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The Relationship between Non-Alcoholic Fatty Liver Disease and Coronary Heart Disease

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Abstract:

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases world-wide. Progressive liver injury is often observed, and some patients may develop cirrhosis and hepatocellular carcinoma. It is associated with increased mortality from cardiovascular diseases, malignancy and hepatic complications. Patients with NAFLD usually have metabolic syndrome and diabetes mellitus, and have dysregulated secretion of proinflammatory and anti-inflammatory cytokines. Recently, NAFLD has also been found to be associated with extrahepatic disorders such as colorectal neoplasm. Owing to the close relationship between NAFLD and metabolic syndrome, it is not surprising that patients with NAFLD have increased risk of coronary artery disease as predicted by the Framingham risk score. Radiological atherosclerosis and endothelial dysfunction are also common in patients with NAFLD. In selected populations such as patients with diabetes, NAFLD also increases the odds of developing cardiovascular events.

Keywords: Non-Alcoholic Fatty Liver Disease, coronary heart disease, NAFLD.

Introduction:

Nonalcoholic fatty liver disease is associated with major cardivasculer risk factor including type 2 diabetes mellitus t2dm, obesity, dyslipidemia, hypertension and insulin resistance and constitutes a new componant of the metabolic syndrome **[1, 2].**

The association of metabolic syndrome and non alcoholic fatty liver disease is strong that non alcoholic liver disease is considered as the hepatic manifestation of metabolic syndrome **[3].**

The clinical implications of non alcoholic fatty liver disease and non alcoholic steato hepatitis are mainly derived from there common occurrence in the general population(15%-30%) **[4]** and there optional to contribute to coronary artery disease **[5],** extra hepatic cancer **[5],** diabetes and progression to fibrosis (30-40%), cirrhosis (20-30%) and hepatocelluler carcinoma **[4, 5].**

Although the mechanisms underlying liver disease progression remain unclear, insulin resistance and obesity related inflammation, obesity related ectopic fat and lipotoxicity play a key role, along with possible genetic, dietary and lifestyle factor **[6].**

Most studies show that metabolic syndrome is associated with a tow fold increase in coronary artery disease risk and a fivefold increased risk for incidences of type 2 diabetes mellitus **[7, 8].**

The importance of the nonalcoholic fatty liver disease component within the metabolic syndrome is now increasingly recognized, and this has stimulated an interest in the possible relationship between nonalcoholic fatty liver disease and cardio vascular disease. Nonalcoholic fatty liver disease affects (15-30%) of the general population **[9].**

The prevelence is also high in over weight and obese children **[10].** Factors contributing to nonalcoholic fatty liver disease including sedentary life style **[10]** and increased consumption of foods with high fat **[11]** and high fructose corn syrup content **[12].**

Steatosis is associated with an increased prevalence and incidence of coronary artery and cardio vascular mortality **[11].**

Classical and new emerging risk factors for nonalcoholic fatty liver disease in atheroscloretic patients. The new risk factors for coronary artery disease include markers for inflammation (crp, lipoprotein a), homocystine, markers of fibrinolytic and homeostatic function (e.g. fibronigin, tissue plasminogen activator and plasminogen activator inhibitor-1).

These markers are also associated with nonalcoholic fatty liver disease **[13, 14].**

The classic common risk factor for nonalcoholic fatty liver disease and coronary artery disease are age and gender **[15]** physical in activities **[16],** type 2 diabetes mellitus **[17],** hyperlipidemia **[18],** obesity **[19].**

These risk factors are well known and beyond the scope of this review. Mechanisms linking nonalcoholic fatty liver disease and coronary artery disease. The biological mechanisms potionally responsible for accelerated atherogenesis in nonalcoholic fatty liver disease patients may either have origin in the liver or have the liver as the target of systemic abnormalities. Here we will discuss the biological mechanisms linking NAFLD and CAD, the novel risk factor for CAD, and the common pathways of both diseases.

Oxidative Stress:

Oxidative stress play an important role in the progression from simple steatosis to steatohepatities **[20].** The role of oxidative stress is supported by different animal modeles of NAFLD which show either increased reactive oxygen species (ROX) formation or evidence of extensive lipid peroxidation **[21].**

The association between oxidative stress and NAFLD in humans is supported by the immunohistochemical detection of lipid peroxidation product and 8- hydroxy-deoxyguanosine in the plasma and liver biopsies from patients with NAFLD **[22].**

The earliest events in the pathogenesis of atherosclerosis are thought to be changes in the endothelial functions, in turn triggered by oxidative modification of low- density lipo protein (LDL), leading to formation of oxidized LDL in the sub entimal space **[23].**

The expression of chemotactic factors such as monocyte chemotactic protein -1 is enhanced by oxidative stress, and oxidized endothelial expression of vascular cell adhesion molecules -1 which is regulated through redox-senestive mechanism promote the adhesion of monocytes to the endothelium. The release of macrophage colony stimulating factor is also stimulated by modified LDL. Expression of these factors result s in the attraction and adhesion of monocytes to the arterial wall and the promotion of their differentiation into tissue macrophage. Exposure to reactive oxygen species activates the nuclear factor kappa (NF- Kappa) regulatory complex and triggers the transcription of several atherosclerosis relater genes (tumer necrosis factor, matrix metalloproteinase MMP) this series of event s lead to the accumulation of macrophage in arterial wall the activity of MMP appears to be closely linked to smooth muscle activation and migration and MMP have also been implicated in the pathophysiology of plaque rupture. Furthermore, (ROX) can lead to platelet activation and thrombus formation. Therefore oxidative stress appears to be important in both the early and later stage of the atherosclerotic process **[24]**.

