Journal of Metabolic Syndrome
ISSN: 2167-0943

Roever et al., J Metabolic Synd 2015, 5:1
DOI: 10.4172/2167-0943.1000191

Short Communication Open Access

The Role of Hepatokines in Cardiovascular Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is considered a hepatic manifestation of metabolic syndrome, and associated with the risks of developing cardiovascular disease (CVD) and type 2 diabetes mellitus (DM2). A group of liver-derived proteins called hepatokines directly affect the pathogenesis of atherosclerosis by modulating endothelial dysfunction and infiltration of inflammatory cells. In this review we summarize the role of the representative hepatokines in the progression of CVD.

Keywords: Heart disease; Hepatokines; Non-alcoholic fatty liver disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of chronic liver disease in many developed countries. A third of the population has evidence of steatosis on imaging (70%–90% - simple steatosis). It is a progressive liver disease, including simple steatosis, steatohepatitis, fibrosis and cirrhosis [1-8]. NAFLD includes four categories:

Type 1: Isolated Steatosis

Type 2: Steatosis plus lobular inflammation

Type 3: Steatosis, lobular inflammation and ballooning of hepatocytes

Type 4: Steatosis, lobular inflammation, ballooning of hepatocytes, and Mallory bodies and/or fibrosis

A NAFLD is the result of the accumulation of lipids, and is associated with one or more features of the metabolic syndrome. Many mechanisms may lead to a NAFLD: (A); decreased hepatic very low density lipoprotein–triglyceride secretion; (B) decreased free fatty oxidation oxidation; (C) increased de novo hepatic lipogenesis (DNL) and (D) increased free fatty acids supply due to increased lipolysis from both visceral/subcutaneous adipose tissue and/or increased intake of dietary fat [9,10].

A NAFLD is an ectopic fat accumulation combined with a low-grade chronic inflammatory state, and the accumulation of fat droplets decreases the efficacy of insulin signaling, leading to an endoplasmic reticulum stress, which leads to activation of c-Jun N-terminal kinases and nuclear factor kB (NF-kB), which regulate the inflammatory pathways which can inhibit the phosphorylation of insulin receptor-1 substrate [11,12].

The mechanism by which NAFLD increases the risk of CVD is still rises investigation. It is still controversial whether NAFLD is an independent risk factor for cardiovascular disease or is a risk marker in patients with increased risk of CVD. The mechanism proposed is based on inflammation visceral adipose tissue, through which a high flow of free fatty acids (FFAs) into the portal vein for direct transport to the liver and subsequent accumulation of liver fat. This leads to an intra-hepatic inflammation through the activation of NF-kB pathways that exacerbate the insulin resistance in the liver both locally and systemically, that will release a variety of pro-atherogenic factors, pro-inflammatory and diabetogenic (hsCRP, fibrinogen , PAI-1)[13,14].

Recent studies suggest that NAFLD is an emerging risk factor for cardiovascular disease (CVD), which may be directly involved in the pathogenesis CVD. In this review we summarize the relationship between NAFLD and CVD, with emphasis on the relationship of hepatokines derived from the liver and the progression of CVD (Figure 1).

Recent studies suggest that hepatokines (Fibroblast growth factor 21 (FGF-21), fetuin-A) and selenoprotein P (SEP) directly affect the metabolism of glucose and lipids [15].

In a study that evaluated the flow-mediated dilation of the brachial artery (FMD), a reduction was observed in 48% in subjects with NAFLD and NAFLD predicted a reduced proportion of FMD (odds [OR], 6.7; range 95% confidence [CI], 1.26 to 36.1) after adjustment for age, sex, BMI and insulin resistance [16]. In another study that used CT, fatty liver was significantly associated with the presence of vulnerable plaques with a lipid core [17].

A systematic review of 27 studies showed that NAFLD is associated with subclinical atherosclerosis independent of traditional risk factors and metabolic syndrome. This study examined the association of NAFLD with carotid intima media thickness (CIMT) which showed a significant increase in CIMT average in individuals with NAFLD compared with the control group [18].

In a study of 7.3 years of follow-up, a high level of γ-glutamyl transferase, was significantly associated with increased risk of all-cause and cardiovascular mortality in men, even after adjusting for other metabolic risk factors [19].

In a study of 2839 patients with type 2 diabetes mellitus (DM2), those with NAFLD had higher prevalence of coronary, cerebrovascular and peripheral vascular disease than those without NAFLD, independent of conventional risk factors for CVD, medication history, and the variables related to diabetes [20].

