Review Article:

Role of adipokines in the pathogenesis of nonalcoholic fatty liver disease

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome. The increased prevalence of obesity, diabetes, hypertension, hypertriglyceridaemia and hypercholesterolemia are considered to be the potential causative factors for NAFLD. NAFLD is emerging as a major clinical problem worldwide. Recently much attention has been focused in India as the prevalence of obesity and diabetes is rising. NAFLD is responsible for unexplained raise in transaminases, and an important cause of cryptogenic cirrhosis and cryptogenic hepatocellular carcinoma in India. NAFLD is a spectrum of disease ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), potentially leading to fibrosis and cirrhosis. Studies have suggested that the adipokines are involved in the pathogenesis of NAFLD and its progression to NASH, through their metabolic and pro- or anti-inflammatory activity. Adipokines in particular tumor necrosis factor-α and interleukin-6 are believed to mediate the shift in pathology from steatosis to steatohepatitis. In addition, other adipokines such as adiponectin, leptin and resistin also play a crucial role in the development and progression of NAFLD through their metabolic and pro–or anti-inflammatory activity. This suggests that imbalance between pro-inflammatory and anti-inflammatory cytokines may have a role in the development of liver damage in NAFLD. Understanding the relationship between adipokines and NAFLD may play an important role in the early identification/diagnosis, treatment and also help in preventing disease progression.

Key words: *Adipokines, Non alcoholic fatty liver disease, Inflammation*

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome.[1] It is characterized mainly by excessive deposition of free fatty acids and triglycerides in the hepatic parenchyma.[2] The increased prevalence of obesity, diabetes, hypertension, hypertriglyceridemia and hypercholesterolemia are considered to be the potential causative factors for NAFLD. [3] Visceral obesity is frequently associated with NAFLD. The coexistence of visceral obesity and NAFLD in an individual increases the likelihood of advanced forms of liver disease. NAFLD is emerging as a major health problem worldwide and has been increasingly recognized as a major cause of liver-related morbidity and mortality.[4] Recently awareness regarding NAFLD in India is picking up as the prevalence of obesity and diabetes is rising.[5] NAFLD has been shown to be responsible for unexplained raise in transaminases, and an important cause of cryptogenic cirrhosis and cryptogenic hepatocellular carcinoma in India.[6]

Epidemiology

Worldwide prevalence of NAFLD is 10% - 24% in the general population. [7] There are limited epidemiological data on the prevalence of NAFLD in the general population in India. A study showed that the prevalence of NAFLD is around 9% to 32% of general population in India and the prevalence of NAFLD increases with overweight, obesity, prediabetes and diabetes.[4] Another community-

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based epidemiological study performed in a non obese rural Indian population showed prevalence of NAFLD to be 8.7% .[8]

Pathogenesis

NAFLD is a complex metabolic condition in which both lifestyle and genetic factors have a pathogenic role.[9] It represents a spectrum of disease ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), potentially leading to fibrosis and cirrhosis.[10] Within this spectrum, steatosis alone is apparently benign. NASH, where in necro-inflammatory reactions is also observed in addition to accumulation of triglycerides, may progress to cirrhosis and hepatocellular carcinoma.[8,11] The pathogenesis of NAFLD (Figure 1) is thought to involve a multiple-hit process with the 'first hit' being the accumulation of liver fat, linked with insulin resistance (IR)[12] and 'second hit' being an increase in fatty acid beta oxidation, adipokines, oxidative stress and endotoxaemia.[13]

Adipokines in NAFLD

Adipose tissue adipocytes secrete a number of cytokines termed adipokines, that have a variety of local, peripheral, and central effects. [14]