Insulin resistance:

NAFLD is strongly associated with hepatic adipose tissue insulin resistance (IR), as well as reduced whole –body insulin sensitivity **[25]** the spectrum of metabolic disturbance s associated with IR extended beyond hyper glycemia and include dyslipedimia, obesity hypercoagulability , and inflammation **[26].** There are increase level of non esteritfied fatty acid (NEFA), lipotoxicity and disturbance in adipokine secretion this believed to be related to insulin resistance. Increase level of (NEFA) may might affect endothelial nitric oxide production, there by impairing endothelium dependent vasodilation. They may increase myocardial oxygen

requirement and there for ischemia **[27],** overall, growing evidence suggested that fat accumulate in liver induce hyperglycemia. subclinical inflammation, dyslipedmia and the secretion of heptokines (e,g feutin-A) this induce insulin resistance and atherosclerosis **[28].**

Sub clinical inflammation:

Ectopic fat deposition in visceral adipose depots, heart and other depots increase the expression of visceral proinflamatory mediators such as monocytes chemotactic protein -1 and IL -6 leading to local macrophage infiltration and associated systemic inflammation **[29]** hepatic steatosis is associated with production of pro inflammatory cytokines by hepatocytes and non parenchemal cell, including kupffer cell and hepatic stellet cell increases expression intrahepatic cytokine expression results from local NF-KB activation, mediated by hepato-celluler damage and fat-derived factors and is likely to play major role in NAFLD progression and CVD pathogenesis **[30].**

Adiponectin:

Mature adipocytes act as an active endocrine and paracrine organ, secreting an increasing number of growth factors, that affect in processing of metabolic syndrome particularly insulin resistance **[31]** the reduced production of adiponectin associated with obesity and may contribute to the progression of NAFLD **[32].** Adiponectin selectively suppress endothelial cell apoptosis **[33]** this suggest adiponectin protect plaque rupture by inhibition of matrix metaloprotienase function **[34].**

Myocardial lipo toxicity:

Increasing plasma free fatty acids for a few hours cause endothelial dysfunction and production systemic inflammation, free fatty acid impair nitric oxide production by endothelial cells there is a significant correlation between the development of fatty liver and abnormality in left ventiriculer energy metabolism **[35]** liver fat accumulation originates from peripheral fats stored in adipose tissue this flow to the liver throw plasma non esterified fatty acid pool, fatty acid newly made within the liver through denovo lipogenesis and from dietary fatty acid uptake , the fat of lipid entering the liver may be secreted as very low density lipo protein ,tri glyceride , this is oxidesed or stored. The major component of dyslipidemia in NAFLD is an elevation of triglycerides which comes mainly from increase concentration of VLDL. in addition to increase synthesis of VLDL and also decrease clearance of triglycerol–rich lipoprotein **[36]**. Other component of dyslipidemia increase formation of low- density lipo protein this is closely associated with insulin resistance and hyper triglyceridemia **[37]**. There are increased activity of hepatic lipase in NAFLD and IR this leading to decrease level of high density lipo protein HDL and increase level of HDL elimination **[38].** In summary, patients with NAFLD have increased level of VLDL, TG, LDL PARTICLES and decrease level of HDL, the presence of LDL particles associated with increased CVD risk **[39],** LDL particles can move through endothelial fenestration, entering the subendothelial space where inflammation and transformation into plaque can occur **[40],** further, alternation in smooth muscle ions channels, Ca handling and cell signaling may be important mechanism leading to coronary micro vascular dysfunction **[40],** there are exaggerated post prandial lipemia in patient with insulin resistance and it is one of risk factor of CVD **[41].** The astherosclerotic risk of post prandial of hyperlipedmia is derived from an increase of remment lipoprotein (RLP) **[42].** In patients with IR, an increase of post prandial RLP values usually occur and becomes a coronary risk factor , the RLP is easily taken into the macrophage in the arterial wall via the apolipoprotien receptor, promoting foam cell formation of macrophage and performing the astherosclerotic lesion as is oxidized LDL **[43]**.

Coronary heart disease:

Coronary heart disease refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to presentations found in NON–ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina. It is almost always associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery **(44).**

The release of sensitive markers of myocardial necrosis (e.g. troponins) is regarded as indicative of myocardial cell necrosis and fulfills the definition of myocardial infarction. If no rise in markers is detected, the

term UA is used and non cardiac differential diagnoses must be considered. The third universal definition of myocardial infarction is myocardial cell death due to prolonged myocardial ischemia **(45).**

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