

WJG 20th Anniversary Special Issues (12): Nonalcoholic fatty liver disease**Non-alcoholic fatty liver disease and obesity: Biochemical, metabolic and clinical presentations**

Sandra Milić, Davorka Lulić, Davor Štimac

Sandra Milić, Davorka Lulić, Davor Štimac, Division of Gastroenterology, Department of Internal Medicine, University Hospital Rijeka, Rijeka 51000, Croatia

Author contributions: Milić S, Lulić D and Štimac D performed data acquisition and wrote the manuscript; Milić S revised the manuscript; Štimac D approved the final manuscript version.

Correspondence to: Sandra Milić, MD, PhD, Professor, Division of Gastroenterology, Department of Internal Medicine, University Hospital Rijeka, Krešimirova 42, Rijeka 51000, Croatia. smilic05@gmail.com

Telephone: +385-51-658122 Fax: +385-51-658826

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world. Presentation of the disease ranges from simple steatosis to non-alcoholic steatohepatitis (NASH). NAFLD is a hepatic manifestation of metabolic syndrome that includes central abdominal obesity along with other components. Up to 80% of patients with NAFLD are obese, defined as a body mass index (BMI) > 30 kg/m². However, the distribution of fat tissue plays a greater role in insulin resistance than the BMI. The large amount of visceral adipose tissue (VAT) in morbidly obese (BMI > 40 kg/m²) individuals contributes to a high prevalence of NAFLD. Free fatty acids derived from VAT tissue, as well as from dietary sources and *de novo* lipogenesis, are released to the portal venous system. Excess free fatty acids and chronic low-grade inflammation from VAT are considered to be two of the most important factors contributing to liver injury progression in NAFLD. In addition, secretion of adipokines from VAT as well as lipid accumulation in the liver further promotes inflammation through nuclear factor kappa B signaling pathways, which are also activated by free fatty acids,

and contribute to insulin resistance. Most NAFLD patients are asymptomatic on clinical presentation, even though some may present with fatigue, dyspepsia, dull pain in the liver and hepatosplenomegaly. Treatment for NAFLD and NASH involves weight reduction through lifestyle modifications, anti-obesity medication and bariatric surgery. This article reviews the available information on the biochemical and metabolic phenotypes associated with obesity and fatty liver disease. The relative contribution of visceral and liver fat to insulin resistance is discussed, and recommendations for clinical evaluation of affected individuals is provided.

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Key words: Fatty liver; Insulin resistance; Intra-abdominal fat; Metabolism; Non-alcoholic fatty liver disease; Obesity

Core tip: This article reviews biochemical, metabolic and clinical relationships between non-alcoholic fatty liver disease and obesity. Visceral adipose tissue influences hepatic steatosis to a greater extent than the body mass index, despite evidence that liver fat may develop independent of skeletal muscle and adipose tissue insulin resistance. Obese individuals with non-alcoholic fatty liver disease usually present with symptoms of metabolic syndrome or its components.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most

common liver disease worldwide^[1]. It is comprised of a spectrum of disorders characterized by liver steatosis with > 5% of hepatocytes infiltrated with fat in individuals with no history of alcohol abuse (< 30 g/d in men and < 20 g/d in women) and no competing etiologies for hepatic steatosis^[2,3]. The presentation of the disease ranges from what can be considered as “silent liver disease”, or fatty steatosis, to non-alcoholic steatohepatitis (NASH)^[4]. Approximately 10%-25% of patients with silent liver disease develop NASH, and 5%-8% of those will develop liver cirrhosis within 5 years^[2,5]. Furthermore, 12.8% of patients with liver cirrhosis will develop hepatocellular carcinoma (HCC) within 3 years^[6]. NASH is considered to be a major cause of cryptogenic cirrhosis as 70% of patients have risk factors for NAFLD^[7], including metabolic syndrome and its components, a sedentary lifestyle and a high-fat diet (HFD)^[8,9]. NAFLD is also associated with an increased risk for developing cardiovascular disease, insulin resistance (IR), type 2 diabetes (T2D), obesity, chronic kidney disease, post-operative complications after major liver surgery and colorectal cancer^[10-12]. The prevalence of NAFLD is influenced by age, gender, ethnicity, and the presence of sleep apnea and endocrine dysfunctions (hypothyroidism, hypopituitarism, hypogonadism, and polycystic ovary syndrome)^[13,14].

