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Association of Adipokines with Development and Progression of Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease affecting 30% of the general population and 40% to 70% of obese individuals. Adipose tissue plays a crucial role in its pathogenesis, as it produces and secretes pro- and anti-inflammatory cytokines called adipokines. Adiponectin and leptin have well-determined actions in terms of NAFLD pathophysiology. Adiponectin deficiency is associated with a pro-inflammatory condition, as it is observed in obesity and other metabolic disorders. On the other hand, increased leptin levels, above the normal levels, act as a pro-inflammatory stimulus. Regarding other adipokines (resistin, visfatin, chemerin, retinol-binding protein 4, irisin), data about their contribution to NAFLD pathogenesis and progression are inconclusive. In addition, pharmacological agents like thiazolidinediones (pioglitazone and rosiglitazone), that are used in the management of NAFLD exert favourable effects on adipokine levels, which in turn may contribute to the improvement of liver function. This review summarizes the current knowledge and developments in the association between adipokines and NAFLD and discusses possible therapeutic implications targeting the modulation of adipokine levels as a potential tool for the treatment of NAFLD.

Keywords: Non-alcoholic fatty liver disease; Adipokines; Adiponectin; Leptin; Resistin; Nicotinamide phosphoribosyltra; Chemerin; Retinol-binding protein 4

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), a chronic liver disease affecting 30% of the general population and 40% to 70% of obese individuals [1,2], is considered the hepatic manifestation of metabolic syndrome [3-6] and its prevalence increases continuously and concurrently with obesity and type 2 diabetes mellitus (T2DM) [7-10]. NAFLD is defined as the accumulation of excessive fat in the liver of patients without history of alcohol abuse or other causes of hepatic steatosis. NAFLD comprises a wide spectrum of diseases ranging from simple steatosis (SS) (i.e., fat accumulation in the liver) to nonalcoholic steatohepatitis (NASH), in which steatosis is combined with inflammation and fibrosis [11]. NAFLD can also progress to cirrhosis and is associated with increased risk for the development of hepatocellular carcinoma [12,13].

The pathogenesis of NAFLD is multifactorial. Factors like dietary elements (e.g., high fructose and fat intake) [14], insulin resistance (IR), inflammation, lipotoxicity [10,15], genetic predisposition and increased gut-derived microbial components

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[16] are supposed to contribute to the development and progression of the disease [11,17]. The liver closely interacts with adipose tissue [18], which is not only an energy-storage organ but also an endocrine organ secreting polypeptides called adipokines [19]. A growing body of literature demonstrates that adipokines are involved in various processes, such as inflammation, immunity, insulin sensitivity, simple liver steatosis, and NASH [10]. This review accumulates knowledge obtained by recent advances in the field of adipokines in relation to NAFLD (Table 1).

ADIPONECTIN

Adiponectin is an adipose tissue-expressed hormone which improves hepatic and peripheral IR and has anti-inflammatory and hepatoprotective activities [20]. The anti-inflammatory effects are achieved through blocking the activation of nuclear factor κB, by stimulating the secretion of anti-inflammatory cytokines such as interleukin-10 (IL-10) and IL-1 receptor antagonist and by suppressing the release of pro-inflammatory cytokines such as the tumor necrosis factor α (TNF-α), IL-6, and interferon-γ. Adiponectin peptide is detected in the circulation in various isoforms, such as trimers (low-molecular weight), hexamers (middle molecular weight), and 18-mers (high-molecular weight [HMW]). HMW is responsible for most of the metabolic actions of this hormone [21]. Adiponectin is involved in the AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor α (PPARα) pathway [21] and it acts through two receptors (AdipoR1 and AdipoR2) [22]. Genetic deletion of them in mice resulted in metabolic dysfunction [23]. Moreover, adiponectin deficient mice showed high levels of TNF-α mRNA expression in adipose tissue and high TNF-α protein concentrations in the circulation [24]. In contrast to other adipokines, adiponectin serum levels paradoxically decrease with the onset of obesity while weight loss induces adiponectin production [25]. It is noteworthy that transgenic mice, which were morbidly obese (MO), had increased levels of circulating full-length adiponectin and showed a constriction in systemic inflammation and an improved metabolic profile [26]. Treatment with adiponectin reduces body weight and blood glucose levels in obese mice fed a high fat diet [27,28]. This is achieved by improving insulin sensitivity [27], increasing fat oxidation and regulating inflammatory response mainly through innate rather than adaptive immune system mechanisms [28].

