LIVER RESEARCH

Openventio PUBLISHERS

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-107

Mini Review

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Volume 1 : Issue 2
Article Ref. #: 1000LROJ1107

Article History
Received: July 10th, 2015
Accepted: July 27th, 2015
Published: July 29th, 2015

Citation
de Siqueira ERF, Pereira LMMB, Sanyal AJ. Cardiovascular disease and NASH. *Liver Res Open J.* 2015; 1(2): 41-44. doi: 10.17140/LROJ-1-107

Cardiovascular Disease and NASH

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) and Non-alcoholic steatohepatitis (NASH) are associated with cardiovascular events and Metabolic Syndrome (MetS). NAFLD is considered to be a hepatic manifestation of MetS and has become an important public health issue because of its high prevalence. It is currently being considered an independent Cardiovascular disease (CVD) risk factor. In this clinical review, we will briefly review the mechanisms linking NAFLD to the complement system, endothelial dysfunction and the atherosclerosis.

KEYWORDS AND ABBREVIATIONS: NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; CVD: Cardiovascular disease; MetS: Metabolic Syndrome: AF: Atrial Fibrillation; CAC: Coronary Artery Calcium; CT: Computed Tomography; FFAs: Free Fatty Acids; LDL-C: Low-density Lipoprotein-Cholesterol; HMGCR: HMG CoA Reductase; VLDL: Very-low-density lipoprotein; CAD: Coronary Artery Disease.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has become a predominant cause of chronic liver disease in many countries. Excess body weight predisposes individuals to chronic diseases such as cardiovascular disease (CVD), Type 2 Diabetes Mellitus (T2DM) and NAFLD. NAFLD and cardiovascular disease is obesity related MetS and it is increasing virtually in all age groups worldwide.[1] Approximately 10-30% have the potentially progressive form of NAFLD to Non-alcoholic steatohepatitis (NASH), which is associated with hepatocellular injury, inflammation and ultimately resulting in cirrhosis in 20-30%.[2-4]

A population-based study of 980 NAFLD patients and 6,594 controls followed long term (mean: 8.7 years) showed that NAFLD patients had significantly increased all-cause mortality and cardiovascular mortality, especially in the 45-54 years age group.[5] Another study that linked NHANES III participants to follow-up mortality data showed that cardiovascular disease was the leading cause of death in patients with NAFLD.[6]

Several evidences support the association of NAFLD/NASH and the occurrence of cardiovascular events, such as increased carotid intima-media thickness, increased coronary artery calcification, impaired flow-mediated vasodilatation and arterial stiffness independent of traditional risk factors and MetS.[7-9]

The finding that NAFLD is associated with an increased risk of Atrial Fibrillation (AF) in people without evidence of co-existing valvular heart disease supports the assertion that NAFLD may also be an emerging risk factor for cardiac arrhythmias.[10,11] Another marker of early coronary atherosclerosis is association of NAFLD and increased Coronary Artery Calcium (CAC) score on cardiac Computed Tomography (CT).[12]

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-107

In this clinical review, we will briefly review the mechanisms linking NAFLD to the risk of cardiovascular events.

MECHANISMS LINKING NAFLD WITH CARDIOVASCULAR EVENTS

Data in the literature are still controversial regarding the increased cardiovascular risk with NASH. A large North American database reported a higher prevalence of CVD risk factors and events in patient with NAFLD in comparison with those without. Nonetheless, the rate of CVD mortality was not high in subjects with NAFLD.[13] Previous studies have already demonstrated the presence of NAFLD independently increased the risk for Coronary Artery Disease (CAD) and NAFLD was more commonly found in patients as the extent of CAD increased (P=0.001).[14] It has also been shown that risk, after adjustment for age, sex, race, ethnicity, body mass index, and hyperinsulinemia, children with MetS had 5.0 times the odds of having NAFLD as overweight and obese children without MetS.[15]