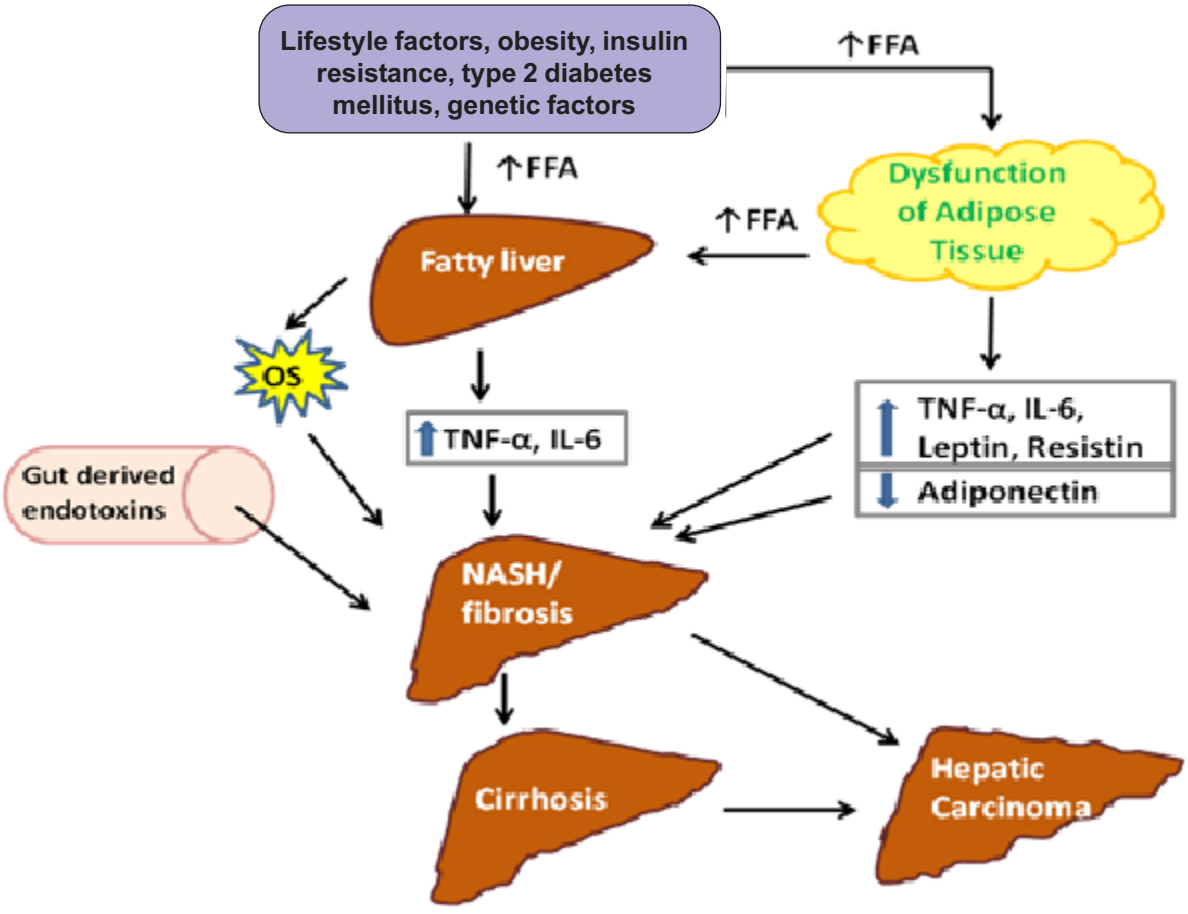

Figure 1: Conditions such as sedentary life style, obesity, insulin resistance, and diabetes mellitus affects hepatic fat accumulation by increasing mobilization of free fatty acids from adipose tissue, increasing *denovo* synthesis of fatty acids and triglycerides in the liver. Pro-inflammatory cytokines such as TNF-α and IL-6, which are secreted from adipose tissue and liver, are believed to mediate the shift in pathology from steatosis to steatohepatitis in turn to cirrhosis and hepatocellular carcinoma. Alteration in levels of other adipokines, that is decreased adiponectin, increased leptin and resistin contribute to hepatic steatosis and also promote hepatic steatosis to turn into steatohepatitis. Oxidative stress and gut-derived endotoxins also promote progression of NAFLD.

