Non-Alcoholic Fatty Liver Disease as Risk of Cardiovascular Disease: Myth or Reality?

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Abstract: Nonalcoholic fatty liver disease (NAFLD) includes a wide spectrum of liver conditions ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) and advanced hepatic fibrosis. Taking into account that NAFLD shares many common risk factors with cardiovascular diseases, it is evident that NAFLD may promote to increased cardiovascular morbidity and mortality.

Cumulative evidence suggests that NAFLD is linked to atherosclerosis, coronary artery disease, obesity, type 2 diabetes, and also predicts the clustering of risk factors for cardiovascular diseases.

To our opinion, the role of NAFLD in the prediction of cardiovascular risks should be investigated for coronary artery disease (CAD) prognosis assessment

This review focuses on the pathophysiologic relationships between NAFLD and cardiovascular diseases, subclinical and clinical cardiovascular manifestations in NAFLD.

Keywords: Nonalcoholic fatty liver disease, Cardiovascular risk, Coronary artery disease, Atherosclerosis.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common hepatic disease in developed countries and represents not only liver related morbidity and mortality but also affecting other systems and regulatory pathways.

The main focus of the NAFLD related extrahepatic pathologies has involved cardiovascular diseases and type 2 diabetes mellitus. Several studies confirm that patients affected by NAFLD have a higher risk of developing cardiovascular (CV) abnormalities and events [1, 2]. Studies may provide pathophysiologic evidence of relationships between NAFLD and development of cardiovascular complications, particularly metabolic, systemic vascular inflammation, hypercholesterolemia. Based on clinical research data the development of CVD is substantially influenced by NAFLD and NASH (non-alcoholic steatohepatitis), and its prevention may provide an indication to therapy of NAFLD and NASH.

PATHOGENESIS AND RESULTS OF STUDIES

Several clinical investigations provide evidence of NAFLD pathogenetic role in the development of cardiovascular diseases and relationships between NAFLD and subclinical CAD. Both in cross-sectional and in follow-up studies, NAFLD has been shown to be an independent risk factor for the presence or future development of increased intima-media thickness and of impaired flow-mediated vasodilatation; the presence of carotid atherosclerotic lesions; an increased coronary artery calcium score on cardiac computed tomography; and abnormal coronary flow reserve as a marker for impaired coronary microcirculation. These data are confirmed by report of recent meta-analysis of 27 studies [3]. Recently in a cohort of 755 consecutive otherwise healthy adult men [4, 5] also presented a strong and independent association between NAFLD and carotid artery inflammation, which is reflecting plaque vulnerability evaluated by F-fluorodeoxyglucose positron emission tomography [6]. The review of several studies shows that NAFLD is an independent predictor for clinical CAD, measured as the severity of the atherosclerotic lesions on coronarography or the occurrence of fatal and number of non-fatal CAD events [7, 8]. At the same time, few studies did not confirm the independent relationship of NAFLD with incident CAD or showed it to be confined to patients with NAFLD who concomitantly met the diagnosis of the metabolic syndrome [9]. Several studies also showed a link between NAFLD and alterations in cardiac metabolism, structure and hemodynamic function, such as myocardial insulin resistance and mitochondrial adenosine triphosphate (ATP) production, cardiac steatosis, myocardial hypertrophy and left ventricular diastolic dysfunction, not attributable to concomitant diabetes, obesity or arterial hypertension. The severity of these cardiac

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abnormalities correlated with the severity of the NAFLD.

Interestingly, recent data have shown that NAFLD is also independently linked with cQT interval prolongation, a major risk factor for ventricular arrhythmias and sudden cardiac death, which might explain in part the increased CV mortality associated with NAFLD [10].

Several data showed that NAFLD promotes to the progression of diastolic heart failure (independently of hypertension) and aortic valve sclerosis [11].

