMI: body mass index; PBC: primary biliary cirrhosis; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; AIH: autoimmune hepatitis; HOMA–IR: homeostasis model assessment–insulin resistance.
adipokines and viral factors may be independent contributors to liver injury in chronic hepatitis B [130].

3.2.2. Cholestatic hepatic diseases and autoimmune hepatitis

Patients with biliary liver diseases and cholestasis have the highest adiponectin levels, indicating that the liver is possibly involved in its excretion through bile [122]. Although some studies suggest renal excretion of adiponectin [140,141], Tacke et al. [122] demonstrated higher levels of adiponectin in human bile from patients with cholestatic hepatic disease and in mice after bile duct ligation, indicating that biliary secretion is involved in adiponectin clearance. However, recent evidence suggesting the participation of bile acids in the process of adiponectin liberation by adipocytes has revealed a new potential mechanism for elevated levels of this adipokine in cholestatic diseases [105]. Salman et al. [131] observed that levels of adiponectin were higher in patients with cirrhosis and cholestasis than in those without cholestasis, and also that adiponectin correlated with liver cell injury, a marker of inflammation, liver synthetic function and markers of cholestasis. In patients with primary biliary cirrhosis (PBC), the increase in adiponectin levels was also higher than in patients with NASH [128]. It was therefore suggested that this increase in adiponectin levels might be a protective factor against atherogenesis, a theory based on the fact that cardiovascular risk in PBC patients is not increased compared with the general population despite the higher rates of hypercholesterolaemia observed in such individuals [128].

Only one study has investigated adiponectin in patients with autoimmune hepatitis (AIH) [129], and found that levels were significantly higher than in either healthy controls or patients with NASH. The significant correlation between adiponectin levels and serological features of cholestasis suggest an association with biliary function, and indicate that adiponectin may serve as a possible marker of disease progression in AIH [129].

3.2.3. Liver cirrhosis

Several studies have reported significantly elevated serum levels of adiponectin in patients with advanced cirrhosis, regardless of aetiology [74,75,98,125,127,131,133]. Moreover, there was a positive correlation between adiponectin levels and markers of hepatic fibrosis (transient elastography, fasting serum bile acids and hyaluronate) [75]. Various mechanisms have been proposed to explain the raised levels of adiponectin with fibrosis progression, such as an imbalance between the production of adiponectin by adipocytes and its excretion by the liver [142], an increase in adiponectin production by hepatic stellate cells (HSC) [86] and anti-inflammatory mechanisms [143].

Tietge et al. [74] investigated adiponectin levels in 20 patients with cirrhosis and found an association between adiponectinaemia and parameters of hepatic synthesis (albumin and prothrombin time) and haemodynamics (portal pressure, hepatic vascular resistance and effective hepatic blood flow). In that study, variables related to body composition and metabolism had no influence on adiponectin levels. Similar findings were described in two other studies in which adiponectin levels in cirrhosis were associated with variables related to liver dysfunction, but not with IR [122,131]. However, these studies were limited by their relatively small numbers of patients, and lack of stratification by gender and adjustments for other important variables. Thus, the factors related to elevated levels of adiponectin in cirrhosis have yet to be ascertained.

4. Perspectives

Over the past 10 years, there has been a considerable increase in our awareness of the relationship between adipose tissue and liver disease pathophysiology. The central role of the liver in metabolic syndromes explains the large number of studies of adipokines in NAFLD and other components of such syndromes. Several studies have looked at the connection between adipokines and mechanisms of hepatic lesions and, not surprisingly, reported controversial results [144]. As in chronic kidney disease [145], the effect of increased plasma adiponectin levels in liver diseases is complex, and it may be hypothesized that, in cirrhosis, high adiponectin levels reflect protein energy malnutrition, impaired hepatic function and reduced adiponectin excretion by the liver. However, the impact of increased adiponectin levels on insulin metabolism, body composition and cardiovascular function in cirrhotic patients remains unclear.

Independent studies suggesting the therapeutic use of recombinant adiponectin have been promising, especially because of its insulin-sensitizing properties, and cardioprotective, hepatoprotective and antiangiogenic functions [146,147]. Strategies directed towards increasing adiponectin production and its circulating concentrations include lifestyle interventions (diet and weight loss), pharmacological therapy (thiazolidinediones, angiotensin converting-enzyme inhibitors, endocannabinoid antagonists) and possibly nutritional supplements (soya protein, linoleic acid), and have proven to be effective approaches for the prevention and treatment of IR, the metabolic syndrome, DM2 and cardiovascular disease [5,56]. AdipoR activation to mimic adiponectin actions may also prove beneficial in the reduction of metabolic risk factors in conditions such as obesity, in which low adiponectinaemia prevails [146]. It is possible that these might also be viable options for the treatment of liver diseases either as a primary approach (as in cases of NAFLD) or as adjunctive treatment, with a goal to slow the evolution of fibrosis in various liver diseases.

However, many questions still need answering before adiponectin can be used as a therapeutic target. Indeed, the presence of various adiponectin oligomeric isoforms and production sites, the gender dimorphism of adiponectin concentrations and oligomeric isoform distributions, and the identification of multiple receptors with different affinities for adiponectin oligomers all add to the complexity of adiponectin activities across a wide array of physiological processes and diseases [148]. More studies are now needed to better evaluate the relationship between adipokines and various liver diseases, and especially to investigate its role in the maintenance of liver integrity through the regulation of insulin sensitivity and inflammatory responses [89].
5. Conclusion

Major advances have recently been made in our understanding of the relationship between adiponectin and the pathophysiology of liver disease. In the liver, adiponectin manifests antisteatotic, anti-inflammatory and antifibrogenic properties, and actively participates in events related to NAFLD progression. In addition, an important role for the liver in the regulation of adiponectin liberation by adipocytes, mediated by bile acids, has recently been proposed. These findings represent opportunities for the evaluation of new therapeutic strategies focused on the use of inductor agents or adiponectin itself for the treatment of liver disease, particularly NAFLD.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabete.2013.11.004.

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