Adiponectin, a key adipokine in obesity related liver diseases

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Non-alcoholic fatty liver disease (NAFLD) comprising hepatic steatosis, non-alcoholic steatohepatitis (NASH), and progressive liver fibrosis is considered the most common liver disease in western countries. Fatty liver is more prevalent in overweight than normal-weight people and liver fat positively correlates with hepatic insulin resistance. Hepatic steatosis is regarded as a benign stage of NAFLD but may progress to NASH in a subgroup of patients. Besides liver biopsy no diagnostic tools to identify patients with NASH are available, and no effective treatment has been established. Visceral obesity is a main risk factor for NAFLD and inappropriate storage of triglycerides in adipocytes and higher concentrations of free fatty acids may add to increased hepatic lipid storage, insulin resistance, and progressive liver damage. Most of the adipose tissue-derived proteins are elevated in obesity and may contribute to systemic inflammation and liver damage. Adiponectin is highly abundant in human serum but its levels are reduced in obesity and are even lower in patients with hepatic steatosis or NASH. Adiponectin antagonizes excess lipid storage in the liver and protects from inflammation and fibrosis. This review aims to give a short survey on NAFLD and the hepatoprotective effects of adiponectin.
insulin resistance\textsuperscript{7,8}. Despite comparable fatness between MHO and control cohorts that develop insulin resistance, MHO subjects have 49% less visceral fat which further emphasizes the unfavourable characteristics of this fat depot\textsuperscript{9}. Lean body mass may be associated with a higher insulin sensitivity and is significantly lower in MHO subjects\textsuperscript{10}. A recent study even describes an independent association of lean body mass with impaired glucose disposal and systemic C-reactive protein (CRP) levels in centrally obese postmenopausal women that may exacerbate the harmful effects of visceral fat mass\textsuperscript{10}. These studies further point to the highly complex interplay of various factors associated with metabolic diseases like the metabolic syndrome.

Various epidemiological studies have identified central obesity as an independent risk factor for metabolic diseases and highlight the crucial role of impaired production or activity of adipose tissue released protein\textsuperscript{11,12}. Most of the adipokines identified so far are elevated in obesity and raised chemokine C-C motif ligand 2 (CCL2) contributes to the increasing number of adipose tissue resident macrophages\textsuperscript{11,13}. They produce inflammatory proteins like interleukin-6 (IL-6) and tumour necrosis factor (TNF) whose circulating levels are increased in obesity, a state of low-grade, chronic inflammation\textsuperscript{13}. TNF impairs insulin signaling and plays a crucial role in non-alcoholic steatohepatitis (NASH) progression\textsuperscript{14,15}. Visceral fat released proteins are directly transported to the liver by the portal vein and the anatomical feature of this fat depot may explain the harmful metabolic effects of visceral adiposity\textsuperscript{16}. IL-6 is preferentially released from visceral fat and upregulates suppressor of cytokine signalling 3 (SOCS3) in the liver that causes hepatic insulin resistance\textsuperscript{16-18}. Furthermore, IL-6 is a well known inducer of CRP, a marker protein for systemic inflammation\textsuperscript{19} (Figure 1). Leptin is mainly produced by adipocytes, and obesity is characterized by elevated systemic levels and central and peripheral leptin resistance\textsuperscript{16}. Leptin prevents lipid accumulation in non-adipose tissues like the liver. Leptin lowers stearoyl-CoA desaturase that catalyzes the rate-limiting reaction of monounsaturated fatty acid synthesis and thereby may ameliorate hepatic insulin sensitivity\textsuperscript{20}. Animal studies have proven that leptin directly promotes fibrogenesis. Leptin induces transforming growth factor β (TGF-β) and connective tissue growth factor (CTGF) production in hepatic stellate cells through indirect effects on Kupffer cells\textsuperscript{21}. In humans, a direct association of circulating leptin and liver fibrosis has not been confirmed yet and locally produced leptin and/or leptin resistance may have to be taken into account\textsuperscript{21,22}.