In humans, circulating blood levels of adiponectin are markedly diminished in visceral obesity and states of IR, such as NASH or T2DM [29]. A meta-analysis of 27 cross-sectional studies by Polyzos et al. [30] including 2,243 individuals (1,545 patients with NAFLD and 698 controls) demonstrated that pass-

Table 1. Circulating Levels of Adipokines in Individuals with Insulin Resistance or with Specific Histological Lesions of Nonalcoholic Fatty Liver Disease (i.e., SS, Hepatic Inflammation, Hepatic Fibrosis)[a]

Adipokine	Insulin resistance	SS	Hepatic inflammation	Hepatic fibrosis	Level of evidence
Adiponectin	Decreased [30]	Decreased [30]	Decreased [30]	Decreased compared both to controls and to SS [30]	Meta-analysis
Leptin	Increased [51]	Increased [51]	Increased [51]	Increased compared both to controls and to SS [51]	Meta-analysis
Resistin	Increased [56]	Increased [63] or similar [64]	Increased [63] or similar [64] compared to controls	Increased or similar compared to controls [63,64] or SS [65,66]	Observational studies
Visfatin	Controversial [72]	Increased [75] or similar [73,74]	Increased [75] or similar [73,74]	Increased or similar compared to controls [73-75] or SS [76]	Observational studies
Chemerin	Increased [80]	Increased [85]	Increased [85]	Increased [85] or similar [84] compared to controls or SS	Observational studies
RBP-4	Increased [89]	Increased [93]	Increased [93]	Increased [93] compared to controls Similar [93] or lower [94] compared to SS	Observational studies
Irisin	Increased [99]	Increased [95]	Increased [95]	Increased compared to controls [95] or SS [104,105]	Observational studies

SS, simple steatosis; RBP-4, retinol-binding protein 4.
[a]Compared to healthy controls unless otherwise stated.

ing from SS to NASH, a further decrease in circulating adiponectin levels is observed. However in later stages, when NASH progresses to cirrhosis, adiponectin levels increase [31]. Two possible mechanisms have been suggested for this elevation in adiponectin levels in cirrhosis: the impaired hepatic clearance of adiponectin and a redeeming increase towards the exaggerated release of proinflammatory cytokines in cirrhosis [32]. It is also interesting that adiponectin levels increase in the late stage of NASH and of cirrhosis of any cause and are significantly associated with hepatic fat loss, independent of metabolic or liver dysfunction [33]. Finally, it has been suggested that HMW rather than total adiponectin is positively associated with the degree of liver steatosis [34].

Several prospective studies have investigated how adiponectin levels change in NAFLD with the course of the disease. A 3-year prospective study including 52 patients with biopsy-proven NAFLD and paired biopsies at month 36 showed that the changes in adiponectin levels from baseline to month 36 were not related to progression of liver fibrosis in these patients [35]. In contrast, a 7-year prospective study (n=213) with NAFLD diagnosis based on metabolic parameters and ultrasonographic findings demonstrated that baseline adiponectin was lower among individuals without NAFLD at baseline who developed the disease in the next 7 years of follow-up compared with these individuals who remained NAFLD free. Nevertheless, this finding could still not accurately predict NAFLD incidence [36]. In addition, three single nucleotide polymorphisms (SNPs) of adiponectin gene (rs2241767, rs1501299, rs3774261) have been suggested to increase NAFLD progression [37]. However, it was not examined whether these SNPs lead also to reduce circulating levels of adiponectin. Therefore, further studies are needed to identify the role of both various isoforms and polymorphisms of adiponectin gene.

