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## WJG 20<sup>th</sup> Anniversary Special Issues (12): Nonalcoholic fatty liver disease

# Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver disease

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endocrine organ with a key role in energy homeostasis, is responsive to both central and peripheral metabolic signals and is itself capable of secreting a number of proteins. These adipocyte-specific or enriched proteins, termed adipokines, have been shown to have a variety of local, peripheral, and central effects. In the current review, we explore the role of adipocytokines and proinflammatory cytokines in the pathogenesis of NAFLD. We particularly focus on adiponectin, leptin and ghrelin, with a brief mention of resistin, visfatin and retinol-binding protein 4 among adipokines, and tumor necrosis factor- $\alpha$ , interleukin (IL)-6, IL-1, and briefly IL-18 among proinflammatory cytokines. We update their role in NAFLD, as elucidated in experimental models and clinical practice.

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**Key words:** Nonalcoholic fatty liver disease; Cytokines; Adipokines; Adiponectin; Leptin; Tumor necrosis factor- $\alpha$ ; Interleukin-6; Interleukin-1; Interleukin-18; Ghrelin

## Abstract

Nonalcoholic fatty liver disease (NAFLD) is a condition in which excess fat accumulates in the liver of a patient with no history of alcohol abuse or other causes for secondary hepatic steatosis. The pathogenesis of NAFLD and nonalcoholic steatohepatitis (NASH) has not been fully elucidated. The "two-hit" hypothesis is probably a too simplified model to elaborate complex pathogenetic events occurring in patients with NASH. It should be better regarded as a multiple step process, with accumulation of liver fat being the first step, followed by the development of necroinflammation and fibrosis. Adipose tissue, which has emerged as an

**Core tip:** The pathogenesis of nonalcoholic fatty liver disease (NAFLD) is still not fully elucidated. We explored the role of the following adipocytokines and proinflammatory cytokines in the pathogenesis of NAFLD: adiponectin, leptin, ghrelin, resistin and visfatin among adipokines, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-6 and IL-1 among proinflammatory cytokines. Although a definite conclusion is complex, from analyzed data we could conclude that adiponectin, des-acyl ghrelin and leptin are adipokines that decrease, while TNF- $\alpha$  and IL-6 are cytokines that enhance insulin resistance and subsequently NAFLD. Acting on these premises, new therapeutic possibilities emerge; however, much work remains to be done.

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## INTRODUCTION

In nonalcoholic fatty liver disease (NAFLD) excess fat accumulates in the liver of a patient with no history of alcohol abuse or other causes for secondary hepatic steatosis<sup>[1]</sup>. NAFLD represents a complex spectrum of diseases, and is usually classified into nonalcoholic fatty liver (simple steatosis) and nonalcoholic steatohepatitis (NASH). Simple steatosis is characterized by the presence of steatosis without evidence of significant inflammation or fibrosis, while in NASH, steatosis is associated with hepatic inflammation that may be histologically indistinguishable from alcoholic steatohepatitis, and is often accompanied by progressive fibrosis. Long-standing NASH may progress to liver cirrhosis and is probably an important cause of cryptogenic cirrhosis; end-stage liver disease and hepatocellular carcinoma may be possible outcomes<sup>[2]</sup>.

NAFLD is regarded as a hepatic manifestation of metabolic syndrome (MS), and patients with NAFLD, particularly those with NASH, often have one or more components of the MS: obesity, hypertension, dyslipidemia and raised fasting plasma glucose levels or overt type 2 diabetes (T2DM).

The epidemiological data for NAFLD vary depending on the population and region studied, but estimated prevalence of NAFLD worldwide is around 20%, with 2%-3% of adults having NASH. It is the most common liver disorder in the Western industrialized countries, where the major risk factors for NAFLD are common. Clinical studies have revealed an increasing prevalence of NAFLD worldwide, and especially worrying data come from studies of children and adolescents where NAFLD is on the rise, together with obesity and MS, and such an early onset of the disease may provide more time for its deleterious evolution through the lifetime. The pathogenesis of NAFLD and NASH is still extensively researched. Although it is sometimes explained by a “two-hit” hypothesis, it should be better regarded as a multiple step process, with accumulation of liver fat being the first step, followed by the development of necroinflammation and fibrosis<sup>[3]</sup>.

Strong epidemiological, biochemical, and therapeutic evidence implicate insulin resistance (IR) as the primary pathophysiological derangement and the key mechanism leading to hepatic steatosis<sup>[4]</sup>. Insulin actions are altered in IR and MS, resulting in increased lipolysis and synthesis of free fatty acids (FFA) and decreased apolipoprotein B-100 in the liver.

Accumulation of triglycerides in the liver thus represents the primary insult or the “first hit” in the pathogenesis of NAFLD, but the progression of NASH requires the presence of additional pathophysiological abnormalities. The next step or the “second hit” is the result of reactive oxygen species (ROS) that increase oxidative stress within the hepatocytes, and by that mediate progression from steatosis to steatohepatitis and fibrosis. Also a “third hit” has been proposed, based on the fact that oxidative stress causes progressive cell death with diminished replication of mature hepatocytes and subsequent increased progenitor cell expansion, leading to progression of liver cirrhosis and hepatocellular carcinoma.

A number of recent reviews have pointed out the importance of gut microbiota, which is now considered also as a metabolic organ, in the pathogenesis of metabolic and inflammatory diseases such as obesity and T2DM<sup>[5-7]</sup>. Aron-Wisniewsky *et al.*<sup>[8]</sup> summarized the influence of gut microbiota in promoting NASH in five steps. Dysregulated microbiota promotes energy yield from food, as was observed in animal (obese animals had a greater capacity to extract and store energy in comparison with lean ones) and human studies (obese patients had increased Firmicutes and decreased Bacteroidetes compared with lean ones)<sup>[9]</sup>. Secondly, microbiota regulates gut permeability, participating in that way in the innate and adaptive immune responses as well as in contributing to low grade inflammation<sup>[10]</sup>. Gut permeability and bacterial overgrowth of the small intestine have been associated with the stage of steatosis and higher endotoxin levels as found in adults and children with NASH<sup>[11]</sup>. Another mechanism is the alteration of the choline metabolism. Namely, dysregulated microbiota produces enzymes that catalyze the breakdown of choline into toxic methylamines which can, through enterohepatic circulation, induce liver inflammation<sup>[12]</sup>. Furthermore, dietary saturated fats influence the composition of bile acid metabolism, which is not only important in the digestion and absorption of metabolites but also for antimicrobial activity, thus promoting dysbiosis<sup>[13]</sup>. Finally, patients with NASH had an increase of alcohol producing bacteria, such as *Escherichia*, which is important, since metabolites of endogenously produced alcohol can influence the production of ROS and subsequently cause liver inflammation<sup>[14]</sup>.

Factors that determine the presence and extent of necroinflammation are not yet well understood. Several possible mechanisms have been theorized, including host factors, such as defects in mitochondrial structure and function, altered expression of proinflammatory cytokines, impaired free oxygen radical scavenging, increased hepatic iron, and hepatotoxic byproducts of intestinal bacteria. The factors involved in hepatic fibrogenesis are slowly becoming understood. Activation of both lobular stellate cells and hepatic progenitor cells has been observed in NAFLD.

Most of the data on the pathophysiology and natural

course of the disease therefore come from animal studies. In the last few years, animal studies have yielded an impressive list of molecules associated with NAFLD and NASH pathogenesis. Animal models of NAFLD/NASH are classified into genetic models, nutritional models, and combined models of genetic and nutritional factors<sup>[15-17]</sup>. Numerous rodent models of NAFLD/NASH have been reported to date; however, no animal model completely reflects liver histopathology and pathophysiology of human NAFLD/NASH.