FFA = free fatty acids; OS = oxidative stress; NASH = nonalcoholic steatohepatitis; TNF-α = tumour necrosis factor-α; IL-6 = interleukin-6

Table1: Sources and metabolic actions of adipokines

Adipokine	Source	Metabolic actions
TNF-α	Adipocytes, liver, stromal vascular fraction cells	proinflammatory, antagonism of insulin signalling
IL-6	Adipocytes, liver, muscle, stromal vascular fraction cells	Proinflammatory, Impairs insulin signaling, impairs energy regulation
Adiponectin	Adipocytes	Anti-inflammatory, anti-lipogenic, anti-atherogenic, improves hepatic and peripheral insulin sensitivity
Leptin	Adipocytes	Proinflammatory, impairs insulin signalling, appetite control, energy homeostasis
Resistin	Adipose tissue and macrophages	Insulin resistance, regulates the secretion of IL-6
Retinol binding protein-4	Hepatocytes and adipocytes	Impairs insulin signaling and induces insulin resistance
Visfatin	Adipocytes	Exerts insulin – mimicking effects by activating insulin receptor, stimulates insulin secretion, stimulates proinflammatory cytokines (IL-6 andTNF-α)
Omentin	Adipocytes	Exerts insulin sensitizing effects and enhances insulin-stimulated glucose transport inadipocytes
Chemerin	Liver and adipocytes	Stimulates adiponectin expression andInhibits proinflammatory cytokines (IL-6 andTNF-α)

TNF-α = tumour necrosis factor-α; IL-6 = interleukin-6

Adipokines are critically involved in the physiology of a healthy liver and in the pathophysiology of many acute and chronic liver diseases as they mediate hepatic inflammation, liver cell death, cholestasis, and fibrosis.[15] Among the many recognized adipokines (Table1), only a few have been widely studied. These include interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), adiponectin, leptin and resistin. Studies have suggested that these adipokines are involved in the pathogenesis of NAFLD and its progression to NASH, through their metabolic and pro- or anti-inflammatory activities.[13]

TNF-α

TNF-α is a pro-inflammatory cytokine which is produced by adipocytes, macrophages, lymphocytes, natural killer cells and neurons.[16,17] Elevated circulating TNF-α levels are found to be associated with obesity and insulin resistance (IR) both in animal models and humans.[13] TNF-α has a central role in the development of fatty liver and subsequently NASH[18] by antagonizing the effects of adiponectin and suppressing the transcription of adiponectin in adipocytes thereby contributing to IR.[19] Increased TNF-α causes desensitization of insulin signaling through specific phosphorylation of serine residues in the insulin receptor and insulin receptor substrate-1.[20]

TNF-α activates harmful pro-atherogenic pathways partially through the reduction of high-density lipoprotein cholesterol and elevated expression of cholesterogenic genes, accompanied by an increase in potentially harmful pre-cholesterol metabolites.[21] TNF-α also stimulates hepatic fatty acid synthesis, increases serum triglyceride levels and stimulates very low-density lipoprotein production from liver.[22] TNF-α can induce both hepatocyte cell death and hepatocyte proliferation, and is critically involved in the pathogenesis of liver fibrosis in NASH model.[3] A prospective cross-sectional pilot study conducted at New Delhi, India showed

significant increase in TNF-α among NAFLD patients compared to subjects with chronic hepatitis B and healthy controls.[23] Similarly in another study conducted in Cochin, TNF-α levels were elevated significantly in NAFLD patients with severity of the disease compared to the normal subjects.[3]

Studies in animals and humans have demonstrated enhanced TNF-α expression in patients with NASH.[15,21] Mice genetically deficient in TNF receptor 1 have proved resistant to NASH induced by two different diets[24,25] while treatment of leptin-deficient mice with TNF-α antibodies improved hepatic IR and fatty liver.[26]

IL-6

IL-6 is produced by adipocytes, immune cells, fibroblasts, endothelial cells and monocytes. The circulating levels of IL-6 are found to be elevated in obese subjects which was found to decrease in parallel with weight loss and associated decrease in IR.[27-29] IL-6 impairs insulin signaling in hepatocytes, resulting in increased hepatic gluconeogenesis, followed by hyperglycaemia and compensatory hyper-insulinaemia.[13] IL-6 increases IR by up-regulating suppressor of cytokine signalling-3, which, in turn, impairs insulin-induced insulin receptor and insulin receptor substrate 1 phosphorylation.[17] Liver expression of IL-6 was markedly increased in NASH patients and positively correlated with inflammation and fibrosis.[30] In a study of 36 morbidly obese patients and 12 healthy controls, IL-6 was reported to be an independent predictor of steatosis and NASH.[31] Serum IL-6 was found to be significantly elevated in subjects with NAFLD than controls,[3,23] even after correction for age, sex and body-mass index (BMI).[32]