In another prospective, Japanese study of 1221 apparently healthy subjects, patients with NAFLD showed an increased incidence of CVD events (1.0% *vs.* 5.2%; P<0.001) and NAFLD emerged as an independent predictor of CVD.[16] However, there were no differences in the incidence of fatal CVD, non-fatal myocardial infarction, and coronary revascularization after the follow up.[17]

The CVD is characterized by critically narrowing (stenosis) or occlusion (atherothrombosis) of blood vessels. Key processes in CVD are endothelial dysfunction, atherosclerosis, and impaired regulation of coagulation and fibrinolysis. The complement system may be involved in all these processes based on its immune, inflammatory and metabolic functions.[18]

Furthermore, systemic complement levels may be involved in coagulation and fibrinolysis, which together with endothelial dysfunction and atherosclerosis result in cardiovascular disease.[18] The complement-C3 has shown independent associations with insulin resistance, liver dysfunction and in the risk of MetS and T2DM.[19,20]

Circulating levels of several inflammatory markers (C-reactive protein, interleukin-6, monocyte chemotactic protein 1, and TNF-a), procoagulant factors (plasminogen activator inhibitor 1, fibrinogen, and factor VII), and oxidative stress markers are highest in patients with NASH independent of obesity and other potentially confounding factors.[21] NAFLD seems to be not simply a marker of cardiac and arrhythmogenic complications but also may play a part in their pathogenesis possibly *via* atherogenic dyslipidemia and the hepatic secretion of several pathogenic mediators.[22,23]

Central obesity can provoke inflammation and insulin resistance in adipose tissue and the release of proinflammatory adipokines and Free Fatty Acids (FFAs). Relation of hepatic steatosis to atherogenic dyslipidemia results from previous studies that liver fat is associated with an increased number of higher Low-density Lipoprotein-Cholesterol (LDL-C), in special the small dense LDL (sdLDL) particles, which have higher atherogenic properties than larger less dense LDL-C particles.[24-26]

These lipoproteins are associated with increased activity of hepatic lipase favoring the production of sdLDL particles.[27] Patients with NASH can have the transcriptional regulation of proatherogenic genes altered and it is associated with the activation of molecular events that may also be responsible for the local production of mediators or modifiers of circulatory homeostasis.[28]

In particular, NASH presents a distinct panel of regulatory genes which are dysregulated compared to the control and subjects with simple steatosis. Increased activation of genes involved in cholesterol biosynthesis and metabolism by Sterol Regulatory Element-binding Protein-2 (SREBP-2), the principal transcriptional activator of the HMG CoA Reductase (HMGCR), the metabolic pathway that produces cholesterol and other isoprenoids, is a key factor driving both the LDL-C and accumulation of hepatic free cholesterol.[29,30]

NAFLD is associated with increased Very-low-density lipoprotein (VLDL) particle concentration and apolipoprotein b (ApoB), sdLDL particle concentration and cholesterol content. The triglyceride levels, VLDL particle concentration and size as well as ApoB were directly related to the degree of fasting insulin levels which is consistent with the known effects of insulin on triglyceride synthesis.[31]

The atherogenecity of the increase in sdLDL is likely to be further compounded by our previously noted decrease in LDL receptor expression in NASH.[29] From a cardiovascular point of view the direct relation between LDL-C and HMGCR expression suggests that the liver disease contributes to LDL-mediated cardiovascular risk.[29]

CONCLUSION

In this context, the liver represents also a contributor to systemic inflammatory changes, insulin resistance and hyperlipidemia determining a progression of vascular diseases and atherosclerosis. NAFLD/NASH are associated with an increased risk of incident cardiovascular disease, independently of the traditional risk factors. Therefore, a multidisciplinary approach to patients with multiple risk factors including MetS and T2DM is required to monitor for cardiovascular and liver complications.

DECLARATION OF INTEREST

The authors declare that they have no competing interests.

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