Adipose tissue, as an endocrine organ, participates in energy balance. Adipose tissue, in response to peripheral tissue and central brain signals, secretes various chemokines. These adipokines are characterized by a spectrum of local, peripheral, and central effects<sup>[18]</sup>. These chemokines activate macrophages, which release pro- and anti-inflammatory cytokines, and by this enhance inflammatory and suppress anti-inflammatory adipokines<sup>[19,20]</sup>. Obesity, which is often associated with IR, is therefore often seen as a chronic systemic low-grade inflammation, in which adipose tissue and its hormones have a central role<sup>[21-23]</sup>.

Here, we explore the role of adipocytokines and proinflammatory cytokines in the pathogenesis of NAFLD. We particularly focus on adiponectin, leptin and ghrelin, with a brief mention of resistin, visfatin and retinol-binding protein 4 (RBP4) among adipokines, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), IL-1, and briefly IL-18 among proinflammatory cytokines. We update their role in NAFLD, as elucidated in experimental models and clinical practice.

## ADIPOKINES AND NAFLD

Adipose tissue is, as mentioned earlier, not only a source of lipids, but also an endocrine organ, since it produces adipokines that have local, peripheral and central effects<sup>[24]</sup>. Although adipose tissue secretes the majority of adipokines, they are also produced by other organs, such as the gastrointestinal tract, and these other sources of adipokine production should not be disregarded. Thus, adipokines represent a heterogeneous group of mediators such as adiponectin, leptin, resistin, visfatin, ghrelin, and RBP4, but more than 50 others have been described so far.

## ADIPONECTIN AND NAFLD

In 1999 Arita *et al.*<sup>[25]</sup> isolated a product of the *apM1* gene, previously cloned by Maeda *et al.*<sup>[26]</sup>, a kind of soluble matrix protein, which they named adiponectin. Adiponectin circulates as several oligomeric isoforms in serum and isoform-specific effects have been described in the literature<sup>[27-29]</sup>. The three most common isoforms are: trimers (low molecular weight-LMW), hexamer (middle molecular weight-MMW) and oligomeric complexes (high molecular weight-HMW)<sup>[30]</sup>. In serum it can also exist as a proteolytic cleavage fragment of the full-length protein known as globular adiponectin<sup>[25,31]</sup>.

Two transmembrane proteins, AdipoR1 and AdipoR2, are identified as adiponectin receptors. Both receptors are mostly present in skeletal muscle and moderately expressed in the liver<sup>[32]</sup>. Although AdipoR2 is more abundant in the liver, AdipoR1 can be found in human hepatocytes, pointing out the important part played by both receptors in the pathogenesis of liver diseases<sup>[33]</sup>.

A great number of studies, reported in Table 1, have investigated in human, animal and *in vitro* models the pathogenesis and molecular mechanisms through which adiponectin influences obesity, IR, NAFLD and other components of MS. Plasma concentrations of adiponectin were found to be significantly lower in obese subjects (visceral fat predomination), although adiponectin is secreted only from adipose tissue<sup>[25,34-38]</sup>. Serum levels of adiponectin were reduced in T2DM and IR<sup>[39-44]</sup>, which was confirmed in animal studies as well as through various molecular mechanisms<sup>[45-47]</sup>. Certain genotypes of the adiponectin gene were associated with a higher risk for developing IR and T2DM<sup>[48,49]</sup>. *In vivo* studies showed that low serum levels of adiponectin were associated with MS, NAFLD and tumor formation<sup>[50-63]</sup>. *In vitro* and *in vivo* studies suggest that oligomeric complexes of adiponectin can modulate the biological actions of several growth factors by controlling their bioavailability at a pre-receptor level and that this effect might partly account for the anti-atherogenic, anti-angiogenic, and anti-proliferative functions<sup>[64-69]</sup>. However, not all mentioned studies concur regarding the level of adiponectin receptor and adiponectin itself, a phenomenon which could be explained by an adiponectin resistant state; more studies are needed to draw firm conclusions. There have been reports of adiponectin as a good predictor of the necroinflammatory grade and fibrosis in NAFLD through mechanisms which were clarified *in vitro*<sup>[70-73]</sup>. Regarding the treatment protocols with adiponectin, in humans a diet high in polyunsaturated fatty acids is recommended (it enhances adiponectin expression), but larger studies are needed to confirm the benefit of such therapy<sup>[74]</sup>. Different distribution of specific adiponectin isoforms and lower levels of HMW adiponectin were found in obese patients compared to normal weight individuals. This explains the metabolic complications related to obesity and T2DM, and in future, evaluation of adiponectin actions, specific isoforms should be taken in account<sup>[75-78]</sup>.

## LEPTIN AND NAFLD

Leptin is a peptide hormone secreted mainly by adipocytes of white adipose tissue (WAT). It is a product of the *ob* gene. Leptin modulates food intake, body fat composition, insulin activity, thermogenesis, angiogenesis, and the immune system<sup>[79]</sup>. It is considered an anorexigen hormone; in the brain it decreases food intake and increases energy expenditure. Leptin circulates in the plasma as a free adipokine, or bound to proteins. Leptin requires an interaction with a specific transmembrane



**Table 1** Studies and their findings on adiponectin

Study	Finding	Ref.
Human	Adiponectin levels reduced in obese individuals	[25,34,35]
	Adiponectin levels higher in women	[36]
	Adiponectin levels reduced in T2DM	[37]
	Hypoadiponectinemia associated with visceral fat accumulation	
	High concentrations of adiponectin correlated with a decreased risk of developing T2DM	[41-43]
	Adiponectin mRNA decreased in obese T2DM	[40]
	SNP +45T>G genotypes and lower adiponectin level associated with higher FBG, insulin levels and HOMA-IR in obese women	[48]
	SNPs: 3971 A/G (rs822396), +276 G/T (rs1501299), -4522 C/T (rs822393) and Y111H T/C (rs17366743) significantly associated with hypoadiponectinemia	[49]
	High adiponectin/leptin ratio associated with lower plasma triglyceride, HOMA-IR and higher HDL	[44]
	Lower adiponectin levels an independent risk factor for NAFLD	[51]
	In human liver biopsies, hepatic adiponectin receptor mRNAs increased in biopsy-proven NASH	[52]
	Similar levels of adiponectin receptor mRNA in normal, steatotic liver and NASH	[53,54]
	Reduced AdipoR2 protein in NASH compared to steatotic liver	[55]
	Adiponectin levels lower in NASH and correlated with the progression of the disease	[56,70-72]
	HMW adiponectin isoforms increased after biliopancreatic diversion in obese subjects	[77]
Animal	Adiponectin lowers gluconeogenesis in the liver, increases fatty acid oxidation in muscle and reduces IR	[45]
	Disruption of both adiponectin receptors (adipo R1 and R2) increased tissue triglyceride content, inflammation, oxidative stress and IR	[46]
	Adiponectin enhanced the progression of hepatic steatosis, fibrosis, and hepatic tumor formation in NASH	[57]
	Adiponectin prevents lipid accumulation by increasing $\beta$ -oxidation and by decreasing synthesis of FFA in hepatocytes in NASH	[47,58-60]
	Association of NAFLD and reduced expression of hepatic adiponectin receptors not consistently reported	[61,62]
	Peripheral injection of adiponectin resulted in reduction in body weight and improvement of peripheral IR	[47]
	Adiponectin reduced TNF- $\alpha$ and induced IL-10 release from Kupffer cells	[63]
	Pretreatment with adiponectin ameliorated D-galactosamine/LPS induced elevation of serum AST and ALT levels, and the apoptotic and necrotic changes in hepatocytes	[64]
<i>In vitro</i>	Adiponectin inhibited TNF- $\alpha$ induced expression of endothelial adhesion molecules and decreased LPS induced TNF- $\alpha$ production	[66]
	Adiponectin mediated anti-inflammatory activity by lowering NF $\kappa$ B action	[67]
	Adiponectin increased IL-8 and monocyte chemotactic protein-1 production, and activated the proinflammatory transcription factor NF $\kappa$ B	[68]
	Adiponectin acted antifibrotic through antagonizing leptin-induced STAT3 phosphorylation in activated hepatic stellate cell who promote fibrosis	[73]
	Lower HMW adiponectin closely associated with obesity-related metabolic complications and T2DM	[75]

