REVIEW ARTICLE

The adipokines in the pathogenesis and treatment of nonalcoholic fatty liver disease

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Abstract
Insulin resistance, abdominal obesity, and inflammation play important roles in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). Several adipokines, particularly adiponectin but also leptin, resistin, irisin, ghrelin, and visfatin modulate these pathogenetic mechanisms and appear to play a role in the development of hepatic steatosis and the progression to steatohepatitis and cirrhosis. Accordingly, these adipokines might represent attractive targets in patients with NAFLD. Notably, both lifestyle changes and many pharmacological agents that are used in the management of NAFLD, particularly pioglitazone and statins, exert favorable effects on adipokine levels. However, it is unclear whether these effects play a role in the improvement in liver histology. Therefore, mechanistic studies are needed to clarify the contribution of changes in adipokine levels to the effects of these interventions on hepatic steatosis, inflammation, and fibrosis. In parallel, the development of novel agents that specifically target adipokine levels might offer additional insights into the potential role of adipokines as therapeutic targets in NAFLD. Hippokratia 2016, 20(4): 259-263

Keywords: Nonalcoholic fatty liver disease, leptin, adiponectin, resistin, irisin, ghrelin, visfatin, insulin resistance, fibrosis, steatosis, inflammation

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the excessive accumulation of fat in the liver, in the absence of a history of alcohol abuse or of other causes of secondary hepatic steatosis[1]. NAFLD is considered the hepatic manifestation of metabolic syndrome, a cluster of metabolic abnormalities, such as impaired glucose tolerance, hypertension, dyslipidemia, and central obesity and is strongly associated with visceral obesity and insulin resistance[2,3]. The pathological spectrum of NAFLD ranges from isolated steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis[4]. The most widely accepted theory for the pathogenesis of NAFLD is the "two-hit" hypothesis[5]. According to this hypothesis, the first "hit" is the increased flux of free fatty acids (FFAs) to the liver[5]. The second "hit" involves oxidative stress, inflammation, mitochondrial dysfunction, and apoptosis, that induce hepatic inflammation and fibrosis[5]. Abdominal obesity and insulin resistance (IR) play pivotal roles in both "hits"[2,3]. This review aims to discuss the significance of adipokines in the pathogenesis of NAFLD and their potential role as therapeutic targets in these patients.

The role of adipokines in the pathogenesis of NAFLD

Accumulating data suggest that several adipokines, particularly adiponectin, leptin, resistin, ghrelin, and visfatin are involved in the pathogenesis of NAFLD. Adiponectin appears to play a key role in the progression of NAFLD. It is the only adipokine whose levels are down-regulated in obesity[6]. Adiponectin reduces body fat and is inversely associated with body mass index[7]. It also improves insulin sensitivity[7] and inhibits lipid accumulation in the liver by promoting β-oxidation of FFAs and by reducing the de novo synthesis of FFAs within hepatocytes[8]. Furthermore, adiponectin appears to exert anti-inflammatory, antifibrotic and antiapoptotic effects[9]. In mice, administration of recombinant adiponectin prevents steatosis and suppresses hepatic inflammation[10]. In clinical studies, adiponectin levels are lower in patients with NAFLD than in controls and are also lower in patients with NASH than in patients with isolated steatosis[11]. Adiponectin levels also correlate negatively with the severity of hepatic steatosis and inflammation[11]. Moreover, the expression of adiponectin receptors in the liver is lower in patients with NASH than in those with isolated steatosis and correlated negatively with the degree of inflammation and fibrosis[12,13].

Leptin acts as an anorexigenic hormone and regulates food intake, body fat, and insulin activity[14]. In animal models, leptin prevents lipid accumulation in non-adipose tissues[15]. In the liver, it appears to contribute to both "hits" of the NASH pathogenesis. Specifically,

it aggravates IR and consequently, steatosis and, on the other hand, it promotes liver fibrosis[16,17]. In rats, administration of leptin augments both proinflammatory and fibrogenic responses in the liver via increased expression of procollagen-I and transforming growth factor-β1[18]. In contrast, leptin-deficient mice show decreased fibrogenesis in response to liver injury[19]. However, it is unclear whether these findings are applicable to humans. Serum leptin levels are higher in patients with NASH than in controls[20,21]. An early study also reported a positive correlation between leptin levels and the severity of steatosis[20]. However, others did not confirm this association[22,23]. Furthermore, leptin levels do not appear to correlate with the degree of inflammation or fibrosis[21-24].

Resistin also induces hepatic IR[25]. Moreover, this adipokine exerts proinflammatory effects[26], is implicated in hepatic lipogenesis and triggers liver fibrogenesis[27]. In patients with NAFLD, serum resistin levels correlate with the severity of steatosis, inflammation and fibrosis[28-30].

Irisin is a newly discovered, exercise-induced adipokine[31]. It increases energy expenditure due to heat loss, independently of exercise or food intake and it improves glucose homeostasis, reduces IR and induces weight loss[31]. Irisin levels are higher in patients with NAFLD than in lean controls and are positively associated with the presence of portal inflammation, probably as a part of a compensatory mechanism[32].