Pathogenetic role of NAFLD influences to the progression of atherosclerosis and several cardiovascular pathologies include abnormalities of myocardial metabolism and fat accumulation, increased incidence of atrial fibrillation [12] and prolongation of QT interval [13], obesity with left ventricular diastolic dysfunction [14], aortic valve sclerosis [15], NAFLD, type 2 diabetes mellitus, metabolic syndrome and cardiovascular diseases share many metabolic features and risk factors, leading to the theory that they belong to a complex multi-system disease with several organ manifestation and complex interplay between the different mechanisms, with multiple bidirectional cause-effect relationships. There are several mechanisms interplaying in pathogenesis of cardiovascular complications in NAFLD, where each of them may contribute independently to the progression of cardiovascular morbidily. So far as the liver is a key organ in both glucose and lipid homeostasis, it is not surprising that evidence is accumulating that NAFLD plays a role in the development of type 2 diabetes mellitus and the metabolic syndrome, which are by themselves are cardiovascular risk factors. NAFLD has indeed been shown to contribute to the development of diabetes mellitus. Several studies with NAFLD confirmed by ultrasound or liver enzymes, have shown that NAFLD proceeds and predict the future development of T2DM independent of obesity and other factors of the metabolic syndrome [16].

It is clear also that NAFLD may be associated with an atherogenic lipid profile. In NAFLD, production of triglyceride-rich VLDL particles is increased [17]. Insulin normally inhibits adipose tissue lipolysis (the main source of FFA flux to the liver for hepatic triglycerides synthesis) and hepatic VLDL secretion, both of which are hence increased in association with hepatic and adipose tissue insulin resistance [18]. Subsequently, HDL-cholesterol levels fall and LDL-cholesterol levels rise, both of which are highly atherogenic conditions.

Endothelial dysfunction has been shown to be an early event in the development of atherosclerosis. Several studies have recently highlighted that insulin resistance at the endothelial level occurs early in the development of NAFLD and is already present after a few days of high fat feeding, when steatosis develops but inflammation seems still to be absent [19].

In addition to macrovascular changes, NAFLD is also associated with microvascular complications, such as nephropathy, retinopathy, and neuropathy. Accumulating evidence has demonstrated that NAFLD is associated with increased prevalence and incidence of chronic kidney disease, defined as presence of microalbuminuria, overt proteinuria or an estimated glomerular filtration rate (GFR) <60 ml/min/1.73 m^2, in both non-diabetic and diabetic individuals [20].

Hepatic insulin resistance has been shown to be increased in severe steatosis and this occurs due to endothelial damage. Furthermore, steatosis also induces structural abnormalities of liver vasculature, contributing to the associated increase in intrahepatic resistance. Angiogenic factors have been shown to play a role in the intrahepatic vascular changes in cirrhosis and are also studied in NASH. Altered levels of angiogenic factors, well documented in the atherosclerosis [21], have been observed in the peripheral blood of patients with NASH.

Adiponectin, which is lower in patients with NAFLD, is another factor that might represent a link between NAFLD and CVD. Adiponectin has anti-atherogenic properties and directly affects endothelial function. It also stimulates circulating angiogenic cells.

Inflammatory cytokines, which are activated in NAFLD and NASH may play pathogenic role to the systemic vascular inflammation and proatherogenic effects [22].

Recent studies suggest the NAFLD/NASH is characterized by inflammation of the liver which may secrete pro-inflammatory, pro-fibrogenic, and anti-fibrinolytic substances, including fetuin-A, tumor necrosis factor-alpha and plasminogen activator inhibitor-1, all causing kidney injury. The above mentioned meta-analysis also found that even mild renal impairment may promote NAFLD generation, within a vicious cycle, with cardiovascular diseases and metabolic consequences suggesting that kidney

diseases may contribute to the pathogenesis of NAFLD [23, 24].

Although all these mechanisms are plausible links between the liver affected by NAFLD and the development of CVD, no studies to date have scientifically proven a cause-effect relationship. Most probably, several mechanisms are concomitantly present, and might substantially differ between patients. Further study is therefore needed to gain mechanistic insights into the pathophysiology of the NAFLD-CVD axis, with an individualized preventive and therapeutic as the ultimate goal.

Figure **1** illustrates the pathophysiological relationships between NAFLD end cardiovascular complications

TREATMENT

Currently there is no approved pharmacological treatment for NAFLD. Although it can be hypothesized that improving NAFLD reduces the risk of CVD, there is currently limited data on potential changes in the risk of CVD in relation to the success of NAFLD treatment. Interestingly, two recent studies on the effects of statins on CV events demonstrated a significantly reduced CV event rate in those patients with baseline elevation of liver tests (used as a surrogate marker for the presence of NAFLD) as well as significantly improved liver tests in one of the studies [25]. The cardio-protective effect of statins was less pronounced in patients with normal liver tests at baseline. Glitazones also improve CV risk, but it is unclear to what extent this can be attributed to their beneficial effect on NAFLD. Furthermore, as outlined previously, it is not clear whether the risk of CVD is increased in all subtypes of NAFLD. Therefore, no evidence-based recommendation can be formulated at present.