There are several potential confounding factors that are related to the serum concentrations of adiponectin and may also explain some discrepancies between different studies. For example, the investigators of the Western Australian Pregnancy Cohort (Raine) Study (www.rainestudy.org.au) observed after a cross-sectional evaluation of 1,170 adolescents in Australia that men had lower adiponectin levels compared to women [38]. Furthermore, a recent study showed that lean patients with NAFLD have lower adiponectin concentrations compared to lean healthy subjects [39].

Lifestyle interventions consisting of healthy eating habits and physical exercise seem to increase adiponectin levels [40]. In a study which enrolled one hundred obese patients with NASH, it was demonstrated that the patients who received moderate aerobic exercise training in addition to diet regimen increased their adiponectin levels by approximately 40% [41] and improved noninvasive markers of hepatic function, such as alanine transaminase (ALT) and aspartate aminotransferase (AST) [42]. Moreover, it has been suggested that weight loss (>10%) elevates adiponectin [20]. Also, it has been shown that PPARγ agonists lead to an increase in circulating adiponectin in parallel with histological improvements in NASH patients [43]. Specifically, a sub-study of the DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) Trial included 190 participants with T2DM who underwent abdominal computed tomography and dual-energy X-ray absorptiometry scans. Subjects receiving rosiglitazone for 3.5 years, after adjusting for total fat, had increased adiponectin 15 μg/mL compared to placebo (0.4 μg/mL). Moreover, rosiglitazone's effect on fat distribution was dependent from changes in adiponectin [44]. Furthermore, 1-year metformin treatment decreased ALT and AST levels while serum adiponectin levels tended to increase in patients with NAFLD [45]. However, there are no interventional studies investigating improvement of NAFLD by altering of adiponectin levels.

LEPTIN

Leptin is expressed principally in adipose tissue and it is involved in the regulation of energy homeostasis, neuroendocrine function (i.e., appetite and hypothalamic-pituitary hormonal axes), hematopoiesis and angiogenesis [41,46]. Leptin levels reflect the amount of fat stored in adipose tissue. Additionally, leptin has proinflammatory functions and prevents lipid accumulation in non-adipose tissues [47].

In the liver, leptin acts through its receptor (leptin receptor type b [LEPRb]) and decreases the expression of sterol regulatory element-binding transcription factor 1 (SREBP-1) [48]. SREBP-1 regulates genes required for glucose metabolism, fatty acid, and lipid production [49]. Leptin has also a key-role in hepatic fibrogenesis [50] by up-regulating the expression of transforming growth factor β1, leading to activation of stellate cells; thereby, augmenting the fibrogenic response in the liver.

In humans, in a meta-analysis of 33 studies which included 2,612 individuals (775 controls and 1,837 NAFLD patients) [51], patients with SS and patients with NASH had higher circulating leptin levels compared to controls and elevated leptin concentrations were associated with increased severity of the disease. Similarly, in a 3-year prospective study with paired bi-

opsies it was demonstrated that patients with stable or improved disease status had a higher reduction of circulating leptin (–5.8 ng/mL), compared to those with disease progress (–2.2 ng/mL). Nevertheless, the multivariate analysis revealed that only the increase in body mass index (BMI) remained as an independent factor associated with disease progression [35]. In another 7-year prospective study, subjects without NAFLD at baseline that developed though NAFLD in the next 7 years had higher baseline leptin concentrations compared with those who remained free of disease [36]. Furthermore, it has been suggested that polymorphisms like LEPR Q223R lead to a predisposition for NAFLD and coronary atherosclerosis [52].

An interventional study which demonstrated the beneficial effect of combined low dose of spironolactone plus vitamin E in patients with NAFLD did not report a significant decrease of leptin levels in the group which received the regimen [53]. Similarly, another study with rosiglitazone treatment in patients with NAFLD showed that the significant improvement in liver function was not accompanied by significant changes in plasma leptin levels [54].