T2DM: Type 2 diabetes mellitus; HOMA-IR: Homeostasis model assessment-estimated insulin resistance; FBG: Fasting blood glucose; HDL: High-density lipoprotein; NAFLD: Non-alcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; HMW: High-molecular weight; IR: Insulin resistance; FFA: Free fatty acids; TNF- $\alpha$ : Tumor necrosis factor alpha; IL-10: Interleukin-10; LPS: Lipopolysaccharide; NF- $\kappa$ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; IL-8: Interleukin-8; STAT-3: Signal transducer and activator of transcription 3.

receptor for its metabolic effect. Ob-R, which represents the leptin receptor, is a member of the class-1 cytokine receptor family. In lean individuals it is mostly bound to proteins, and in the obese it circulates in the free form<sup>[80,81]</sup>. The levels of leptin in adipose tissue and plasma are dependent on the amount of adipose tissue as well as the status of energy balance. Therefore, leptin levels are higher in obese individuals (central obesity) and increase with overfeeding<sup>[82-86]</sup>. Leptin downregulates transcription of the preproinsulin gene and insulin excretion, which could be connected with high leptin levels in IR<sup>[84,87]</sup>. Studies on a non-lipoatrophic diabetes population (human and animal models) lead to the conclusion that total absence of leptin leads to obesity. However, in non-lipoatrophic obese individuals, although total leptin levels are elevated, its action is not amplified due to the condition called leptin resistance (reduced sensitivity to the anorectic response to exogenous administered leptin), which has also been confirmed in animal studies<sup>[88-104]</sup>.

Women have higher circulating levels of leptin than men, which could be associated with a stimulating role of estrogen, or a suppressing role of androgens on leptin production, since studies<sup>[105-107]</sup> have demonstrated that higher leptin levels in women were independent of fat mass.

Certain inflammatory and infectious stimuli, such as IL-1, lipopolysaccharides (LPS) and TNF- $\alpha$ , can also increase leptin levels, which correlate with the level of inflammation. Levels of leptin are enhanced by pro-inflammatory cytokines and help to perpetuate the loop of chronic inflammation in obesity<sup>[108,109]</sup>.

IR and T2DM are correlated with higher leptin levels in plasma independently of adipose tissue<sup>[110,111]</sup> although not all studies concur<sup>[112]</sup>. Genetic polymorphism of the leptin receptor and leptin itself were investigated, and certain genotypes were associated with MS, IR and obesity in human and animal studies<sup>[113-115]</sup>.

Leptin seems to participate in both hits of NASH development (contributing to IR and steatosis as

**Table 2** Studies and their findings on leptin

Study	Finding	Ref.
Human	Leptin levels higher in obese individuals and increased with overfeeding	[82,83]
	Higher leptin levels in women independent of fat mass	[104-107]
	Body mass index and IR strongly correlated with leptin levels	[84]
	Central obesity correlated with higher leptin levels in comparison with non-central obesity	[86]
	Administration of leptin to individuals with lipoatrophic diabetes resulted in reduction of triacylglycerol concentrations, liver volume, glycated hemoglobin and discontinuation, or a large reduction in antidiabetes therapy	[89]
	Leptin inhibited insulin secretion and transcription of the preproinsulin gene	[87]
	IR associated with elevated plasma leptin levels independently of body fat	[110]
	Leptin/adiponectin ratio predicted T2DM in both sex	[111]
	Leptin C2549A AA genotype found at a higher rate in T2DM	[114]
	Leptin levels significantly higher in NASH, and correlated with the severity of hepatic steatosis, but not with the grade of necroinflammation or fibrosis	[116-118]
	Leptin not found as a predictor of histological severity of NASH	[119]
	No significant difference in leptin concentrations between NASH patients and controls, or in connection to the severity of liver fibrosis	[120,121]
	IR and low leptin levels predictors of steatosis in the liver	[122]
Animal	Mice lacking the <i>ob</i> gene became severely obese	[91]
	Leptin infusion attenuated hepatic steatosis and hyperinsulinemia	[92]
	Mice without leptin signaling had an increased lipid accumulation in liver	[93]
	Leptin prevented lipid accumulation in nonadipose tissue through SREBP-1 modulation	[94]
	After long-term exposure to high-fat diet (> 20 wk), mice resistant to leptin even when directly infused into the brain	[95-98]
	Hyperleptinemia itself contributed to leptin resistance by down regulating cellular response to leptin	[99]
	Mice with poly (ADP-ribose) polymerase-1 deficiency susceptible to diet-induced obesity, hyperleptinemia, and IR	[115]
	Leptin-deficient, insulin-resistant mice developed leptin resistance on a high fat diet independently of hyperleptinemia, c-Jun	[100]
	N-terminal kinase inflammatory pathway relevant in the induction of diet-induced glucose intolerance	
	Leptin increased expression of procollagen-I, transforming growth factor beta1, smooth muscle actin and TNF- $\alpha$ and thus increased liver fibrosis and inflammation	[101]
<i>In vitro</i>	Leptin-resistant mice exhibited significantly reduced fibrogenic response	[102,103]
	Fibrogenic effect of leptin accomplished through hepatic stellate cells, leptin a potent mitogen and apoptosis inhibitor	[23]

IR: Insulin resistance; T2DM: Type 2 diabetes mellitus; NASH: Nonalcoholic steatohepatitis; SREBP-1: Sterol regulatory element-binding protein 1; ADP-ribose: Adenosine diphosphate ribose.

mentioned earlier), and through the proinflammatory role in regulation of hepatic stellate cells (HSCs) in promoting liver fibrosis<sup>[24]</sup>. Leptin levels are increased in NASH patients and are related to the grade of hepatic steatosis<sup>[116-119]</sup>. In contrast, there have been studies that did not show a considerable discrepancy in leptin concentrations comparing patients with steatohepatitis and healthy subjects, or in connection to the severity of liver fibrosis<sup>[120-122]</sup>.

Regarding the reviewed studies, leptin levels correlate with obesity and steatosis, while it is still unclear how leptin is upregulated in NASH and how it contributes to fibrosis; locally produced leptin and/or leptin resistance may have a crucial role<sup>[123]</sup>. To facilitate the understanding of certain studies in different animal, human and *in vitro* models, findings of those studies together with references regarding the role of leptin are stated in Table 2. Larger studies with carefully matched controls are needed to draw further conclusions regarding the influence of leptin in NAFLD.

## GHRELIN AND NAFLD

Ghrelin is a peptide hormone that was discovered in 1999, and it acts as a ligand of the growth hormone secretagogue receptor (GHS-R) with a unique post-translational modification of the Ser3 residue. It is

produced by the stomach, pancreas and the large intestine<sup>[124]</sup>. Ghrelin has a part in appetite stimulation and control of body mass<sup>[125]</sup>. Ghrelin O-acyl transferase (GOAT) is the enzyme which acylates the ghrelin peptide to form acyl-ghrelin (AG)<sup>[126]</sup>. Recent studies have shown that des-acyl ghrelin (DAG) is no longer regarded as an inert product of AG. Ghrelin stimulates liver gluconeogenesis, and prevents suppression of glucose production by insulin; however, DAG inhibits liver glucose production<sup>[127]</sup>. Studies involving ghrelin role in NAFLD and other components of MS are reported in Table 3.