Obesity is a chronic disease defined by a body mass index (BMI) > 30 kg/m², and morbid obesity, one of the most rapidly growing subgroups, is defined as a BMI > 40 kg/m²^[15]. Its prevalence is increasing in adults and children, and has been described by the World Health Organization as a global epidemic with an estimated 500 million obese adults and 1.5 billion overweight or obese individuals worldwide^[16,17]. Obesity is associated with an overall increase in mortality and a decrease in lifespan of up to 20 years^[18]. Considered as a state of chronic low-grade inflammation, obesity has been associated with complications such as T2D, cardiovascular disease, hypertension, stroke, gallbladder disease, osteoarthritis, and psychosocial problems^[18,19]. Obesity has also been associated with a spectrum of cancer types (colon, breast, endometrium, kidney, esophagus, stomach, pancreas and gallbladder), and together with IR, represents a risk factor for developing HCC^[20].

NAFLD is strongly linked to obesity, with a reported prevalence as high as 80% in obese patients and only 16% in individuals with a normal BMI and without metabolic risk factors^[21,22]. Fatty liver severity in the morbidly obese also correlates with the degree of impaired glycaemic status^[23]. Hepatic steatosis is correlated with BMI, but is more closely associated with visceral adiposity (measured as waist circumference), as visceral adipose tissue (VAT) is more lipolitically active on a per unit weight basis than subcutaneous fat^[24-26]. However, Stefan *et al*^[27] identified a form of metabolically benign obesity where insulin sensitive obese individuals have a lower percentage of accumulated liver fat compared to IR obese subjects. This implies that the prevention and reduction of hepatic fat accumulation may lower IR even in subjects

with increased adiposity^[27,28].

BIOCHEMICAL PRESENTATION

Both the liver and VAT contain hepatocytes and adipocytes in close proximity to immune cells (natural killer and natural killer T cells), hepatic stellate cells, Kupffer cells, endothelial cells and macrophages, with prompt access to blood vessels and similar biochemical signaling pathways^[29,30]. In the liver, the inhibitor of nuclear factor kappa-B kinase subunit beta/nuclear factor kappa-B (IKK- β /NF- κ B) signaling pathway is activated by obesity and a HFD. This pathway is associated with the chronic inflammation that occurs in hepatic steatosis, as transgenic mice selectively expressing constitutively active IKK- α in hepatocytes demonstrated subacute inflammation in a study by Cai *et al*^[31]. Furthermore, the hepatic production of the proinflammatory cytokines tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and IL-1 β were increased in these mice to a similar extent as those induced by a HFD in wildtype mice, indicating that lipid accumulation in the liver leads to subacute hepatic inflammation through NF- κ B activation and downstream cytokine production. Free fatty acids (FFAs) are able to activate this pathway in the liver, and increase hepatic diacylglycerol (DAG) content, the activity of protein kinase C- δ and plasma levels of monocyte chemoattractant protein-1 (MCP-1), thus explaining the VAT-induced FFA increase in hepatic circulation that leads to chronic low-grade inflammation and IR in fatty liver^[32]. Overexpression in mice of MCP-1, a high-affinity ligand for the C-C motif chemokine receptor-2, contributes to macrophage infiltration into adipose tissue, IR, and hepatic steatosis associated with obesity^[33].

Increased lipid metabolites such as DAG can cause IR by interfering with the ability of insulin to phosphorylate insulin receptor substrate-2 through activation of protein kinase C- ϵ ^[34]. In a murine model of HFD-induced NAFLD, paradoxical lowering of hepatic DAG content by the inhibition of diglyceride acyltransferase 2, an enzyme that catalyzes the formation of triglycerides from DAG and acyl-CoA, protected against fat-induced hepatic IR and improved hepatic steatosis, hepatic insulin signaling, and *in vivo* hepatic insulin sensitivity^[35]. However, this inhibition increases circulating levels of FFAs, cytochrome P4502E1, and other markers of lipid peroxidation/oxidant stress, resulting in lobular necroinflammation and fibrosis, suggesting that the accumulation of triglycerides may be a protective mechanism to prevent progressive liver damage in NAFLD^[36]. Also, inhibition of suppressors of cytokine signaling (SOCS) in obese subjects with persistently elevated cytokine levels improves insulin sensitivity, normalizes increased expression of sterol regulatory element binding protein-1c, the key regulator of fatty acid synthesis in liver, and dramatically ameliorates hepatic steatosis and hypertriglyceridemia^[37]. Furthermore, FFAs activate c-Jun N-terminal kinase 1, resulting in the secretion of IL-6 by adipose tissue, which

may lead to increased expression of liver SOCS-3^[38,39].