Ghrelin reduces the release of pro-inflammatory cytokines and attenuates apoptosis, oxidative stress, inflammation, and restores hepatic lipid metabolism[33]. Visfatin also has proinflammatory properties and is increased in patients with IR. Visfatin levels correlate with the severity of hepatic steatosis and fibrosis[34] (Table 1).

Interventions targeting adipokines

Given the role of adipokines in the pathogenesis of NAFLD, interventions aiming at modulating adipokine levels might have beneficial effects on liver histology. Notably, both lifestyle changes and many pharmacologic agents used in the management of NAFLD affect adipokine levels. Lifestyle changes represent the cornerstone of the management of NAFLD[1]. However, weight loss induced by diet and exercise did not affect adiponectin levels in most studies[35]. However, others reported that low-carbohydrate diets could increase adiponectin levels, particularly when weight loss >10 % is achieved[36]. Orlistat, a lipase inhibitor, reduces body weight but also has no effect on adiponectin levels in patients with NASH[37]. On the other hand, adiponectin levels consistently increase following bariatric surgery, again suggesting that substantial weight loss is required to increase adiponectin levels[38].

Several studies have shown that pioglitazone improves liver histology in patients with NASH[39,40]. An increase in adiponectin levels has also been observed during treatment with pioglitazone[39]. Vitamin E is another choice for the management of patients with NASH[1,40]. Limited data suggest that vitamin E might also increase adiponectin levels[41]. On the other hand, ursodeoxycholic acid does not appear to affect adiponectin levels[41] and also has no effect on liver histology in patients with NASH[42]. Metformin decreases adiponectin levels[43] and does not improve liver histology in NAFLD[44,45].

Accumulating data suggest that statins are safe in patients with NAFLD, reduce transaminase levels and might also improve liver histology[46-49]. However, conflicting data have been reported regarding the effects of statins on adiponectin levels, with most studies reporting an increase[50,51] but others showing no change[52] or even a decrease[53]. Limited data suggest that fibrates might also reduce transaminase levels in patients with NAFLD[48,54] and that they increase adiponectin levels[55]. Angiotensin receptor blockers exert antioxidant actions in addition to blood pressure lowering and have thus been evaluated in some small studies in patients with NAFLD yielding promising results[56]. These agents also increase adiponectin levels[57-59].

There are more limited data on the effects of various treatments of NAFLD on leptin, resistin, irisin, ghrelin, and visfatin levels. Weight loss consistently lowers leptin levels[60,61] but has no effect on resistin levels[62]. Additionally, irisin levels increase with exercise[63]. Pioglitazone and metformin reduce both leptin and resistin levels[64-66]. In contrast, treatment with vitamin E, ursodeoxycholic acid or statins does not appear to affect leptin or resistin levels[41]. On the other hand, preliminary data suggest that metformin reduces whereas statins increase irisin levels[67,68]. The effects of vitamin E, pioglitazone and ursodeoxycholic acid on this novel adipokine have not been evaluated yet (Table 2).

Conclusions

Adiponectin appears to play an important role in the pathogenesis and progression of NAFLD. Leptin, resistin, and visfatin might also be implicated in the development of hepatic steatosis and the progression to NASH whereas irisin and ghrelin might play a protective role. Both lifestyle changes and most pharmacological agents that are used in the management of NAFLD affect adipokine levels. Notably, interventions that improve liver histology also exert favorable effects on adipokine levels whereas less effective treatments do not change adipokine levels. Therefore, the use of medications directly targeting adipokines appears to represent an attractive and promising possibility. However, there are no studies that evaluated whether the changes in adipokine levels during lifestyle changes or pharmacotherapy correlate with the change in liver histology. Moreover, there are no agents that specifically modulate adipokine levels. Therefore, both mechanistic studies using established treatments of NAFLD and development of agents specifically targeting adipokines are needed to clarify the role of adipokines as targets of treatment in patients with NAFLD.

Conflict of interest

Authors have no conflict of interest to declare.

Table 1: Effects of adipokines on insulin sensitivity and liver histology.

	Adiponectin	Leptin	Resistin	Irisin
Insulin sensitivity	Improvement	Worsening	Worsening	Worsening
Liver histology	Inhibits steatosis and fibrosis	Promotes steatosis, inflammation and fibrosis	Promotes inflammation and fibrosis	Inhibits steatosis

Table 2: Effects on adipokine levels of therapeutic interventions used in patients with nonalcoholic fatty liver disease.

	Adiponectin	Leptin	Resistin	Irisin
Lifestyle changes (weight loss, diet, exercise)	Conflicting data	Decrease	No effect	Increase
Orlistat	Increase	Decrease	No effect	No data
Bariatric surgery	Increase	Decrease	Decrease	No effect
Pioglitazone	Increase	Decrease	Decrease	No data
Vitamin E	Increase	No effect	No effect	No data
Ursodeoxycholic acid	No effect	No effect	No effect	No data
Metformin	Decrease	Decrease	Decrease	Decrease
Statins	Conflicting data	No effect	No effect	Increase
Fibrates	Increase	No effect	No effect	No data
Angiotensin receptor blockers	Increase	No effect	No effect	No data

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