Studies have shown that obese individuals have lower concentrations of DAG than lean ones, while no difference was noticed in the concentrations of AG. It seems that obesity changes the concentration of DAG and AG with a relative AG excess or DAG deficiency which leads to obesity-associated IR in MS<sup>[128-130]</sup>.

After assessing the influence of ghrelin on insulin sensitivity, other groups of investigators concentrated on the potential role of ghrelin in NAFLD. IR is a major factor controlling ghrelin levels in subjects with NAFLD, but the correlation with the progression of the disease shows conflicting results since all studies did not take into consideration DAG and AG concentrations<sup>[54,131,132]</sup>.

Possible mechanisms through which ghrelin influences NAFLD progression were investigated *in vitro*, some

**Table 3** Studies and their findings on ghrelin

Study	Finding	Ref.
Human	AG and the AG/DAG ratios positively associated with HOMA-IR in obese children	[128]
	IR obese subjects had elevated AG/DAG ratio compared with non IR obese subjects because of decreased DAG and total ghrelin levels	[129]
	Obese patients with MS had lower total ghrelin and DAG, comparable AG and higher AG/DAG, AG/DAG ratio correlated with IR	[130]
	Ghrelin significantly correlated with HOMA-IR, but was reduced in NAFLD	[131]
	Ghrelin levels were higher in higher stages of fibrosis in morbidly obese patients with NAFLD	[132]
	Higher total ghrelin concentrations in patients with NASH in comparison with steatosis and normal liver	[54]
<i>In vitro</i>	Adipocytes after incubation with AG and DAG significantly increased PPAR $\gamma$ and SREBP-1 mRNA levels and accumulated lipids	[133]
	Ghrelin inhibited AMP-activated protein kinase activity, through which also influenced PPAR- $\gamma$ in liver and in adipose tissue	[134]
	Administration of ghrelin attenuated NAFLD-induced liver injury, oxidative stress, inflammation, and apoptosis partly through the action of serine/threonine kinase/AMPK and phosphoinositide 3-kinase/protein kinase B pathways in rats	[135]

AG: Acyl-ghrelin; DAG: Des-acyl ghrelin; IR: Insulin resistance; MS: Metabolic syndrome; HOMA-IR: Homeostasis model assessment-estimated insulin resistance; NAFLD: Non-alcoholic fatty liver disease; PPAR- $\gamma$ : Peroxisome proliferator-activated receptor gamma; SREBP-1: Sterol regulatory element-binding protein 1; AMP: Adenosine monophosphate.

taking into account AG and DAG respectively<sup>[133-135]</sup>. Summarizing these investigations, one can conclude that ghrelin has an important role in insulin sensitivity but its role in NAFLD has not yet been clarified. Further studies are needed, which should differentiate between the concentrations of DAG and AG.

## RESISTIN AND NAFLD

Resistin is an adipocyte-derived signaling polypeptide that was initially found to be upregulated in obesity and IR<sup>[136,137]</sup>. It has a scarce tissue distribution, with the highest levels in adipose tissues<sup>[138]</sup>. Resistin circulates in two states, the high-molecular-mass hexamer that has a higher concentration and the low-molecular-mass complex which is more bioactive<sup>[139]</sup>. Peripheral blood mononuclear cells are main producers of resistin<sup>[140]</sup>. Studies have conflicting results regarding the influence of resistin in glucose metabolism, obesity and IR. There are numerous studies that have connected obesity with higher circulating resistin levels compared to lean controls in human and animal studies with conflicting results<sup>[141-143]</sup>. The correlation between resistin, obesity, T2DM and IR also remains controversial<sup>[144-148]</sup>. In NAFLD, concentrations of resistin were higher than in controls and positively correlated with liver inflammation and fibrosis severity, but this was not consistent in all undertaken studies<sup>[118,149-151]</sup>. Findings of the previously mentioned studies are displayed in Table 4.

Data of *in vitro* studies concluded that resistin participates in the progression of inflammation<sup>[152]</sup>. Considering the connection between adipocytokines and inflammatory pathways, resistin may represent a link between MS and inflammation. Resistin and its role in the pathogenesis of NAFLD are still not sufficiently studied and new studies are needed.

## VISFATIN AND NAFLD

Visfatin is also a hormone whose plasma levels are associated with obesity, visceral fat, T2DM, as well as MS. Secretion of visfatin was enhanced by glucose

administration, and the glucose-derived rise of visfatin could be interrupted by co-administration of insulin or somatostatin<sup>[153]</sup>. Studies related to visfatin and its roles in metabolic processes are shown in Table 4. Plasma visfatin was higher in obese individuals, and those with T2DM and MS<sup>[154-156]</sup>. Some studies, however, did not confirm the previous association<sup>[157,158]</sup>. There are scarce data on the role of visfatin in NAFLD. Although the visfatin level was lower in NASH compared to NAFLD patients, a positive correlation with portal inflammation was found<sup>[159,160]</sup>.

## RETINOL-BINDING PROTEIN 4 AND NAFLD

RBP4 is predominately produced in visceral adipose tissue. Serum RBP4 concentration was elevated in insulin-resistant obese humans and in T2DM. It was found elevated in individuals who had a family history of T2DM and had normal glucose levels<sup>[161,162]</sup>. An association between increased RBP4 and MS was found, but other studies failed to detect the connection with single components of MS<sup>[163-171]</sup>.

RBP4 levels were found to be associated with the inflammatory response in obese individuals<sup>[168,172]</sup>. The role of RBP4 in the pathogenesis of NAFLD is not sufficiently elucidated. Circulating RBP4 levels were higher in subjects with advanced stages of NAFLD<sup>[173-175]</sup>. However, some studies differed in their results<sup>[176,177]</sup>. All mentioned studies and their results are reported in Table 4.

## PROINFLAMMATORY CYTOKINES AND NAFLD

Proinflammatory cytokine is a general term for those immunoregulatory cytokines that favor inflammation. They represent a heterogeneous group of molecules secreted by various cell types with numerous biological effects. They act as endogenous pyrogens, upregulate the synthesis of secondary mediators and other

**Table 4 Studies and their findings on resistin, visfatin and retinol binding protein 4**

Adipocytokines	Finding	Ref.
Resistin	Resistin levels increased in morbidly obese humans	[142]
	Resistin levels in T2DM patients 20% higher when compared to non-diabetic patients	[144]
	No correlation between resistin and components of MS on T2DM patients	[145]
	Resistin did not correlate with BMI but significantly correlated with IR	[146]
	G/G -180C>G homozygotes for resistin had significantly higher resistin mRNA levels in abdominal subcutaneous fat	[148]
	Serum resistin levels not associated with the presence of NASH	[149]
	Serum resistin levels higher in NAFLD than in controls and positively correlated with liver inflammation and fibrosis severity	[118,150]
	Resistin serum levels in NAFLD patients were associated with histological severity of the disease but not with IR	[151]
	Expression of resistin in human peripheral-blood mononuclear cells upregulated by TNF- $\alpha$ and IL-6	[152]
	Secretion of visfatin enhanced by glucose administration	[153]
Visfatin	Plasma visfatin elevated in patients with T2DM	[154]
	Visfatin plasma concentrations markedly elevated in obese subjects	[155]
	Bariatric surgery reduced body mass index, visfatin, leptin and increased adiponectin after 6 mo	
	Plasma visfatin levels elevated in subjects with MS	[156]
	Significantly higher visfatin mRNA in visceral fat of obese subjects compared with lean controls, and positively correlated with body mass index	[158]
	Visfatin level lower in NASH compared to NAFLD patients and healthy controls	[159]
	Visfatin level positively correlated with portal inflammation	[160]
	Serum RBP4 concentration elevated in IR, obese humans, T2DM and in subjects with a strong family history of T2DM	[161,162]
Retinol binding protein 4	Strong association of increased circulating RBP4 levels with IR and MS	[163-166]
	No connection of RBP4 with obesity, IR, or components of the MS	[167-171]
	RBP4 levels associated with inflammatory response in obese individuals	[168,172]
	Circulating RBP4 levels higher in subjects with NAFLD	[173]
	RBP4 liver expression higher in moderate/severe NASH compared to mild forms	
	RBP4 level a risk factor for fibrosis $\geq 2$ in NASH	[174]
	RBP4 and HOMA-IR independently associated with steatosis in patients with chronic hepatitis C	
	In NAFLD patients, serum RBP4 significantly lower compared with controls, did not correlate with IR	[175]
	RBP4 liver tissue expression enhanced in NAFLD patients and correlated with NAFLD histology	
	Serum RBP4 levels did not correlate with BMI, HOMA-IR, fasting blood glucose, or insulin levels in patients with simple steatosis and NASH	[176,177]
	Patients with cirrhosis and fibrosis had higher RBP4 compared to controls	