VAT is also a source of a number of secreted adipocyte-derived cytokines called adipokines^[40]. The most well described adipokines are adiponectin, an insulin sensitizer, and leptin, a hormone mainly secreted by adipocytes^[41], which play functional roles in NAFLD pathogenesis. Obesity is considered a state of central and peripheral leptin resistance, and obese individuals, as well as individuals with NAFLD and NASH, have higher circulating levels of leptin^[42-44]. Leptin regulates energy intake and energy expenditure, metabolism and reproductive function^[45], and also prevents lipid accumulation in non-adipose tissues, such as liver^[41]. Leptin may play an important role in improving hepatic IR as it suppresses stearoyl-CoA desaturase activity, an enzyme that plays an important role in metabolism and catalyzes the rate-limiting reaction of monounsaturated FA synthesis^[46]. Leptin indirectly mediates hepatic stellate cell activation and liver fibrosis in animals by inducing the production of transforming growth factor- β and connective tissue growth factor in Kupffer cells^[45].

Adipose tissue macrophages secrete high amounts of TNF- α and IL-6, which suppress the production of adiponectin^[47,48]. The decreased levels of circulating adiponectin in NAFLD are related to hepatic IR and to the amount of liver fat^[49]. Adiponectin acts as a modulator of the inflammatory response, as it increases liver fat oxidation by inactivating acetyl-CoA carboxylase and activating AMP-activated protein kinase, and by enhancing expression of the peroxisome proliferator-activated receptor- α gene^[49,50]. Adiponectin also decreases the activity of another enzyme involved in FA synthesis, FA synthase^[51]. An additional source of inflammatory mediators has been described that may play a role in NAFLD pathogenesis, such as from gut-derived portal endotoxemia^[52]. Consumption of high amounts of refined sugar and saturated fat may cause derangement of the gut flora^[53]. Small intestinal bacterial overgrowth and translocation result in excessive ethanol production and release of bacterial lipopolysaccharides^[54,55]. Both ethanol and lipopolysaccharides induce hepatic inflammation by activating TNF- α production in Kupffer cells^[56].

Other adipokines have more recently been implicated in NAFLD. A study by Pagano *et al.*^[57] found higher levels of circulating resistin in one group of patients with NAFLD compared with lean and obese controls, though other studies report varying levels. Visfatin, a protein preferentially expressed in VAT, can predict the presence of portal inflammation in NAFLD patients^[58]. In addition, circulating levels of omentin and adipoline, released by VAT stromovascular cells, are increased in patients with NAFLD and predict hepatocyte ballooning^[59].

METABOLIC PRESENTATION

The liver plays a central role in lipid metabolism and imports serum FFAs and manufactures, stores and exports lipids and lipoproteins^[60]. In the hepatocytes, FFAs can be

metabolized by β -oxidation for the generation of ATP^[61], or by esterification for the production of triglycerides that are either stored in lipid droplets within hepatocytes, or packaged and released into the blood as very low-density lipoprotein particles. FFAs are derived from three distinct sources: dietary sources, *de novo* lipogenesis (DNL) from carbohydrates or amino acids, and release from lipids stored in VAT or subcutaneous fat^[34,62]. Hepatic fat from adipose tissue lipolysis, or from lipoproteins hydrolyzed above a rate that can be taken up by adipose tissue, accounts for 60% of FFAs, with 25% from DNL, and 15% from dietary sources^[63].

