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Review

Mechanistic link between nonalcoholic fatty liver disease and cardiometabolic disorders

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is a chronic condition characterized by fat accumulation combined with low-grade inflammation in the liver. A large body of clinical and experimental data shows that increased flux of free fatty acids from increased visceral adipose tissue can lead to NAFLD related with insulin resistance. Thus, individuals with obesity, insulin resistance, and dyslipidemia are at the greatest risk of developing NAFLD. Conversely, NAFLD is one of the phenotypes of insulin resistance or metabolic syndrome. Many researchers have discovered a close association between NAFLD and insulin resistance, and focused on the role of NAFLD in the development of type 2 diabetes. Further, substantial evidence has suggested the association between NAFLD and cardiovascular disease (CVD). In the current review, we provide a plausible mechanistic link between NAFLD and CVD and the potential of the former as a therapeutic target based on pathophysiology. We also discuss in detail about the role of insulin resistance, oxidative stress, low-grade inflammation, abnormal lipid metabolism, gut microbiota, changes of biomarkers, and genetic predisposition in the pathological linking between NAFLD and cardiometabolic disorders.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of cytoplasmic lipid droplets in more than 5% of hepatocytes in individuals without significant alcohol consumption and negative viral and autoimmune liver disease [1,2]. NAFLD is an umbrella term used to describe a disease spectrum with wide range from simple fat accumulation in the liver to hepatocyte damage. The simple hepatic steatosis is characterized by the deposition of triglyceride as lipid droplets in the cytoplasm of hepatocytes. Hepatic steatosis can progress to nonalcoholic steatohepatitis (NASH), which is distinguished from simple steatosis by the presence of hepatocyte ballooning, inflammation, and fibrosis. NASH can progress to cirrhosis [3].

The prevalence of NAFLD varies according to the diagnostic tools and study population. In the US, liver biopsies performed on potential liver donors revealed that 20% of donors had steatosis more than 30% [4]. Two autopsy series performed in Indians and Greeks revealed a broad spectrum in the prevalence of NAFLD from 16% to 31% [5,6]. A Korean study with 589 liver biopsy samples reported 51% of NAFLD prevalence [7]. Including results from non-invasive imaging techniques, the prevalence of NAFLD in the adults' population is estimated to be 20%–40% in Western countries [8] and 10%–30% in Asian countries [9,10], and it is increasing over time corresponding to increase of obesity [11].

NAFLD is recently considered as the hepatic component of the metabolic syndrome because it is a condition associated with obesity in which there is ectopic accumulation of triglycerides in the liver parenchyma [12]. Importantly, many NAFLD patients die from cardiovascular disease (CVD), which is leading cause of death in metabolic syndrome, more than from liver-related complications [13,14]. This fact suggests that there is potential link between NAFLD and cardiometabolic disorders. Along this line, insulin resistance and oxidative stress have been thought to be driving factors in progression of NAFLD to NASH, and both are well-known contributors to type 2 diabetes [15] and its macrovascular complications [14].

NAFLD shares a common pathophysiology with CVD, such as insulin resistance, oxidative stress, low-grade inflammation, and atherogenic

Abbreviations: NAFLD, nonalcoholic fatty liver disease; CVD, cardiovascular disease; NASH, nonalcoholic steatohepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; PKC, protein kinase C; IRS1, insulin receptor substrate-1; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; AMPK, AMP-activated protein kinase; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; AGE, advanced glycation end-product; SREBP-1c, sterol regulatory element binding protein-1c; TLR, Toll-like receptor; LPS, lipopolysaccharide; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor-1; PPAR, peroxisome proliferator-activated receptor.

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dyslipidemia [16–18]; however, it also has unique pathophysiological features, such as changes in gut microbiota [19]. In this review, we focus on updated information regarding these mechanisms and highlight the clinical implications of NAFLD from a therapeutic perspective.

2. Mechanistic link between NAFLD and cardiometabolic disorders

There is a growing body of evidence that NAFLD is specifically linked with metabolic syndrome. The Multi-Ethnic Study of Atherosclerosis (MESA) showed that more subjects with NAFLD had metabolic syndrome than NAFLD-free subjects (6.6% vs. 31.9%, $P < 0.001$) [18]. The Framingham Heart Study has shown that NAFLD is associated with dyslipidemia and abnormal glucose regulation independent of visceral adipose tissue [20]. Based on these findings, NAFLD has been widely regarded as liver manifestation of metabolic syndrome [21].

Several studies have investigated the relationship between NAFLD and the incidence of CV events. For example, it was reported that patients with NAFLD had a significantly higher risk of developing CV events than did the matched controls [22]. Another study from the US reported that intrahepatic lipid depots were more closely linked to cardiometabolic risk than to abdominal visceral fat [23]. Very recently, NAFLD was found to be independently associated with subclinical left ventricular dysfunction [24] and an independent predictor of faster progression of pulse wave velocity [25]. Thus, NAFLD is emerging as a possible independent predictor of incident CV events in patients with type 2 diabetes as well as in normal subjects [20,26,27].

Furthermore, CVD mortality is high among patients with NAFLD. A 14-year follow-up study reported that patients with NAFLD died from CVD more than from liver-related death [13]. Another clinical trial indicated that mortality rate from CVD was the second most common cause of death in subjects with NAFLD followed-up for 18 years [28]. These data underscore the importance of increased fat accumulation in the liver as a marker of the cardiometabolic disorders and related death.