T2DM: Type 2 diabetes mellitus; MS: Metabolic syndrome; NASH: Nonalcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease; IR: Insulin resistance; TNF- $\alpha$ : Tumor necrosis factor alpha; IL-6: Interleukin 6; RBP4: Retinol binding protein 4; HOMA-IR: Homeostasis model assessment-estimated insulin resistance.

proinflammatory cytokines by both macrophages and mesenchymal cells, stimulate the production of acute phase proteins, or attract inflammatory cells. The major proinflammatory cytokines that have been studied in the pathogenesis of NAFLD include TNF- $\alpha$ , IL-6, IL-1 $\alpha$ , IL-1 $\beta$  and IL-18.

## TUMOR NECROSIS FACTOR ALPHA AND NAFLD

A balance between proinflammatory and anti-inflammatory cytokines seems to have a major role in systemic, local metabolic and inflammatory processes involved in the development of NAFLD and IR. TNF- $\alpha$  is the proinflammatory cytokine characterized by various biological effects including metabolic, inflammatory, proliferative but also necrotic, with enhanced expression in liver and adipose tissue thus making it an optimal causative agent for NAFLD. It is secreted by macrophages infiltrated in adipose tissue of obese models, by hepatocytes, Kupffer cells, and other cell types, as a response to chronic inflammatory activity.

This was confirmed in numerous studies in which increased expression of TNF- $\alpha$  was found in adipose tissue of diverse animal models of obesity, IR and T2DM suggesting TNF- $\alpha$  is a key link in obesity-induced IR<sup>[178,179]</sup>. Among all proinflammatory cytokines involved in the pathogenesis of obesity, IR and NAFLD, TNF- $\alpha$  is the most commonly investigated and characterized by conflicting results, because of heterogeneity in study populations, small sample sizes and factors that possibly interfere with serum TNF- $\alpha$  level detection. Human<sup>[180]</sup> and experimental studies in dietary-induced NAFLD models with or without genetic modulation resulting in its impaired signaling or neutralization with antibodies, implied that TNF- $\alpha$  had a role in development of every setting of NAFLD (liver steatosis, necrosis, apoptosis and fibrosis) as well as IR; this is shown in Table 5.

The complexity of TNF- $\alpha$  mechanisms of action has been extensively investigated. Once produced in adipose tissue, TNF- $\alpha$  causes impaired insulin-derived peripheral uptake of glucose by increasing serine phosphorylation of insulin receptor substrate 1 (IRS-1) and consequently inhibition of translocation of glucose transporter type 4



**Table 5 Studies and their findings on tumor necrosis factor alpha**

Study	Finding	Ref.
Human	Healthy subjects with highest serum TNF- $\alpha$ levels had significantly greater risk of developing NAFLD	[180]
	TNF- $\alpha$ infusion in healthy humans impaired insulin signaling <i>via</i> increased phosphorylation of p70 S6 kinase, extracellular signal-regulated kinase-1/2, c-Jun NH(2)-terminal kinase, and serine phosphorylation of IRS-1 as well as impaired phosphorylation of Akt substrate 160 thereby GLUT4 translocation and glucose uptake in skeletal muscle	[181]
	TNF- $\alpha$ gene polymorphism in the -238 A allele associated with susceptibility to NAFLD, correlated with IR and increased BMI in Chinese population	[202,203]
	TNF- $\alpha$ polymorphism at position 1031C and 863A in a Japanese population associated with NASH without significant difference between NAFLD patients and controls	[188]
	TNF- $\alpha$ and soluble TNFR2 plasma levels increased in NASH patients, independently of IR, compared to controls, but not among different stages of NAFLD	[187], [192]
	Serum TNF- $\alpha$ /TNFR1 increased in NASH patients as compared with other stages	[189]
	In obese NASH patients expression of liver and adipose TNF- $\alpha$ mRNA and its p55 receptor increased and correlated with advanced fibrosis	[190]
	In children serum TNF- $\alpha$ and leptin associated with a NAFLD activity score of 5 or more	[191]
	TNF- $\alpha$ mRNA cut-off of 100 ng/mL predicted NASH	[192]
	In morbidly obese NASH patients high TNF- $\alpha$ mRNA expression in liver correlated with plasma levels of LPS-binding protein	[200]
	Treatment with TNF- $\alpha$ inhibitor (pentoxifylline) for 6 mo reduced liver enzymes, serum TNF- $\alpha$ level and improved IR	[204]
	In NAFLD/NASH patients probiotic therapy decreased TNF- $\alpha$ levels	[208]
	Patients with MS with or without NAFLD treated with fish oil for 6 mo resulted in the reduction of oxidative stress and production of proinflammatory cytokines (TNF- $\alpha$ and IL-6)	[214]
Animal	Prolonged infusion of TNF- $\alpha$ in rats decreased ability of insulin to suppress hepatic gluconeogenesis and stimulate peripheral glucose utilization	[178]
	Obese mice with impaired TNF- $\alpha$ signaling protected from obesity-derived IR in peripheral tissues and had lower levels of circulating free fatty acids	[179]
	Mice deficient in both TNF- $\alpha$ receptors fed with MCD diet had attenuated liver steatosis, fibrosis and number of recruited Kupffer cells	[193]
	TNF- $\alpha$ administration induced tissue inhibitors of metalloproteinases 1 mRNA expression in activated HSC and suppressed their apoptosis	
	On MCD-diet induced NASH mice model NASH developed independently of TNF- $\alpha$ synthesis	[186]
	Fructose overfeeding in mice led to endotoxemia, increased TNF- $\alpha$ and liver steatosis that was reduced after treatment with antibiotics	[197]
	Mice lacking TNFR1 were resistant to fructose-induced steatosis (increased phospho AMPK and AKT levels, decreased SREBP-1 and FAS expression in the liver as well as RBP4 plasma levels)	[198]
	Dietary oleate reduced hepatic steatosis, inflammation, fibrosis and mRNA expression of TNF- $\alpha$ in MCD diet-induced NASH animal model	[216]
	TNF- $\alpha$ levels in liver were lower in dietary induced NASH animal model treated with glutamine	[217]
	$\alpha$ - and $\gamma$ -tocopherol protected against LPS-triggered NASH in an obese mouse model, by decreasing liver necroinflammatory activity, levels of TNF- $\alpha$ , without affecting body mass or hepatic steatosis	[219]
	Obese mice on a HFD treated with thalidomide (100 mg/kg per day for 10 d) showed improvements in insulin sensitivity, through restoration of the hepatic insulin IRS-1 and AKT phosphorylation, an improvement in hepatic steatosis was also noticed, which correlated with reduced TNF- $\alpha$ levels	[218]
	Statins (rosuvastatin and pioglitazone) in diet-induced NASH rat models decreased serum TNF- $\alpha$ level	[212,213]
	Treatment with anti-TNF antibodies in ob/ob mice fed with HFD improved liver steatosis, insulin sensitivity, and serum ALT levels	[209]
	Treatment of HFD-rat with monoclonal TNF- $\alpha$ antibody, infliximab, reduced proinflammatory markers (TNF- $\alpha$ , IL-6, IL-1 $\beta$ ), activity of JNK and IKK-B, SOCS-3 expression, and improved insulin signaling through JAK2/STAT-3 and IRS/AKT/FOXO1 pathway in the liver	[210]
	This all led to reduced IR, fat liver accumulation and inflammation	
<i>In vitro</i>	LPS derived TNF- $\alpha$ production enhanced expression of SREBP-1 mRNA leading to hepatic steatosis	[201]
	JNK2/- hepatocytes resistant to TNF- $\alpha$ induced apoptosis	[183]
	Tiazolidinediones reversed TNF- $\alpha$ induced IR	[211]
	Quercetin decreased TNF- $\alpha$ expression in oleic acid induced steatotic HepG2 cells	[215]