The adipokine adiponectin is highly abundant in human serum and is secreted by adipose tissue in inverse proportion to the body mass index\textsuperscript{23}. Adiponectin circulates as trimer, hexamer and higher order multimer in serum and isoform-specific effects have been described\textsuperscript{24-26}. Adiponectin may also form hetero-oligomers with additional members of the C1q/TNF-related protein (CTRP) family like the recently described CTRP\textsuperscript{9}\textsuperscript{27}. Early studies indicate that globular adiponectin, the globular C1q domain of this protein generated by proteolysis of the full-length protein, may also exist in serum\textsuperscript{28}. However, circulating levels seem to be rather low, questioning the biological significance of this protein\textsuperscript{28} that may nevertheless be of therapeutic relevance. Epidemiological studies revealed that low adiponectin levels are associated with NASH independent of insulin resistance and body mass index, and hepatoprotective effects of adiponectin have been identified in animal studies or with isolated liver cells\textsuperscript{29-32}. MHO individuals are insulin sensitive and have adiponectin levels similar to normal-weight controls despite excessive weight and body fat, and this association may further underline the protective effects of this adipokine\textsuperscript{33}.

NAFLD not only compromises the hepatic manifestation of the metabolic syndrome but is linked to a higher risk of develop metabolic disorders like type 2 diabetes or cardiovascular disease\textsuperscript{34,35}. Fatty liver is even associated with dyslipidemia, metabolic syndrome and low adiponectin independent of body mass index (BMI), waist to hip ratio and visceral fat mass\textsuperscript{36}. NAFLD is defined as increase along with the growing epidemic of obesity\textsuperscript{37} and understanding of its pathophysiology is a prerequisite to develop non-invasive diagnostic tools and to establishing effective treatment regimes. Rising adiponectin levels may be beneficial in liver disease and its protective effects in hepatic steatosis and NASH\textsuperscript{38} are summarized in the current review article.

**EPIDEMIOLOGY OF NAFLD**

Diagnosis of NAFLD requires a careful anamnesis to exclude other liver diseases or drug-mediated liver damage. Moderate alcohol intake, defined by most physicians as 20 to 40 g/d in men and 20 g/d in women, has to be en-
Visceral adiposity and insulin resistance are clearly related to NAFLD[36] and genetic variations associated with obesity and disproportionate body fat distribution may predispose to development of steatotic liver. Chemerin is a recently identified adipokine and a common genetic variation is associated with increased visceral fat mass in non-obese subjects but epidemiological studies to link chemerin alleles with NAFLD are still lacking[39]. The adiponectin 45T →G variant contributes to overall fatness and abdominal obesity but is not an important determinant of NAFLD at least in Chinese people[40,41].

Gene variations may influence NAFLD stage, progression and even occurrence. NAFLD is much more likely in Hispanic Americans than among whites[31] and African Americans have a lower degree of hepatic steatosis relative to whites[32]. Familial clustering of NAFLD has been demonstrated, and fatty liver is more common in siblings and parents of children with NAFLD indicating that NAFLD, similar to type 2 diabetes, is a multifactorial disease[38]. Environmental and genetic factors define the individual risk of developing NAFLD and may also explain why only a subgroup of patients develop more progressive liver damage.

Studies in small cohorts have identified genetic associations of microsomal triglyceride transfer protein, an enzyme regulating hepatic VLDL release, the antioxidant mitochondrial enzyme superoxide dismutase 2, the inflammatory cytokine TNF and the main profibrotic cytokine TGF-β with NAFLD[44,50]. Genome-wide association studies find that variations of patatin-like phospholipase domain containing 3 (PNPLA3, adiponectin), a protein with close homology to adipose triglyceride lipase but so far unknown function, contributes to ethnic and inter-individual differences in hepatic steatosis and susceptibility to NAFLD[46,57].

This association has not been confirmed in a recent study in non-Hispanic, Caucasian, women with liver biopsy proven NAFLD, where an association between NASH activity score and single nucleotide polymorphisms (SNPs) within the squalene synthase (FDFT1) gene, a key regulator of cholesterol biosynthesis, is described. Polymorphisms of the pregnancy zone protein, a proteinase involved in clearance of TGF-β, are linked to systemic AST levels, and variants of platelet-derived growth factor α are linked to liver fibrosis[48].

Genetic variations of adiponectin are found to be associated with NAFLD[39,50], and single nucleotide polymorphisms in adiponectin receptor 1 (AdipoR1) and AdipoR2 contribute to variations in hepatic fat accumulation in humans[60].

**SYSTEMIC ADIPONECTIN IN NAFLD**

Systemic adiponectin concentrations are in the μg/mL-range indicating that adiponectin constitutes a substantial fraction of plasma proteins, and these high levels are remarkably constant. Despite its abundant presence in plasma, adiponectin is cleared rapidly by the liver with a half-life of about 75 min[83].