Collectively and based on the current findings, both adiponectin and leptin seem to be related with NAFLD development and progression. Interventional studies with these molecules and/or their antagonists may help therefore to clarify their role in NAFLD and evaluate their potential use as treatments of the more advanced levels of the disease, i.e., NASH with/without fibrosis.

RESISTIN

Resistin is produced by adipose tissue, inflammatory cells, such as macrophages and monocytes, and hepatic stellate cells [55]. The liver seems to be the major target organ of resistin and hyperresistinemia results in increased glucose secretion and hepatic IR [56]. Administration of recombinant resistin in normal mice impairs glucose tolerance and induces IR, whereas dispensing anti-resistin antibody improves insulin sensitivity in a mice model of diet-induced obesity [57]. Resistin is also expressed in the liver, where its production seems to increase with increasing liver damage [55,58]. This peptide decreases the expression of hepatic gluconeogenic enzymes and thus, mice lacking resistin exhibit low glucose levels after fasting due to restricted hepatic glucose production [59].

Although the role of resistin and its association with IR and metabolic dysregulation is adequately recorded in animals, its pathophysiological role in human diseases is unclear, with some studies even reporting no association of resistin with obesity or IR [60]. Nevertheless, it has been suggested that it exerts proinflammatory effects and provokes the release of many cytokines involved in inflammatory processes, such as TNF-α, IL-1β, IL-6, and IL-12 [61,62].

Regarding the association of circulating resistin levels in humans with NAFLD, the studies provided contradictory results so far. Some of them suggested that SS or NASH patients have higher serum resistin levels than controls [63]. However, others did not find any difference between the resistin levels in subjects with SS, NASH or healthy controls [64]. As for the comparison between the levels in NASH and SS, some authors showed higher circulating resistin levels in NASH compared to SS patients [65] and some others reported similar levels [66]. In addition, the 7-year prospective study by Musso et al. [67] demonstrated that resistin levels were not associated with the development and progression of NAFLD. Altogether from 12 studies investigating the association between resistin and liver histological parameters in NAFLD, only six reported significant differences. Among them, the strongest association was with the grade of steatosis and then with portal information [68] Finally, in a recent evaluation of plasma biomarkers in a large well characterized biopsy proven NAFLD population (n=648) by the NASH Clinical Research Network, resistin levels were similar between patients with a definite diagnosis of NASH vs borderline cases and healthy subjects, but were higher in patients with fibrosis stages 2 to 4 versus 0 to 1 (odds ratio, 1.12) [69]. These findings confirm previous results from smaller observational studies, that reported higher resistin levels in patients with histology proven NAFLD and advanced fibrosis [70].

Collectively, current findings show that resistin cannot be reliable used for the differentiation between SS and NASH, but its levels may have diagnostic value for differentiating between different fibrosis stages.

VISFATIN

Visfatin is also called pre-B cell colony-enhancing factor and it is a proinflammatory cytokine that stimulates the secretion of other cytokines such as TNF-α and IL-6. Also, visfatin exerts intracellular activity since it is a key enzyme in nicotinamide adenine dinucleotide production [71]. It has been suggested, that visfatin may be involved in the development of NAFLD by regulating hepatic inflammation as well as glucose homeostasis and IR [72].

Several studies have investigated associations of circulating

and adipose-tissue expressed visfatin with histological parameters of NAFLD, reporting though contradictory results. Most studies showed that there is no difference in serum visfatin levels between SS, NASH patients and controls [73,74]. On the other hand, some authors found higher visfatin levels in NAFLD patients than controls [75] and some reported increased levels with steatosis grade above 33% [70]. Additionally, in a case-control study the levels of visfatin, IL-8, and TNF-α were positively correlated with the presence of NASH [76]. Another group indicated that hepatic expression of this peptide was not associated with liver steatosis and inflammation but was positively associated with the fibrosis stage [77]. In contrast, Aller et al. [78] showed that serum visfatin levels are related to portal inflammation and not to steatosis or fibrosis. In another study including 95 MO women who underwent bariatric surgery and 38 normal weight women, circulating visfatin levels as well as expression of visfatin from the liver was higher in MO group and were both positively associated with inflammatory factors [75]. Finally in a study aiming to develop predictive models, visfatin together with adiponectin, TNF-α and IL-8 were included in the algorithm achieving to differentiate NASH from SS with a sensitivity of 90% and specificity of 66% [76].