TNF- $\alpha$ : Tumor necrosis factor alpha; NAFLD: Non-alcoholic fatty liver disease; BMI: Body mass index; IRS-1: Insulin receptor substrate 1; GLUT4: Glucose transporter type 4; IR: Insulin resistance; NASH: Nonalcoholic steatohepatitis; TNFR1: Tumor necrosis factor receptor 1; IL-6: Interleukin 6; LPS: Lipopolysaccharide; HFD: High-fat diet; JNK: c-Jun N-terminal kinase; MS: Metabolic syndrome; MCD: Methionine and choline deficient diet; HSC: Hepatic stellate cells; TNFR2: Tumor-necrosis factor receptor 2; AMPK: AMP-activated protein kinase; SOCS-3: Suppressors of cytokine signaling-3; Akt: Protein kinase B; SREBP-1: Sterol regulatory element-binding protein 1; FAS: Fatty acid synthase; RBP4: Retinol binding protein 4; IKK-B: Inhibitor of nuclear factor kappa-B kinase subunit beta; STAT3: Signal transducer and activator of transcription 3.

(GLUT4) to the plasma membrane resulting in peripheral IR<sup>[181]</sup>. It also stimulates hormone sensitive lipase resulting

in increased serum FFA and their influx in the liver.

Lipid accumulation in the liver induces Bax (pro-

apoptotic Bcl-2 family member) translocation to lysosomes causing their destabilization and release of lysosomal cysteine protease cathepsin B, through activation of inhibitor of nuclear factor kappa-B kinase (IKK- $\beta$ ) in hepatocytes this activates nuclear factor-kappaB (NF $\kappa$ B), and enhances gene expression of proinflammatory cytokines including TNF- $\alpha$ <sup>[182]</sup>. Additional generators of TNF- $\alpha$  in the liver are Kupffer cells in response to bacterial endotoxins, mediated by toll-like receptors (TLR). In hepatocytes, TNF- $\alpha$  induces suppressors of cytokine signaling (SOCS) that leads to decreased insulin signaling, as well as to induction of sterol regulatory element-binding protein-1c (SREBP-1c) and thus to liver steatosis. By activation of cytosolic sphingomyelinase, TNF- $\alpha$  produces ceramide that activates several kinases resulting in impaired insulin signaling, but also increases ROS synthesis. ROS further enhance TNF- $\alpha$  production, which increases mitochondrial permeability, releases mitochondrial cytochrome c, and aggravates ROS formation, resulting in hepatocyte death. Although two different TNF- $\alpha$  receptors exist, tumor necrosis factor receptor 1 (TNFR1) and 2 (TNFR2), only TNFR1 is a mediator of hepatocyte apoptosis. Some of the proposed mechanisms involved in hepatocyte apoptosis are TNF-related apoptosis inducing ligand (TRAIL), Fas-mediated apoptosis *via* proteolytic caspase-8, and JNK2 pathway<sup>[183,184]</sup>.

All these biological effects of TNF- $\alpha$  result in evolution of NAFLD and are extensively investigated *in vivo* and *in vitro*, all in order to better understand the underlying insulin-mediated pathologic mechanisms, enabling new therapeutic strategies in NAFLD<sup>[185,186]</sup>. In humans it was shown that even healthy individuals with high basal TNF- $\alpha$  levels had significantly greater risk of developing NAFLD<sup>[180]</sup>. A great number of studies in adults and children revealed increased expression of TNF- $\alpha$  and its receptors in IR-derived NASH patients<sup>[180,187-192]</sup>. Although study results regarding the correlation of TNF- $\alpha$  with the progression of the disease are contradictory<sup>[187]</sup>, quite a number of newer animal and human studies state that TNF- $\alpha$  is a predictor of NASH and correlates with advanced stages<sup>[189-193]</sup>. Indeed, *in vitro* and in an over-nutritioned animal model that lacks both TNF- $\alpha$  receptors, it was shown that TNF- $\alpha$  produced by Kupffer cells enhanced expression of tissue inhibitor of metalloproteinase 1 (TIMP-1) mRNA in activated hepatic stellate cells and suppressed their apoptotic induction, thereby confirming its role in liver fibrosis<sup>[193]</sup>.

*In vitro* and *in vivo* studies have shown that fructose-induced NAFLD correlates with endotoxemia which leads to activation of hepatic Kupffer cells in the liver and subsequently TNF- $\alpha$  production<sup>[194-201]</sup>.

Genetic predisposition to NASH has lately been a matter of great interest; TNF- $\alpha$  polymorphism in certain populations was associated with susceptibility for NAFLD<sup>[188,202,203]</sup>.

Since numerous studies confirmed TNF- $\alpha$  involvement in the complex net that leads to development of NAFLD,

diverse therapeutic options were proposed. Pentoxifylline, a TNF- $\alpha$  inhibitor, was the most extensively studied. It was shown that patients with NASH, after treatment with pentoxifylline for 6 mo, had significantly reduced liver enzymes, serum TNF- $\alpha$  level and improved IR; after a year of treatment, additional improvements in steatosis, stage of fibrosis and lobular inflammation were noticed<sup>[204-207]</sup>. Furthermore, regarding the important role of microbiota in gut permeability and endotoxemia, therapeutical options with probiotics were also investigated and studies reported improved insulin sensitivity, liver histology, decreased TNF- $\alpha$ , total fatty acid content and serum ALT levels<sup>[208,209]</sup>. Treatment with the monoclonal TNF- $\alpha$  antibody, infliximab, reduced IR, hepatic fat accumulation and inflammation<sup>[210]</sup>. In experimental models of NASH, *in vivo* and *in vitro*, thiazolidinediones<sup>[211-213]</sup>, fish oil<sup>[214]</sup>, quercetin<sup>[215]</sup>, dietary oleate<sup>[216]</sup>, glutamine<sup>[217]</sup>, thalidomide<sup>[218]</sup> and  $\alpha$ - and  $\gamma$ -tocopherol<sup>[219]</sup> were therapeutic options that decreased proinflammatory activity, TNF- $\alpha$  among others, implying their possible benefit in NAFLD treatment.

Based on extensive literature from published studies, we can conclude that TNF- $\alpha$  is associated with IR, enhanced peripheral lipolysis, liver steatosis, inflammation, necrosis, apoptosis and fibrosis.