Visceral adiposity is associated with elevated circulating free fatty acids and higher concentrations of most adipose tissue released proteins[80]. Adiponectin differs from the adipokines described so far because its systemic levels are decreased in obesity[23]. In high fat diet induced obese rodents and in ob/ob mice adiponectin levels are reduced in plasma and clearance is significantly prolonged, indicating markedly impaired adiponectin synthesis in obesity[82,84]. Visceral fat accumulation is associated with hyypoadiponectinemia and negative associations of visceral fat with systemic adiponectin have been identified[86,87].

Besides adiponectin, circulating levels of omentin predominantly released from the stromalvascular cells of visceral fat are found reduced in obesity and serum omentin levels are increased in patients with NAFLD and independently predict hepatocyte ballooning[90].
In healthy Caucasians, BMI and adiponectin, but not insulin resistance, predict serum concentrations of both ALT and GGT\textsuperscript{[88]}. Low adiponectin levels are even found associated with NASH independent of insulin resistance and BMI\textsuperscript{[89]}. Multivariate regression analysis identifies decreased adiponectin as an independent predictor of liver steatosis and elevated ALT and GGT levels in healthy obese individuals\textsuperscript{[92]}. In NAFLD patients low adiponectin levels are closely associated with the degree of hepatic steatosis, necroinflammation and fibrosis\textsuperscript{[93-95]}. Shimada \textit{et al}\textsuperscript{[96]} reported that 90\% of patients with early-stage NASH can be predicted by a combined evaluation of the serum adiponectin level, homeostasis assessment model-insulin resistance (HOMA-IR) score, and serum type IV collagen 7S level.

Circulating adiponectin levels in the μg/mL range by far exceed concentrations commonly required for receptor-dependent signalling. This may indicate receptor independent functions of adiponectin and binding to growth factors like platelet derived growth factor (PDGF), extracellular matrix proteins, low density lipoprotein (LDL) and opsonization of apoptotic cells to stimulate phagocytosis have been described\textsuperscript{[71-74]}.

Systemic adiponectin is about 20\% to 60\% lower in NAFLD than healthy controls\textsuperscript{[75-77]} but considering the high levels in the circulation and a half-maximal effective dose of 0.85 μg/mL full-length adiponectin for AdipoR2 stimulated fatty acid oxidation\textsuperscript{[78]} the question arises whether impaired receptor-mediated signalling due to reduced concentrations is a reasonable explanation for metabolic complications associated with hypoadiponectinemia. Therefore, it is likely that adiponectin receptor signal transduction pathways are also impaired in NAFLD.

**ADIPONECTIN RECEPTORS IN NAFLD**

Two 7-transmembrane proteins, AdipoR1 and AdipoR2, have been identified to function as adiponectin receptors\textsuperscript{[79]}. Although initial studies using rodent tissues reveal preferential expression of AdipoR2 in the liver, in human tissues AdipoR1 and AdipoR2 mRNAs are most abundant in skeletal muscle and both are moderately expressed in the liver\textsuperscript{[80]}. AdipoR1 protein is easily detected in human hepatocytes indicating that both receptors may play a role in liver physiology\textsuperscript{[81]}. Although there is a well documented relationship between low adiponectin and liver disease, an association of NAFLD and reduced expression of hepatic adiponectin receptors is not consistently reported. Furthermore, mainly mRNA expression has been analysed and this may not necessarily predict protein abundance\textsuperscript{[82,83]}. In animal models of obesity, hepatic adiponectin receptor mRNAs are found unchanged or even increased\textsuperscript{[84,85]}. In human biopsies, hepatic adiponectin receptor mRNAs are increased in biopsy-proven NASH compared to steatotic livers\textsuperscript{[86]}. Other studies, however, describe similar levels of adiponectin receptor mRNA in normal liver, steatotic liver and NASH\textsuperscript{[87,88]}. There are also reports on reduced AdipoR2 mRNA in NASH compared to simple steatosis or lower AdipoR2 mRNA in fatty liver with no further reduction in NASH\textsuperscript{[89,90]}. Data on AdipoR2 proteins are sparse and one study demonstrates reduced AdipoR2 protein in human NASH compared to steatotic liver\textsuperscript{[91]}. Treatment of hepatocytes with palmitate is used as an in vitro model for hepatocyte steatosis and 200 μmol/L of this fatty acid reduce AdipoR2 protein in HuH7 cells\textsuperscript{[92]}. Activating transcription factor 3 (ATF3) is induced upon endoplasmic reticulum stress and in the liver of ob/ob mice, and suppresses AdipoR2 in HepG2 cells\textsuperscript{[93]}. Therefore, besides low circulating adiponectin, AdipoR2 may be reduced in hepatic steatosis and NASH indicating a possible adiponectin resistant state.