The data inconsistency about visfatin can be attributed to many factors. Since visfatin is produced from many organs, the comorbidities may be an important confounder. Furthermore, circulating visfatin levels probably do not reflect its local hepatic or adipose tissue levels. Therefore, more studies are needed to provide more homogeneous data in terms of visfatin changes in NAFLD and its exact role.

CHEMERIN

Chemerin is an adipokine produced by liver and adipose tissue as well [79]. Its levels are higher in obesity and IR states and decrease after weight loss with parallel significant reduction of high-sensitivity C-reactive protein levels [80]. Binding of chemerin to its chemokine-like receptor 1 (CMLKR-1) promotes the activation of cells of the innate immune system, i.e., macrophages and natural killer cells to tissue injury sites [81]. Regarding the liver, the hepatocytes represent a major source of chemerin production [82]. Chemerin contributes also to inflammatory procedures as it is positively associated with visceral adipose tissue macrophages [83], hepatic expression of CD68 cells (e.g., Kupffer cells) [84], and proinflammatory cytokines, including hepatic expression of TNF-α [82]. This close relationship with inflammation could explain the role of chemerin in NASH.

Most studies have measured higher chemerin serum levels in NAFLD patients than controls [85]. Also, hepatic chemerin expression was higher in NAFLD patients than controls [82]. Comparing chemerin serum levels in NASH and SS patients, some studies found higher levels in NASH [85], while others did not find any differences [84]. One study demonstrated that although the circulating chemerin levels did not differ between NASH and SS patients, NASH patients had higher hepatic chemerin and CMKLR1 mRNA expression than the others [84]. In the context of the association of chemerin levels with specific hepatic lesions in NAFLD data are also controversial. Notably, a study suggested that hepatic chemerin expression is positively associated with hepatic steatosis, lobular inflammation, ballooning, and fibrosis [84]. Also, another study reported that visceral chemerin expression and not hepatic expression or circulating levels were negatively associated with hepatic steatosis and inflammation [86]. Altogether, most studies so far indicate an association of chemerin with NAFLD (NASH or SS). However, chemerin has not been measured in large cohorts or clinical trials involving patients with NAFLD; thus, the available findings should be interpreted cautiously and need to be verified and extended in future studies.

RETINOL-BINDING PROTEIN 4

Retinol-binding protein 4 (RBP-4) was initially identified as a transport protein for retinol (vitamin A) from the liver to peripheral sites [87], but is also secreted by liver [87] and visceral adipose tissue [88] and may therefore have important metabolic effects. RBP-4 increases in IR, obesity, and T2DM [89] and promotes basal glucose production in the liver, since it increases the hepatic expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase [90]. Furthermore, RBP-4 levels seem to be inversely related to the adipocyte glucose transporter 4, which plays a pivotal role in the liver IR [89].

Regarding NAFLD, data about RBP-4 are inconclusive. RBP-4 seems to be positively associated with liver fat in healthy subjects [91] and it is higher in NAFLD patients than controls [92]. However, as it has been reported in a recent systematic review [68], an association between serum RBP-4 levels and liver histology among patients with biopsy proven NAFLD was found only in three out of seven studies. Some authors found higher circulating RBP-4 levels in SS or NASH patients than controls [93]. Comparing NASH with SS patients, some studies reported similar levels [93] and some others found lower levels in NASH than SS [94]. Furthermore, it has been suggested that

circulating RBP-4 levels are positively associated with ballooning [95] and inversely associated with fibrosis [94]. In summary, more studies in larger cohorts are needed in order to investigate whether RBP-4 is related to NAFLD development and progress.