Initial reports supported a protective action of IL-6 in steatotic livers, by suppressing oxidative stress and preventing mitochondrial dysfunction.[33] However, this seems to be a paradoxical effect of short and long-term IL-6 exposure. Long-term IL-6 exposure may sensitize the liver to injury and cause apoptotic cell death.[34]

Adiponectin

Adiponectin is a 30-kDa protein which is abundantly and selectively expressed in white adipose tissue. Its role in IR has been well established.[4] Recently, two adiponectin receptors (AdipoR1 and AdipoR2) have been cloned in mouse and humans, and both are expressed in liver. Binding of adiponectin to its receptors stimulates phosphorylation of AMP activated protein kinase, peroxisome proliferator- activated receptor alpha activity and fatty acid oxidation in liver.[35] In fact, high adiponectin levels have been reported to protect against nonalcoholic fatty liver disease in mice by reducing fatty acid synthesis through inhibition of acyl-CoA carboxylase (ACC) and fatty acid synthase expression and activity.[36] However, liver adiponectin receptors are rapidly down-regulated by insulin, thus suggesting that adiponectin resistance may be involved in disorders of liver metabolism. In a study, NAFLD patients were reported to present with markedly reduced plasma adiponectin and with IR when compared to controls. Moreover, on regression analysis, adiponectin was inversely correlated with homeostatic model assessment (HOMA), a method used to quantify IR, thus supporting the role of adiponectin in the link between IR and NAFLD.[37]

It is well known that inflammation is a key mechanism in the progression of fatty liver to hepatitis and cirrhosis.[38]Adiponectin inhibits liver TNF-α expression and also inhibits expression of several cytokines in hepatic stellate cells.[4] Hence, adiponectin may protect against steatohepatitis through its anti-inflammatory action. In an Indian study[23] the levels of adiponectin were significantly reduced in NAFLD patients compared to healthy controls.[23] Similarly another study found an

inverse correlation between adiponectin levels and liver fat content in diabetic patients as measured by nuclear magnetic resonance.[39] Adiponectin levels are lowered by more than 50% in NASH patients compared with healthy controls[40] and adiponectin expression is decreased by 20%-40% during the development of NAFLD, from simple steatosis to NASH.[41]

Among the known adipokines, adiponectin stands out for its insulin-sensitizing and anti-inflammatory roles. Hence, adiponectin may be a promising drug candidate in the treatment of liver diseases.

Leptin

Leptin is a highly conserved 16-kDa hormone that is predominantly expressed in adipose tissue and is found both in circulation and cerebrospinal fluid. Centrally, it is capable of altering food intake, body weight and energy expenditure. It also has peripheral effects on skeletal muscle, liver, pancreas, adipose tissue, and numerous other cell types. Circulating leptin levels are positively correlated with BMI with concentrations in human serum at approximately 1-10 ng/mL. Leptin also seems to lower insulin secretion and leptin resistance could relate to the hyperinsulinaemia. Conditions with leptin deficiency or resistance, like obesity, are associated with triglyceride accumulation in non-adipose organs like liver, muscle, and pancreas. The resulting lipotoxicity in these organs results in diabetes by causing IR.[42-45]

Leptin is thought to participate in both the hits of NASH development. Initially, it contributes to the development of IR and subsequently steatosis. Furthermore, in the context of liver insult, leptin has a proinflammatory role and is considered to be an essential mediator of liver fibrosis.[46] In fact, leptin increases the expression of TNF-α, transforming growth factor-β1 and type I collagen in liver.[4] In rats which were administered injections of leptin, increased liver fibrosis were observed with an increased expression of procollagen-I, transforming growth factor α1 and smooth muscle actin.[47] A study showed a dramatic increase in serum TNF-α levels after leptin injections, suggesting that leptin may amplify inflammation and independently affect the development of fibrosis.[48]

There are reports including one from India that leptin levels were significantly reduced in NAFLD patients when compared to controls. Other studies reported that leptin levels were significantly higher in NASH patients than controls and correlated with the severity of hepatic steatosis but not of necroinflammation or fibrosis.[23,49,50] However, some studies did not support a role for leptin in the development of NAFLD. Leptin levels did not show any change in subjects with between NASH and there was no association with liver fibrosis. Also, there was no correlation between circulating leptin and leptin receptor expression in liver biopsies of nonalcoholic fatty liver patients.[47,48,51] Thus, larger studies with homogenous population and carefully matched healthy controls are needed to study the association of leptin with NASH.