The increased lipolysis in VAT results in release of excess FFAs into the portal vein^[64]. Isotope dilution/hepatic vein catheterization techniques to measure this release showed that the lipolytic contribution of FFA was 5%-10% in subjects with a normal BMI and up to 30% in individuals with greater amounts of VAT^[65]. In the fasting state, hepatic FFAs are predominantly delivered by systemic circulation^[63], with an increase in portal supply after a meal^[66]. When released into portal circulation, FFAs are then taken up by hepatocytes^[64] mainly through long chain fatty acid synthetase activity provided by members of the FA transporter protein family^[67]. Once within the hepatocyte, FFAs are bound to coenzyme A as fatty acyl-CoAs to form hepatic triglycerides and stimulate the reduction of insulin-induced glucose uptake and induce intracellular inflammation^[64,68,69]. However, high levels of FFAs can induce intracellular inflammation and IR without being converted to fatty acyl-CoAs^[70].

In the process of DNL, excess glucose is released into the hepatic acetyl-CoA pool by glycolysis of carbohydrates for the production and storage of triglycerides^[71]. DNL provides 5%-10% of the hepatic triglyceride pool in the fasting state, with an increased contribution in IR individuals^[65,72]. DNL is modified by total energy intake, dietary fat to carbohydrate ratio, and glucose and insulin concentration^[73]. Thus, the hyperinsulinemia and hyperglycemia that occur with IR create an imbalance in lipid input relative to output and promote hepatic steatosis^[61]. The potent suppressive effect of insulin on hormone-sensitive lipase, the principal regulator of FFA release from VAT, is impaired in IR resulting in an increased efflux of FFAs^[74]. Hyperinsulinemia leads to an upregulation of transcription factors regulating DNL and an inhibition of FFA β -oxidation, further promoting hepatic fat accumulation^[35,64]. However, it has not yet been determined whether fatty liver results from IR of adipose tissue and skeletal muscle or from alteration of hepatic insulin signaling^[64]. Despite the role of VAT in liver fat accumulation through direct hepatic exposure to excess FFAs in the portal circulation, liver fat may be involved in IR in the absence of VAT, presumably by the secretion of hepatokines^[75]. Seppälä-Lindroos *et al.*^[76] concluded that liver fat correlates with IR independent of BMI and visceral adiposity. Fatty liver has also been observed in IR mice lacking VAT and subcutaneous fat and in IR humans with lipodystrophies^[77,78]. Furthermore, metabolic

syndrome was more strongly associated with VAT at lower levels of obesity, and with liver fat at higher obesity levels, independent of each other and of overall adiposity^[75]. Hepatic fat accumulation is a major determinant in T2D, which further contributes not only to hepatic steatosis level, but also to progressive liver damage in NASH, fibrosis, cirrhosis and HCC^[79].

Similar to the adipose tissue inflammation after adipocyte lipid accumulation, subacute inflammatory response in the liver might be induced by hepatic steatosis, involving oxidative stress in the endoplasmic reticulum (ER)^[64,80,81]. ER stress in liver and adipose tissue is induced by nutrient fluctuations and excess lipid levels in genetically or HFD-induced obese mice^[64,82]. Subacute inflammation, together with IR, hepatic steatosis, oxidative stress and impaired adipocytokine ratios, provide a favorable environment for HCC development by promoting cell growth kinetics and DNA damage^[79]. Furthermore, hepatocyte apoptosis induction, inflammatory cell invasion and activation, and fibrogenesis lead to cirrhosis, and possibly to NASH-related HCC^[20].

FA β -oxidation, which occurs in liver mitochondria^[61], may be impaired by the increased FFA load in NAFLD, resulting in the generation of reactive oxygen species^[83]. The resulting oxidative stress leads to liver injury, inflammation and the initiation and progression of fibrosis^[32]. Insufficient mitochondrial function along with structural abnormalities such as enlarged mitochondria, loss of mitochondrial cristae and presence of paracrystalline inclusion bodies, have been observed at all successive steps leading to NASH^[84].

CLINICAL PRESENTATION

NAFLD was initially thought to be more prevalent in women, though opposing results have been reported^[85]. Affected patients typically present between the fourth and sixth decade of life and are often overweight or obese^[40]. The majority of NAFLD patients are clinically asymptomatic, though some may present with fatigue, dyspepsia, dull pain in the liver and hepatosplenomegaly^[86]. Elevated liver enzymes are detected in approximately 20% of NAFLD patients^[86]. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels can be normal or moderately elevated (1.5 to 2 times the upper normal limit) with an AST/ALT ratio < 1, indicating that these enzymes are poor markers of fatty liver^[87,88]. In a large study by Marchesini *et al*^[89] including 799 obese subjects, median ALT and AST levels increased with obesity class and exceeded normal limits in 21% of subjects. Furthermore, alkaline phosphatase and gamma-glutamyl transpeptidase levels may vary, but independently of BMI^[90]. Stranges *et al*^[91] also concluded that BMI was not a reliable indicator, and found that abdominal height was consistently a better correlate of ALT and gamma-glutamyl transpeptidase levels in unrecognized fatty liver.