Currently it is recommended to screen for NAFLD in every patient with risk factors for CVD or established CVD and to screen for NAFLD in every patient with NAFLD. Patient should be treated accordingly with life-style modification. This recommendation is debated, as there are no data on cost-effectiveness and no pharmacological treatment when NAFLD is diagnosed.

CONCLUSION

The prevalence of NAFLD is growing worldwide and NAFLD is a widespread disease because of epidemics of obesity, diabetes, and metabolic syndrome. NAFLD also has an increased risk of multisystem affection particulary cardiovascular syste, with increased morbidity and mortality.

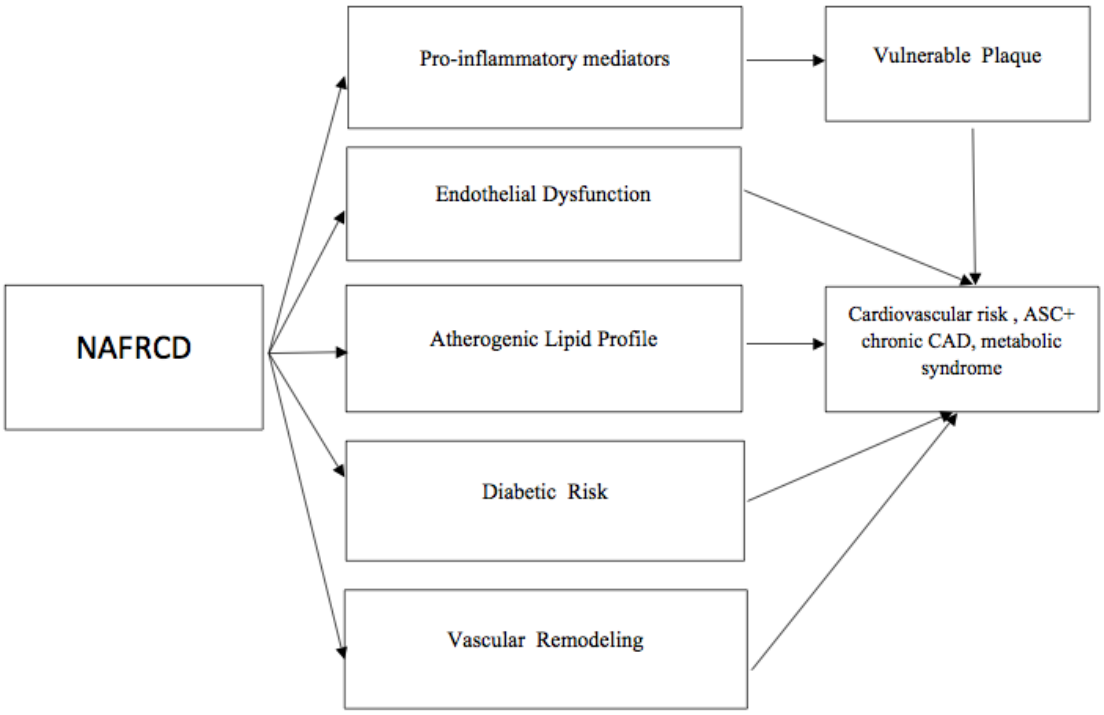

Figure 1: represents the pathophysiological relationships between NAFLD end cardiovascular complications.

The review of pathophysiologic interrelationships between NAFLD and cardiovascular complications and results of several clinical studies and their meta-analyses provide further evidence that NAFLD represents an independent risk factor to the development of atherosclerosis and CAD, metabolic syndrome, with increased cardiovascular mortality. Several clinical states such as metabolic syndrome with atherogenic profile, increased intima-media thickness, high inflammatory markers in blood plasma may serve as clinical indicators of NAFLD cardiovascular unfavorable effects and may contribute to cardiovascular diseases progression and increased cardiovascular risk.