**ANTISTEATOTIC EFFECTS OF ADIPO-NECTIN**

Dyslipidemia is characterized by high circulating triglycerides\textsuperscript{[94]} and low high density lipoprotein (HDL) cholesterol levels, and is frequently accompanied by hepatic steatosis\textsuperscript{[95]}. Adiponectin negatively correlates with serum triglycerides and apolipoprotein B (ApoB), the main apolipoprotein of the triglyceride rich VLDL\textsuperscript{[96]}. Hepatocyte ApoB and triglycerides are reduced by adiponectin indicating lower hepatic VLDL release\textsuperscript{[97,98]}. Furthermore, VLDL catabolism is enhanced by an increased skeletal muscle lipoprotein lipase and VLDL receptor expression\textsuperscript{[99]}. This more favourable lipid profile may be linked to lower hepatic lipid storage.

A choline and L-amino acid deficient diet induces more severe hepatic steatosis in adiponectin deficient mice compared to wild type animals\textsuperscript{[100]}. Adenoviral expression of adiponectin ameliorates lipid deposition in the liver\textsuperscript{[101]}. SREBP-1c is a central regulator of fatty acid synthesis, and is suppressed by adiponectin in hepatocytes and in the liver of db/db mice\textsuperscript{[102]}. AMP-activated protein kinase (AMPK) is physiologically activated by low energy status, and switches on ATP-producing catabolic pathways (such as fatty acid oxidation and glycolysis), and switches off ATP-consuming anabolic pathways (such as lipogenesis)\textsuperscript{[103]}. Adiponectin activates AMPK by binding to AdipoR1\textsuperscript{[71]}. Suppression of SREBP-1c by adiponectin is mediated through AdipoR1/LKB1, an upstream kinase of AMPK, and AMPK pathway\textsuperscript{[99]}. AMPK in addition phosphorylates acetyl-CoA carboxylase (ACC) and this is subsequently associated with a higher activity of carnitine palmitoyltransferase 1 (CPT-1), a rate limiting enzyme in fatty acid oxidation\textsuperscript{[98]}. Signalling via AdipoR2 enhances peroxisome-proliferator activated receptor α (PPARα) activity\textsuperscript{[78,99]}. PPARα up-regulates CPT-1, stimulates β-oxidation, reduces lipid synthesis and thereby prevents excess triglyceride storage\textsuperscript{[104]}.  

**ANTIINFLAMMATORY AND ANTIAPOP-TOTIC EFFECTS OF ADIPO-NECTIN**

Lipopolysaccharide (LPS) is involved in the pathogenesis
of NAFLD and elevated levels of circulating LPS are found in obesity[10,12]. Increased gut permeability and a higher prevalence of small intestinal bacterial overgrowth correlates with the severity of steatosis but not with NASH[8]. Besides age, inflammation was identified as an independent predictor of progression to advanced fibrosis in NASH patients[10]. Hepatic steatosis may be accompanied by inflammatory cell infiltrates composed of neutrophils and mononuclear cells. In several mouse models of immune mediated hepatitis, adiponectin reduces TNF and induces interleukin-10 (IL-10) release from Kupffer cells[109]. Adiponectin lowers CRP synthesis in cytokine stimulated rat hepatocytes, and an inverse correlation of systemic adiponectin and CRP has been identified in obese patients[108,109]. Adiponectin may exert its anti-inflammatory activity by lowering nuclear factor kappa B (NFκB) action in preactivated cells or by inducing tolerance to inflammatory stimuli by a rapid and transient activation of NFκB that subsequently renders the cells inert to further activation[108-111].

Nevertheless, in patients suffering from chronic inflammatory diseases like inflammatory bowel disease or type 1 diabetes that are not associated with adiposity elevated circulating adiponectin levels that even correlate with inflammatory markers are found[112-114], and an induction of inflammatory proteins and activation of NFκB by recombinant adiponectin is described in several studies[25,108,111,113]. Therefore, adiponectin seems to be regulated in the opposite direction in classic versus obesity-associated chronic inflammatory diseases and may even exert opposite activities in resting compared to activated cells[114].