## INTERLEUKIN-6 AND NAFLD

IL-6 is a proinflammatory pleiotropic cytokine produced by adipocytes, hepatocytes, immune and endothelial cells<sup>[18]</sup>. Even though smaller in size, visceral adipocytes are superior cytokine generators compared to subcutaneous adipocytes and it was shown that obese and lean NAFLD patients can display a similar cytokine profile regarding IL-6. Endotoxemia in obesity, resulting from small intestinal bacterial overgrowth, stimulates macrophages through TLR receptors to produce TNF- $\alpha$  that possibly up-regulates IL-6 production from adipocytes and macrophages infiltrated in adipose tissue<sup>[220]</sup>. Hence, adipose tissue in obese subjects has an important role in enhancing low-grade chronic inflammation leading to IR and lipid accumulation in liver. Accumulated FFAs in hepatocytes activate IKK-B and NF- $\kappa$ B, a transcription factor that plays a central role in coordinating the expression of various proinflammatory cytokines, including IL-6<sup>[221]</sup>. The role of IL-6 in glucose metabolism, IR, NASH pathogenesis and disease progression was investigated in experimental models of steatosis and liver injury, as well as in NAFLD patients and the findings of these studies are reported in Table 6.

Its role in the pathogenesis of T2DM was confirmed in several human studies suggesting that even healthy women with higher basal levels of IL-6 have a significantly higher relative risk of developing T2DM<sup>[222-226]</sup>. Experimental models confirmed the role of IL-6 in this manner, but are characterized with conflicting findings regarding peripheral IR. *In*

**Table 6** Studies and their findings on interleukin-6

Study	Finding	Ref.
Human	Increased plasma IL-6 in T2DM	[222]
	Elevated basal IL-6 levels in healthy humans present high relative risk of developing T2DM	[224]
	Obese patients after bariatric surgery who lost weight had decreased IR and IL-6	[225]
		[226]
	IL-6 174C polymorphism associated with NASH and IR	[239]
	IL-6 levels higher in NAFLD patients, especially with advance stages, compared to ones with hepatitis B	[240]
	Increased serum IL-6 levels in biopsy proven NAFLD compared to controls	[241]
	No difference in IL-6 levels among T2DM patients with NASH/advanced fibrosis compared to those without NASH or light fibrosis	[242]
	No difference in serum IL-6 and its intrahepatic mRNA expression between NASH and steatosis	[243,244]
	In morbidly obese patients serum IL-6 levels correlated with progression of steatosis but in NASH declined	[245]
	IL-6 > 4.81 pg/mL predicted liver steatosis	
	Hepatocyte IL-6 expression positively correlated with degree of inflammation, stage of fibrosis and IR	[246]
	Increased circulating IL-6 and its soluble receptor in NASH patients compared with steatosis and healthy volunteers	[189]
	Normal IL-6 values exclude NASH	[247]
	IL-6, total cytokeratin-18 (M65) and adiponectin - a new panel for predicting NASH	[248]
	Decreased IL-6 levels after lifestyle changes and vitamin E administration	[249]
Animal	Chronic administration of IL-6 suppressed hepatic insulin signaling without effect on skeletal muscle	[231]
	Lep(ob) mice neutralized with IL-6 antibody showed increased insulin receptor signaling in the liver but not in peripheral tissues	[232]
	IL-6 decreases overall IR and hepatic inflammation	[233]
	Hepatoprotective and hepatoproliferative role of short-term exposure to IL-6 in ischaemic preconditioning models	[234]
	Treatment of IL-6-deficient mice acutely with IL-6 restored STAT3 binding and hepatocyte proliferation	[235]
	Chronic liver exposure to IL-6 led to cell death <i>via</i> Bax induction, activation of Fas agonist derived caspase-9 and cytochrome c release	[236]
	IL-6 showed inflammatory and antisteatotic effects in liver on mouse NASH model	[237]
<i>In vitro</i>	Hepatoprotective role of IL-6 by STAT3 activation in severe NASH model	[238]
	LPS through TLR receptors stimulated macrophages to produce TNF- $\alpha$ that up-regulated IL-6 production in adipocytes and macrophages	[220]
	IL-6 inhibited insulin-induced glycogenesis in hepatocytes	[227]
	IL-6 promoted IR in hepatocytes and HepG2 <i>via</i> decreased tyrosine phosphorylation of IRS-1, impaired association of the p85 subunit of phosphatidylinositol 3-kinase with IRS-1, inhibition of Akt and glycogen synthesis	[228]
	IL-6 impaired insulin signaling in 3T3-L1 adipocytes through inhibition of gene transcription of IRS-1, GLUT-4 and PPAR $\gamma$	[229]
	IL-6-dependent IR mediated by induction of SOCS-3 protein in HepG2 cells	[230]

IL-6: Interleukin 6; T2DM: Type 2 diabetes mellitus; IR: Insulin resistance; NASH: Nonalcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease; STAT3: Signal transducer and activator of transcription 3; LPS: Lipopolysaccharide; TLR: Toll-like receptor; IRS-1: Insulin receptor substrate 1; Akt: Protein kinase B; GLUT4: Glucose transporter type 4; PPAR- $\gamma$ : Peroxisome proliferator-activated receptor gamma.

*in vitro* studies showed that IL-6 promotes overall IR *via* several mechanisms<sup>[227-230]</sup>. However, in the majority of animal models this effect was only shown in hepatic IR<sup>[231-233]</sup>. The contribution of IL-6 signaling in obesity-induced inflammation also remains controversial because some studies have reported a hepatoprotective and hepatoproliferative role of short-term exposure to IL-6<sup>[234,235]</sup>. Since NAFLD is characterized by chronic necroinflammatory activity, results of short-term liver exposure to IL-6 are not entirely applicable. Chronic exposure to IL-6 led to liver injury, although there were studies that concluded it had a protective role against the progression of hepatic steatosis and paradoxically a hepatoprotective role in advanced stages of NAFLD<sup>[236-238]</sup>. Certain polymorphisms of the *IL-6* gene were associated with development of NAFLD<sup>[239]</sup>. When compared to other chronic liver diseases, such as chronic hepatitis B, IL-6 levels were significantly higher among NAFLD patients, especially with advanced histopathology findings<sup>[240]</sup>. Although numerous human studies have shown a correlation between IL-6 levels and NAFLD, data concerning its relationship with stages of the disease are contradictory<sup>[189,241-247]</sup>. IL-6 as a single noninvasive marker for predicting the presence of NASH is not sufficient, therefore pathophysiological-based non-

invasive panels of serological biomarkers are intensively investigated. A combination of IL-6, total cytokeratin-18 (M65 - a marker of necrosis and apoptosis) and adiponectin gave a good predictive value<sup>[248]</sup>. Several therapeutic options, including vitamin E and dietary quercetin showed a significant decrease in IL-6 levels in NAFLD subjects<sup>[249,250]</sup>. Tocilizumab, a humanized IL-6 receptor antibody, is yet to be investigated as a therapeutic choice in this manner<sup>[251]</sup>.

In conclusion, IL-6 is a proinflammatory cytokine associated with the development of IR, but its exact role in the pathogenesis of NAFLD is still waiting to be determined.

## INTERLEUKIN-1 AND NAFLD

IL-1 family cytokine members are produced by macrophages, endothelial cells and fibroblasts. IL-1 family members can be divided into potentially proinflammatory cytokines such as IL-1 $\beta$  or IL-18, and into antiinflammatory cytokines such as IL-1Ra<sup>[252,253]</sup>. IL-1 $\alpha$ , acutely administered *in vitro*, transiently causes IR, promotes inflammation and liver fibrosis<sup>[254]</sup>. IL-1 $\alpha$  and IL-1 $\beta$  were shown to have a role in the transformation of steatosis to steatohepatitis and liver fibrosis<sup>[255]</sup>.