A number of prognostic markers are commonly used in clinical practice for cardiovascular risk estimation including other systemic abnormalities on the Global Registry of Acute Coronary Events (GRACE) score, on the Thrombolysis in Myocardial Infarction (TIMI) risk score. In all these scores there is no liver pathology related clinical or laboratory scaled data. Taking into consideration that the NAFLD has several overlapping relationships with cardiovascular diseases and endothelial dysfunction, the role of NAFLD in the prediction of cardiovascular risks should be investigated for CAD assessment. Further studies with large population of patients for the assessment of major cardiovascular events of CAD and NAFLD patients, including acute myocardial infarction, may provide evidence in elucidating of this both liver related pathology and problem. Early detection of NAFLD and NASH, advanced fibrosis may lead to the treatment of cardiovascular risk factors with lifestyle measures and multifactorial drug intervention.

REFERENCES

[1] Perseghin G. The role of non-alcoholic fatty liver disease in cardiovascular disease. Dig Dis 2010; 28(1): 210-3. http://dx.doi.org/10.1159/000282088

[2] Dam-Larsen S, Franzmann M, Andersen IB. *et al*. Long term prognosis of fatty liver: risk of chronic liver disease and death. Gut 2004; 53: 750-5. http://dx.doi.org/10.1136/gut.2003.019984

[3] Oni ET, Agatston AS, Blaha MJ, Fialkow J, Cury R, Sposito A. *et al*. A systematic review: burden and severity of subclinical cardiovascular disease among those with nonalcoholic fatty liver; should we care? Atherosclerosis 2013; 258-67. http://dx.doi.org/10.1016/j.atherosclerosis.2013.07.052

[4] Fracanzani AL, Tiraboschi S, Pisano G, Consonni D, Baragetti A. *et al*. Progression of carotid vascular damage and cardiovascular events in non-alcoholic fatty liver disease patients compared to the general population during 10 years of follow-up. Atherosclerosis 2016 Jan 12; 246: 208-13. http://dx.doi.org/10.1016/j.atherosclerosis.2016.01.016

[5] Bonci E, Chiesa C, Versacci P, Anania C, Silvestri L. Association of Nonalcoholic Fatty Liver Disease with Subclinical Cardiovascular Changes: A Systematic Review and Meta-Analysis. Biomed Res Int 2015; 2015: 213737. http://dx.doi.org/10.1155/2015/213737

[6] Moon SH, Noh TS, Cho YS, Hyun SH, Choi JY. *et al*. Association between nonalcoholic fatty liver disease and carotid artery inflammation evaluated by 18F-fluorodeoxy¬glucose positron emission tomography. Angiology 2014, [Epub ahead of print].

[7] Ballestri S, Lonardo A, Bonapace S. *et al*. Risk of cardiovascular, cardiac and arrhythmic complications in patients with non-alcoholic fatty liver disease. World J Gastroenterol 2014; 20: 1724-45. http://dx.doi.org/10.3748/wjg.v20.i7.1724

[8] Ampuero J, Gallego-Durán R, Romero-Gómez M. Association of NAFLD with subclinical atherosclerosis and coronary-artery disease: meta-analysis. Rev Esp Enferm Dig 2015 Jan; 107(1): 10-6.

[9] Yki-Jarvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol 2014; 2: 901-10. http://dx.doi.org/10.1016/S2213-8587(14)70032-4

[10] Hung CS, Tseng PH, Tu CH, Chen CC, Liao WC. Nonalcoholic Fatty Liver Disease is Associated with QT Prolongation in the General Population. J Am Heart Assoc 2015 Jul 21; 4(7). http://dx.doi.org/10.1161/JAHA.115.001820

[11] Bonapace S, Valbusa F, Bertolini L, Pichiri I, Mantovani A. *et al*. Nonalcoholic fatty liver disease is associated with aortic valve sclerosis in patients with type 2 diabetes mellitus 2014; 9(2): e88371.