NFκB promotes cell survival and NEMO-mediated NFκB activation in hepatocytes has an essential physiological function to prevent the spontaneous development of steatohepatitis and hepatocellular carcinoma[117]. Adiponectin activates NFκB in human hepatocytes, and thereby may prevent hepatocyte apoptosis. Adiponectin further upregulates the chemokine interleukin 8 (CXCL8) via AdipoR1 and NFκB dependent pathways in primary human hepatocytes[118]. CXCL8 is an antiapoptotic protein[119] and overexpression of the rodent CXCL8 homologous protein protects the liver from galactosamine and endotoxin induced damage[20].

Adiponectin further antagonizes hepatocyte death by blocking fatty acid-induced activation of c-Jun NH2 terminal kinase[120], by reducing TNF levels[105] and by inhibiting fatty acid mediated upregulation of CD95[122].

### ANTIOXIDATIVE EFFECTS OF ADIPONECTIN

Fatty liver is thought to represent the first incident towards the subsequent development of liver fibrosis[8]. Accelerated β-oxidation of fatty acids in hepatic steatosis is associated with excess reactive oxygen species (ROS), lipid peroxidation, the release of inflammatory cytokines, death of hepatocytes and activation of hepatic stellate cells[8]. ROS and lipid peroxidation are thought to contribute to the progression of liver injury partly by accelerating inflammation that in turn causes ROS production. Oxidative stress is enhanced in human hypoadiponectinemia and in adiponectin knock-out mice fed a choline-deficient L-amino acid deficient diet[123,124]. Hepatic cytochrome P450 2E1 (CYP2E1) is elevated in these animals and in human NASH and may contribute to higher ROS levels[125,126].

Aldehyde oxidase 1 (AOX1) is a xenobiotic metabolizing protein whose physiological role has not been evaluated in detail so far[127]. AOX1 activity has been identified as an important source of ROS[128] and is reduced in hepatocytes by adiponectin via activation of PPARα[129]. Adiponectin also increases ROS detoxifying enzymes and AdipoR2 is involved in the induction of superoxide dismutase 1 and catalase[129].

### ANTIFIBROTIC EFFECTS OF ADIPONECTIN

Liver injury causes activation of otherwise “quiescent” hepatic stellate cells (HSC) and activated cells proliferate, synthesize CTGF and extracellular matrix proteins[130]. TGF-β is the main profibrotic factor in fibrosis and induces CTGF synthesis. CTGF stimulates binding of TGF-β to its receptor and thereby enhances TGF-β activity[131]. CTGF is induced by TGF-β indicating an autocrine or paracrine loop that mutually enhances synthesis of both proteins[130]. Knock-down of AdipoR2 in mice fed a methionine-choline deficient diet to cause progressive fibrosing steatohepatitis is associated with higher levels of steatosis, inflammation and fibrosis[131]. Overexpression of AdipoR2 is protective, and this mechanistically includes inhibition of TGF-β signaling and stimulation of PPARγ activity[131].

Expression of recombinant adiponectin in activated HSC reduces proliferation and lowers α-smooth muscle actin that is induced in activated HSC[132]. Furthermore, apoptotic cell death of activated HSC is augmented[132]. Exogenously added recombinant adiponectin suppresses PDGF-stimulated HSC proliferation by activation of AMPK[133]. Adiponectin may also bind to growth factors like PDGF and thereby inhibits binding to their corresponding receptors[72]. Leptin is a well described profibrotic adipokine and several studies have shown that adiponectin antagonizes leptin bioactivity[134,135]. Adiponectin blocks leptin-induced STAT3 phosphorylation in activated HSC and leptin-mediated upregulation of TIMP-1 release and these in-vitro findings have been confirmed in-vivo[134].

### DIET, EXERCISE AND PHARMACOLOGICAL INTERVENTIONS

Studies analysing the impact of changes in life style and medications in NAFLD have been performed in small patient groups sometimes even lacking suitable controls. Currently weight loss and exercise are recommended as initial strategies to improve NASH[136]. Diet and diet in conjunction with exercise for 6 mo cause a similar reduction in body weight and intrahepatic fat[37]. In 19 sedentary obese

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Adiponectin has emerged as a protective adipokine in insulin resistance and obesity related liver diseases (Figure 3), and drugs that elevate systemic adiponectin may be useful as therapeutics for NAFLD. Adiponectin receptor signaling pathways and potential hepatic adiponectin resistance in NASH, however, have been poorly investigated so far. Identification of molecules downstream of AdipoR1/2 and strategies to enhance adiponectin receptor activity may constitute promising approaches towards treatment of NAFLD.

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