**Table 7 Studies and their findings on interleukin-1 $\alpha$ , interleukin-1 $\beta$ , interleukin-1Ra and interleukin-18**

Cytokines	Finding	Ref.
IL-1 $\alpha$	Acute treatment of 3T3-L1 adipocytes with IL-1 $\alpha$ led to transient IR at IRS-1 level, mediated by its serine phosphorylation	[254]
IL-1 $\beta$		
Human	Weight loss in severely obese patients led to decreased IL-1 $\beta$ in subcutaneous adipose tissue and in liver without effect on adipose IL-1 $\alpha$	[253]
	IL-1 $\beta$ was significantly higher in subcutaneous/visceral adipose tissue than in liver	
	IL-1 $\beta$ genetic variants in Japanese population associated with NASH	[259]
Animal	Hepatic IL-1 $\alpha$ and IL-1 $\beta$ increased in NASH animal models	[255]
	Mice deficient in either cytokine not prone to NASH and fibrosis development	
	In experimental models TLR2 and palmitic acid activated inflammasome in Kupffer cells and produced IL-1 $\alpha$ and IL-1 $\beta$	[257]
	IL-1 $\beta$ /ApoE-deficient mice had less pronounced atherosclerosis	[262]
	Treatment with an IL-1 $\beta$ antibody improved glycemic control and $\beta$ cell function in diet-induced obese mice	[263]
	Animal NASH model showed increased macrophage infiltration in adipose tissue as well as in liver accompanied with increased expression of IL-1 $\beta$	[264]
	Hepatic steatosis partially mediated by Kupffer cells that produced IL-1 $\beta$ which suppressed PPAR- $\alpha$	[266]
	In diet induced NASH mice probiotics decreased hepatic IL-1 $\beta$ mRNA	[268]
<i>In vitro</i>	IL-1 $\beta$ inhibited insulin-induced phosphorylation of the insulin receptor beta subunit, IRS1, protein kinase B and extracellular regulated kinase 1/2 in murine and human adipocytes that lead to IR and inhibition of lipogenesis	[260]
	IL-1 $\beta$ decreased adiponectin	
	IL-1 $\beta$ promoted hepatic fibrosis by upregulating TIMMP-1 in rat HSC mediated by p38 mitogen-activated protein kinases and JNK	[267]
IL-1Ra	IL-1Ra decreased glucose uptake in muscle and was upregulated in WAT of diet-induce obese mice	[270]
	Atherogenic diet in IL-1Ra deficient mice caused severe liver steatosis, inflammation and portal fibrosis	[272]
IL-18	In obese women IL-18 positively correlated with body weight and visceral fat	[275]
	In T2DM patients and non-diabetic controls IL-18 plasma levels positively correlated with HOMA-IR	[276]
	In male patients with NAFLD, IL-18 alone in the absence of metabolic risks cannot contribute to evolution of NAFLD	[278]
	IL-18 enhanced cytokine production by stimulating TNF- $\alpha$ synthesis in immune cells	[279]
	IL-18 administrated with IL-12 induced mouse fatty liver in an IFN- $\gamma$ dependent manner	[280]
	Rosiglitazone in NAFLD rat model reduced IL-18 and caspase-1 in liver as well as improved histology	[277]

IL-1 $\alpha$ : Interleukin 1 alfa; IR: Insulin resistance; IRS-1: Insulin receptor substrate 1; IL-1 $\beta$ : Interleukin 1 beta; IL-18: Interleukin 18; NASH: Nonalcoholic steatohepatitis; TLR2: Toll-like receptor 2; PPAR- $\alpha$ : Peroxisome proliferator-activated receptor alfa; TIMMP-1: Tissue inhibitor of matrix metalloproteinase-1; HSC: Hepatic stellate cells; JNK: c-Jun N-terminal kinases; WAT: White adipose tissue; T2DM: Type 2 diabetes mellitus; HOMA-IR: Homeostasis model assessment-estimated insulin resistance; NAFLD: Non-alcoholic fatty liver disease; TNF- $\alpha$ : Tumor necrosis factor alpha; IL-12: Interleukin 12; IFN $\gamma$ : Interferon gamma.

IL-1 $\beta$  is a member of the IL-1 family most commonly investigated in the pathogenesis of NAFLD. Major generators of IL-1 $\beta$  are Kupffer cells and macrophages in which FoxO1, through NF- $\kappa$ B, induces its production<sup>[256]</sup>. LPS, saturated fatty acids, and others, induce production of pro-IL-1 $\beta$  through TLR in Kupffer cells, which is cleaved by caspase-1 to a mature biologically active form<sup>[257,258]</sup>. *In vivo* and *in vitro*, it was shown that IL-1 $\beta$  in many ways contributes to development of IR-derived NAFLD<sup>[259-261]</sup>. Inhibition of IL-1 $\beta$  decreases the severity of atherosclerosis and hyperglycemia in diet-induced obesity<sup>[262,263]</sup>. IL-1 serum levels were significantly higher among NAFLD patients compared to other chronic liver diseases, with remarkably high levels in advanced stage of fibrosis<sup>[240]</sup>. In experimental models it was shown that IL-1 $\beta$  promotes liver steatosis and fibrosis<sup>[264-267]</sup>. Several treatment options for NAFLD, mediated through reduction of IL-1 $\beta$  action, were investigated<sup>[268]</sup>. The previously mentioned studies that investigated IL-1 actions are displayed in Table 7.

## INTERLEUKIN-1 RECEPTOR ANTAGONIST AND NAFLD

IL-1Ra binds to IL-1 receptor competitively with IL-1 $\alpha$  and IL-1 $\beta$ , thus blocking their activity. It has been shown

*in vivo* and *in vitro* that IL-1 $\beta$  and IL-6 increase its plasma levels<sup>[269]</sup>. IL-1Ra is overexpressed in serum and WAT of obese patients and animal models, where it correlates with BMI and IR<sup>[270]</sup>. A correlation was found between IL-1Ra and the degree of hepatic lobular inflammation, while animal studies suggested that IL-1Ra may have a protective role against NAFLD development<sup>[271,272]</sup>.

## INTERLEUKIN-18 AND NAFLD

IL-18, previously called interferon- $\gamma$  inducing factor, with structural properties of the IL-1 family, is primarily synthesized as a precursor protein, pro-IL-18, which requires activation by caspase-1 cleavage into a bioactive mature form<sup>[273]</sup>. Produced by macrophages, Kupffer cells and endothelial cells, it induces production of chemokines, adhesion molecules and proinflammatory cytokines. IL-18 binding protein, an inhibitor that binds on the same receptor as IL-18, enhances its negative feedback mechanism enabling cell protection from accelerated proinflammatory activity such as NASH.

Early studies showed a positive correlation of IL-18 with IR and obesity, but a reduction in plasma IL-18 was influenced only by changes in IR<sup>[274-277]</sup>. In NAFLD, higher levels of IL-18 and caspase-1 were found when compared to controls if components of MS



were present<sup>[274,277,278]</sup>. Several possible mechanisms of IL-18 involvement in NAFLD were investigated<sup>[279,280]</sup>. Rosiglitazone treatment of NAFLD was investigated because of its inhibitory effect on hepatic IL-18 production<sup>[277]</sup>. Li *et al.*<sup>[281]</sup> has shown that IL-18 itself, as well as its ratio with IL-18 binding protein, was significantly higher in a NAFLD group as compared to controls, implying that IL-18 binding protein should be included in future studies.

In conclusion, IL-18 could be involved in the development of IR-derived NAFLD and exact mechanisms are still waiting to be elucidated. Studies on IL-18 that were mentioned in this review are reported in Table 7.

## CONCLUSION

The pathogenesis of NAFLD is still an unfinished book that needs further experimental and clinical research to fulfill all the pages. On the basis of previous and recent published data, key characters could be proinflammatory cytokines and chemokines that are products of adipose tissue, namely inflammatory cells infiltrating the adipose tissue. Although a definite conclusion on the effect of cytokines described in this review is a highly complex one, we could summarize that adiponectin, des-acyl ghrelin and leptin are adipokines that decrease, while TNF- $\alpha$  and IL-6 are cytokines that enhance IR and subsequently NAFLD. Acting on these premises, new therapeutic possibilities emerge; however, much of the work remains to be done, especially on identifying selective targets for future treatment.

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