2.1. Insulin resistance and a potential role of insulin sensitizers

Many studies from Western countries have shown that elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltranspeptidase (GGT), are predictors of the development of insulin resistance and type 2 diabetes [29,30]. In prospective community-based studies in Korea and Japan, elevated levels of ALT and GGT were associated with about two to four fold increase in the risk of type 2 diabetes after adjusting for traditional risk factors [31,32].

However, recent data indicated that patients with NAFLD or NASH and normal ALT levels showed a severity of liver disease that was similar to that of those with elevated ALT levels [33]. Moreover, the prevalence of NAFLD and NASH was more than 50% in diabetic patients with normal liver enzyme levels [34]. Therefore, elevated liver enzymes may represent the mechanistic link between metabolic syndrome and NAFLD, albeit with limited roles in the prediction of its severity.

Recent studies from both humans and animal models provide a good insight for insulin resistance on the relationship between NAFLD and cardiometabolic disorders. It has been demonstrated that increases in hepatic diacylglycerol content is implicated in NAFLD and it activates protein kinase C (PKC), resulting in deterioration of insulin signaling in the pathogenesis of NAFLD [15]. In addition, fatty acid accumulation in the liver causes hepatic insulin resistance characterized by a lack of suppression of endogenous liver glucose production [35] and acts as a stimulus for further increased whole-body insulin resistance and dyslipidemia, leading to accelerated atherosclerosis [36].

Thus, NAFLD/NASH induces hepatic insulin resistance, thereby contributes to development of cardiometabolic disorders. These findings suggest that fat accumulation in the liver is a critical determinant of metabolic flux, thereby representing an important therapeutic target in type 2 diabetes and possibly CVD [37].

Therapeutic lifestyle changes have led to improvement of insulin resistance and hepatic steatosis [38]. Metformin, an AMPK activator, regulates hepatic lipid metabolism by inducing adipose triglyceride lipase [39]. Interestingly, a recent study using *ob*/*ob* mice showed that metformin alleviates NASH by restoring SIRT1-mediated autophagy induction, which is independent of the AMPK pathway [40]. In contrast, metformin treatment had no beneficial effect on liver histology in two randomized trials [41,42]. Thus, the efficacy of metformin in the treatment of NAFLD has not been confirmed. Ninety six-week treatment with pioglitazone, which is a peroxisome proliferator-activated receptor-γ (PPARγ) agonist, reduced insulin resistance and hepatic steatosis, but did not improve NASH [43]. Therefore, there is insufficient evidence to recommend a specific drug that targets insulin resistance for the treatment of NAFLD or NASH.

2.2. Oxidative stress and antioxidant therapy

Oxidative stress plays an important role in the progression from simple steatosis to steatohepatitis (Fig. 1) [44,45]. Increased delivery of FFAs to the portal circulation results in increased oxidative stress [46]. Thus, oxidative stress induced during development of NAFLD may be involved in the pathogenesis of CVD.

The association between oxidative stress and NAFLD in humans has been demonstrated by the immunohistochemical detection of lipid peroxidation products and 8-hydroxy-deoxyguanosine, an oxidative stress maker, from patients with NAFLD [47]. There is also evidence supporting the activation of oxidative stress and increased levels of homocysteine, a marker of elevated CV risk, in NAFLD [48]. Oxidative stress also induces the hepatic production of adhesion molecules and interleukins, which can perpetuate the vicious cycle of inflammation [49].

Advanced glycation end-product (AGE) synthesis is increased in steatohepatitis [50]. AGE affects gene expression, intracellular signaling, and the secretion of pro-inflammatory factors, and induces reactive oxygen species (ROS) production in the liver [51]. Serum AGE levels appear to be an independent predictor of vascular inflammation [52]. These data suggest that oxidative stress derived from the disease process in NAFLD is involved in the pathogenesis of CVD. Thus, NAFLD promotes oxidative stress and may initiate abnormal glucose homeostasis and develop CVD.

Vitamin E has antioxidant properties, and a 2-year treatment with vitamin E decreased AST and ALT levels, which was accompanied by the improvement of the histological features of NASH [43]. Another study that used a cocktail of vitamins E and C with atorvastatin reduced the development of NAFLD by 70% after 4 years of treatment [53]. However, further studies are needed to establish the effect of antioxidants on NAFLD and their additional CV benefits.

2.3. Low-grade inflammation and anti-inflammatory approaches

Ectopic fat accumulation in the liver and the subsequent activation of the inflammation pathway cause cellular dysfunction [54]. In particular, hepatic steatosis instigates the pathogenesis of CVD through the systemic release of several mediators related with inflammation [55]. Among them, nuclear factor-κB (NF-κB) and c-Jun *N*-terminal kinase (JNK) are known as the main intracellular signaling pathways involved in both NAFLD and inflammation. The activation of the NF-κB pathway in the liver of patients with NAFLD leads to steatosis or NASH, which in turn enhances the transcription of several genes, such as the intercellular adhesion molecule-1 (ICAM-1) and monocyte chemoattractant protein-1 (MCP-1) [56]. On the other hand, JNK aggravates insulin resistance via the phosphorylation and degradation of insulin receptor substrate-1 (IRS1), and contributes to the inhibition of the intracellular signaling pathway downstream of the insulin receptor [57].

Recent studies have shown a crucial role of inflammatory mediators in the link between fat accumulation in the liver and development of cardiometabolic disorders [58,59]. According to the MESA, a longitudinal,