Resistin

Resistin is a 108-amino acid protein expressed in white adipose tissue and mononuclear cells.[52] A major target organ of resistin is the liver, where it induces IR and increases glucose production.[53] A study reported that NAFLD patients had higher serum resistin compared to obese and controls and this increase positively correlated with BMI, blood glucose and IR.[54]

In another study higher serum resistin levels were detected in patients with moderate to severe steatosis, compared with mild steatosis.[53] There are two most likely explanations for this finding. Firstly, resistin may contribute to hepatic steatosis by promoting IR and by

altering insulin signaling in hepatocytes thereby promoting increased intracellular levels of fatty acids. Secondly, resistin may cause hepatic steatosis to turn into steatohepatitis by stimulating pro-inflammatory responses. Moreover, resistin inhibits the role of adiponectin in fatty acid oxidation, therefore increased resistin in NAFLD could result in increased fatty acid synthesis, accumulation of triglycerides, and reduced fatty acid oxidation.[55] Hepatic stellate cells also produce a variety of cytokines, and elevated circulating resistin levels may reflect increased resistin production by these cells within the liver.[52]

Diagnosis

The diagnosis of NAFLD requires all of the following:[56] (i) demonstration of hepatic steatosis by imaging or biopsy; (ii) exclusion of significant alcohol consumption; and (iii) exclusion of other causes of hepatic steatosis. Various radiologic methods can detect NAFLD, but no imaging modality is able to differentiate between the histologic subtypes of nonalcoholic fatty liver (NAFL) and NASH.[57] Our approach in patients who have not already undergone imaging is to obtain an ultrasound. However, computed tomography (CT) and magnetic resonance imaging (MRI) can also detect hepatic steatosis. Imaging is sufficient for diagnosing NAFLD if all of the following conditions are met:1. Radiographic imaging is consistent with fatty infiltration; 2. Other causes for the patient's liver disease have been excluded; and 3.The patient does not have signs or symptoms of cirrhosis. If these criteria are not met, patients will typically require a liver biopsy to make the diagnosis or to assess the degree of liver injury.

Both CT and MRI can identify steatosis but are not sufficiently sensitive to detect inflammation or fibrosis.[58] Magnetic resonance spectroscopy (MRS) has the advantage of being quantitative rather than qualitative or semiquantitative, but it is not widely available.[59] One of the difficulties in determining the sensitivity and specificity of CT and MRI for diagnosis of hepatic steatosis is that not all patients undergo confirmation by liver biopsy. In a study that did use histology as the gold standard, the sensitivity of CT scan for detecting hepatic steatosis was poor, whereas MRI had low specificity.[60] Unlike CT and MRI, MRS allows for quantification of hepatic fat, and may be particularly helpful in patients with small amounts of hepatic steatosis.[61] A study that compared MRS with liver biopsy in 12 patients found a close correlation between the measurement of intrahepatocellular lipid by MRS and the histologic assessment of cirrhosis ($r = 0.94$).[62] However, not all scanners have the capability of obtaining spectroscopic sequences, and it is not routinely used.

A potentially useful non-invasive method for excluding advanced fibrosis is measurement of liver stiffness with transient elastography. However, this approach is not widely available and has not been extensively studied in NASH. Other indirect markers of cirrhosis such as the aspartate aminotransferase to platelet ratio index are also being studied to identify patients with fibrosis.

NAFLD is responsible for significant liver disease. Abnormal liver function tests detected during routine screening may indicate the presence of NAFLD. Undetected, NAFLD can progress to cirrhosis and hepatocellular carcinoma. Adipokines appear to be the main drivers for the development of progressive liver injury in patients with NAFLD. An imbalance in adipokine expression could play a pivotal role in disease progression to NASH and cirrhosis. Hence, understanding the role of adipokines in the pathophysiology of NAFLD

may help in better management and prevention of complications due to NAFLD by providing an additional tool for NASH detection. Also, modulation of endocrine/immune/ inflammatory interactions of adipose tissue may provide novel therapeutic targets for the treatment of NAFLD.

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