Selenoprotein P (SeP), is a 42 kDa glycoprotein produced by the liver that is secreted into the plasma, and is associated with insulin resistance in humans in series by analysis of gene expression. The infusion SeP rats decreased insulin signaling and glucose metabolism

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Received October 20, 2015; **Accepted** November 27, 2015; **Published** December 03, 2015

Citation: Roever L, Resende ES, Borges ASR (2015) The Role of Hepatokines in Cardiovascular Disease. J Metabolic Synd 4: 191. doi:10.4172/2167-0943.1000191

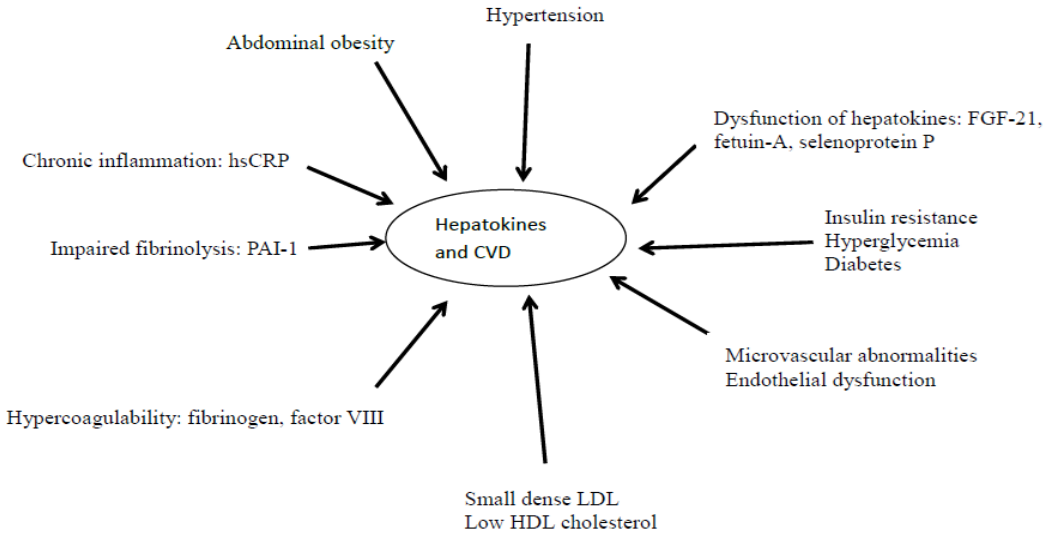

Figure 1: Risk factors in nonalcoholic fatty liver disease (NAFLD) that influence cardiovascular disease (CVD). PAI-1, plasminogen activator inhibitor-1; FGF-21, fibroblast growth factor 21, hsCRP, high-sensitivity C-reactive protein.

in liver and skeletal muscle, while a deficiency in mice was correlated with an increase in insulin signaling and improves glucose tolerance [21]. In patients with type 2 diabetes and NAFLD showed Sep serum levels higher than controls [22]. In another study the circulating level of SeP was associated independently with thickness of carotid intima-media [23].

Fibroblast growth factor 21(FGF-21) is a 181-amino acid peptide hormone that is secreted by the liver and acts as a metabolic regulator. Its infusion in animal models and humans has been shown a decrease in body weight, triglyceride and LDL-C, and improved insulin sensitivity [24-26]. Another study showed that FGF-21 in knockout mice was observed an increase in heart weight and heart dysfunction, which can be improved with treatment with FGF-21 and FGF-21 infusion in experimental infarction was associated with a significantly recovery of cardiac function after myocardial infarction [27-29]. In other studies it was shown that FGF-21 levels as independent factors of occurrence of the carotid and coronary artery disease (OR, 2.98; 95% CI 1.014 to 8.786; $p < 0.05$) [30,31].

Fetuin-A is a 64-kDa phosphorylated glycoprotein that is synthesized by hepatocytes and is a natural inhibitor of the insulin receptor tyrosine kinase, leading to insulin resistance in rodents [32,33]. Fetuin-A promotes insulin resistance and propagates the pro-inflammatory state [34,35]. Several epidemiological studies have found high levels of fetuin-A in obesity and metabolic diseases (diabetes, metabolic syndrome and NAFLD) [36,37].

In other studies it was demonstrated a significant decrease in circulating levels of fetuin-A after 12 weeks of caloric restriction, there was a reduction in visceral fat area, blood pressure, lipid profile, glucose levels, and the incidence of diabetes after adjustment for gender, body mass index, waist circumference, and risk factors for 7 years of follow-up.

Conclusion

The hepatokines influence glucose metabolism, lipid and modulate inflammatory processes that mediate atherosclerosis and they are associated with CVD. More prospective studies should be done to elucidate the association of risk factors, hepatokines and CVD. Strategies for diagnosing and treating disorders related hepatokines of NAFLD and CVD should be implemented to reduce the impact on morbidity and mortality of these diseases.

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