IRISIN

Irisin is primarily a myokine secreted after exercise, but it is an adipokine too, since it is secreted by white adipose tissue [96,97]. Irisin has been associated with increased thermogenesis due to stimulation of "browning" of adipose tissue and improved glucose profile through reduction of IR in mice [96-98]. Additionally, irisin demonstrates hepatoprotective effects by stimulating glycogenesis and by reducing gluconeogenesis, lipogenesis and lipid accumulation [96,97] *in vitro* and *in vivo* animal models.

In humans, circulating levels of irisin have been associated with a wide spectrum of metabolic diseases, ranging from obesity and IR to diabetes [99,100], cardiovascular diseases [101, 102], bone metabolism and thyroid function [102,103]. Regarding NAFLD, data are controversial so far. In the first study including biopsy-proven NAFLD patients, irisin levels did not differ between NASH, SS and obese controls and were lower compared to lean controls [95]. Additionally, irisin levels were associated with portal inflammation and showed a trend to higher levels by increasing steatosis grade, fibrosis, and lobular inflammation [95]. In other studies, irisin levels have been higher in NAFLD group compared to healthy controls and increased with higher fibrosis and steatosis grade [104,105]. Furthermore, irisin has been inversely related to hepatic triglyceride content in an obese Chinese population [106]. Additionally, in a children-cohort irisin levels have been positively associated with the presence of mutations in PNPLA3 (patatin-like phospholipase domain containing 3), which is considered a strong genetic factor for development and progress of NAFLD [107]. There are many possible explanations for the discrepant results in the studies so far. These include mainly differences in the criteria used to diagnose NAFLD, differences between enzyme-linked immunosorbent assays for measurement of irisin and differences in population characteristics (i.e., age, BMI, ethnicity etc.) [108].

Altogether, irisin has hepatoprotective effects in animal and *in vitro* studies, while in human studies the results are inconclusive. Future research should aim to investigate in large prospective cohorts the association of irisin with NAFLD development and progress.

ADIPOKINES AS THERAPEUTIC TARGETS IN NAFLD

Given the role of adipokines in the pathogenesis of NAFLD, interventions aiming at modulating adipokine levels might have beneficial effects on liver histology. Notably, many pharmacologic agents used in the management of NAFLD affect adipokine levels.

Several studies have shown that thiazolidinediones (TZDs), pioglitazone, and rosiglitazone, besides liver histology, also improve adiponectin levels [109]. A recent systematic review of four studies [43] demonstrated an increase in circulating adiponectin levels after TZD treatment. Similarly, statins, that it is speculated to be effective against NAFLD by regulation of dyslipidemia increase significantly circulating adiponectin levels [110]. Finally, metformin that is widely used for treatment of T2DM and exerts hepatoprotective function is associated with increased levels of adiponectin and decreased levels of chemerin [111,112].

The effect of direct replacement of adiponectin or other adipokines on NAFLD has not been investigated yet, since with the exception of leptin, no other "adipokine drug" is currently approved by U.S. Food and Drug Administration. Regarding leptin, treatment with recombinant human leptin (metreleptin) is currently under evaluation in conditions of extreme hypoleptinemia, i.e., in patients with congenital leptin deficiency and congenital or acquired lipodystrophy. In these rare cases, profound IR, dyslipidemia, and accumulation of fat in the liver are observed [113]. Results from interventional study investigating the efficacy of metreleptin in NASH or NAFLD associated with lipodystrophy are expected.

CONCLUSIONS

In conclusion, based on literature, there is no doubt that adipokines play a crucial role in the pathogenesis and progression of NAFLD through their contribution to the low-grade inflammation which is closely related to the disease. Despite the extended investigation that has been conducted by now, a considerable amount of issues remains controversial and further meticulous studies are needed to this direction. Novel pathogenetic evidence may lead to a better comprehension and beyond that, to non-invasive diagnostic and therapeutic tools as well.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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