[12] Käräjämäki AJ, Pätsi OP, Savolainen M, Kesäniemi YA, Huikuri H, Ukkola O. *et al*. Non-Alcoholic Fatty Liver Disease as a Predictor of Atrial Fibrillation in Middle-Aged Population (OPERA Study). PLoS One 2015 Nov 16; 10(11). http://dx.doi.org/10.1371/journal.pone.0142937

[13] Targher G, Valbusa F, Bonapace S, Bertolini L, Zenari L. Association of nonalcoholic fatty liver disease with QTc interval in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis 2014 Jun; 24(6): 663-9. http://dx.doi.org/10.1016/j.numecd.2014.01.005

[14] Mantovani A, Pernigo M, Bergamini C, Bonapace S, Lipari P. *et al*. Nonalcoho¬lic Fatty Liver Disease Is Independently Associated with Early Left Ventricular Diastolic Dysfunction in Patients with Type 2 Diabetes. PLoS One 2015 Aug 7; 10(8). http://dx.doi.org/10.1371/journal.pone.0135329

[15] Mantovani A, Pernigo M, Bergamini C, Bonapace S, Lipari P. *et al*. Heart valve calcification in patients with type 2 diabetes and nonalcoholic fatty liver disease. Metabolism 2015 Aug; 64(8): 879-87. http://dx.doi.org/10.1016/j.metabol.2015.04.003

[16] Zhonghua Liu Xing Bing Xue Za Zhi. Relations between nonalcoholic fatty liver disease and metabolic syndrome 2014 Sep; 35(9): 1062-4.

[17] Lucero D, Zago V, López G, Graffigna M, Fainboim H. Pro-inflammatory and atherogenic circulating factors in non-alcoholic fatty liver disease associated to metabolic syndrome. Clin Chim Acta 2011 Jan 14; 412(1-2): 143-7. http://dx.doi.org/10.1016/j.cca.2010.09.025

[18] Luukkonen PK, Zhou Y, Sädevirta S, Leivonen M, Arola J. Ceramides Dissociate Steatosis and Insulin Resistance in the Human Liver in Non-Alcoholic Fatty Liver Disease. J Hepatol 2016 Jan 9. pii: S0168-8278(16)00005-2.

[19] Cao Y, Li L. Relationship of non-alcoholic steatohepatitis with arterial endothelial function and atherosclerosis. Zhonghua Gan Zang Bing Za Zhi 2014 Mar; 22(3): 205-8.

[20] Musso G, Gambino R, Tabibian JH, Ekstedt M, Kechagias S. *et al*. Association of non-alcoholic fatty liver disease with

chronic kidney disease: a systematic review and meta-analysis. PLoS Med 2014 Jul 22; 11(7): e1001680. http://dx.doi.org/10.1371/journal.pmed.1001680

[21] Tarantino G, Costantini S, Finelli C, Capone F, Guerriero E. *et al*. Carotid intima-media thickness is predicted by combined eotaxin levels and severity of hepatic steatosis at ultrasonography in obese patients with Nonalcoholic Fatty Liver Disease. PLoS One 2014 Sep 30; 9(9): e105610. eCollection 2014.

[22] Coulon S, Francque S, Colle I, Verrijken A, Blomme B. *et al*. Evaluation of inflammatory and angiogenic factors in patients with non-alcoholic fatty liver disease. Inflamationv sksvox 17 poxel Cytokine 2012 Aug; 59(2): 442-9. http://dx.doi.org/10.1016/j.cyto.2012.05.001

[23] Dogru T, Genc H, Tapan S, Aslan F, Ercin CN. *et al*. Plasma fetuin-A is associated with endothelial dysfunction and subclinical atherosclerosis in subjects with nonalcoholic fatty liver disease. Clin Endocrinol (Oxf) 2013; 78: 712-7. http://dx.doi.org/10.1111/j.1365-2265.2012.04460.x

[24] Jin K, Norris K, Vaziri ND. Dysregulation of hepatic fatty acid metabolism in chronic kidney disease. Nephrol Dial Transplant. 2013; 28: 313-20. http://dx.doi.org/10.1093/ndt/gfs350

[25] Copaci I, Lupescu I, Caceaune E, Chiriac G, Ismail G. Noninvasive Markers of Improvement of Liver Steatosis Achieved by Weight Reduction in Patients with Nonalcoholic Fatty Liver Disease. Rom J Intern Med 2015 Jan-Mar; 53(1): 54-62. http://dx.doi.org/10.1515/rjim-2015-0008

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