Low adiponectin levels are closely associated with non-alcoholic hepatic steatosis in healthy obese individu-

als^[92]. Shimada *et al*^[93] reported that the combined evaluation of the serum adiponectin level, homeostasis assessment model-insulin resistance score, and serum type IV collagen 7S level can predict 90% of early-stage NASH cases. Other metabolic markers that should be evaluated include the pro-atherogenic serum lipid profile, uric acid (20% of patients with NAFLD have hyperuricemia), urine microalbumin, high-sensitivity C-reactive protein, serum ferritin levels (1.5 times higher than normal in NASH), as well as fasting glucose, insulin, proinsulin and C-peptide levels^[40,87]. Targher *et al*^[94] have found that plasma concentrations of high-sensitivity C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1 activity are lower in non-obese healthy individuals, intermediate in overweight non-steatotic subjects, and highest in overweight patients with biopsy-proven NASH. In addition, variations in the intestinal microbiota have recently been linked both to obesity and NAFLD^[87]. A study by Muzaki *et al*^[95] identified a greater fecal level of *Clostridium coccoides* and a lower percentage of Bacteroidetes in NASH patients as compared to both simple steatosis and healthy control groups with lower BMIs.

Hepatic steatosis can be detected using noninvasive methods such as ultrasonography, computed tomographic scanning, magnetic resonance tomography and proton magnetic resonance spectroscopy, which is considered more accurate for measuring liver fat as it is a quantitative rather than qualitative or semiquantitative method^[96]. The most available method, ultrasonography, has sensitivity of 100% and specificity of 90% when fat on liver biopsy \geq 20%^[97], though technical difficulties lead to unreliable results in morbidly obese patients^[40]. Transient elastography (fibroscan) can be used to measure liver stiffness, which is a surrogate marker for fibrosis^[87]. However, as noninvasive procedures cannot distinguish simple steatosis from NASH, liver biopsy is considered the gold standard for NAFLD diagnosis^[87].

A study by Ciupińska-Kajor *et al*^[98] reported that morbid obesity is associated with a higher prevalence of more advanced fibrosis, confirming that severe fibrosis and cirrhosis are more common among morbidly obese individuals with NAFLD. Accordingly, the treatment for NAFLD and NASH is focused on weight reduction through lifestyle modifications, anti-obesity medication and bariatric surgery^[99]. In addition to significant weight loss, bariatric surgery promotes improvement in symptoms of metabolic syndrome in most obese patients with NAFLD, including T2D and pathological liver histological features such as grade of steatosis, hepatic inflammation, and fibrosis^[99-101].

CONCLUSION

Obesity reflects a generalized proinflammatory state with high risk for metabolic comorbidities, such as NAFLD, that are highly influenced by the distribution of adipose tissue. Evidence suggests that VAT is directly associated with the development and progression of NAFLD. The

most important pathological mechanisms in hepatic steatosis involve increased VAT secretion of proinflammatory cytokines and adipokines and release of FFAs into the portal system and systemic circulation, causing dyslipidemia and systemic IR. Obese patients with NAFLD usually do not present with specific symptoms besides a high BMI, metabolic syndrome manifestations and normal or moderately elevated liver enzyme levels. These patients should be followed in clinical practice for the development of diabetes and HCC, *via* ultrasound and alpha-fetoprotein every six months. Treatment should be centered on weight loss, exercise, diet and lifestyle changes, which should also be evaluated after six months. Furthermore, blood and platelet counts, as well as liver biochemical tests and prothrombin time should be evaluated twice per year, with screening for cardiovascular risk every one to two years. Importantly, staging of liver damage by liver biopsy, or newer non-invasive methods like transient elastography, if available, should be performed every three to five years.

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