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Association Between Fatty Liver and Cardiovascular Disease: Mechanism and Clinical Implications

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1. Introduction

NAFLD is associated with major cardiovascular risk factors including type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, hypertension and insulin resistance and constitutes a new component of the metabolic syndrome (MetS) [1-2]. The association of MetS and NAFLD is so strong that NAFLD is considered as the hepatic manifestation of MetS [3]. The clinical implication of NAFLD and nonalcoholic steatohepatitis (NASH) are mainly derived from their common occurrence in the general population (15%-30%) and their potential to contribute to CAD, extra hepatic cancer, diabetes, and progression to fibrosis (30%-40%), cirrhosis (20%-30%) and hepatocellular 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 life style factors [6].

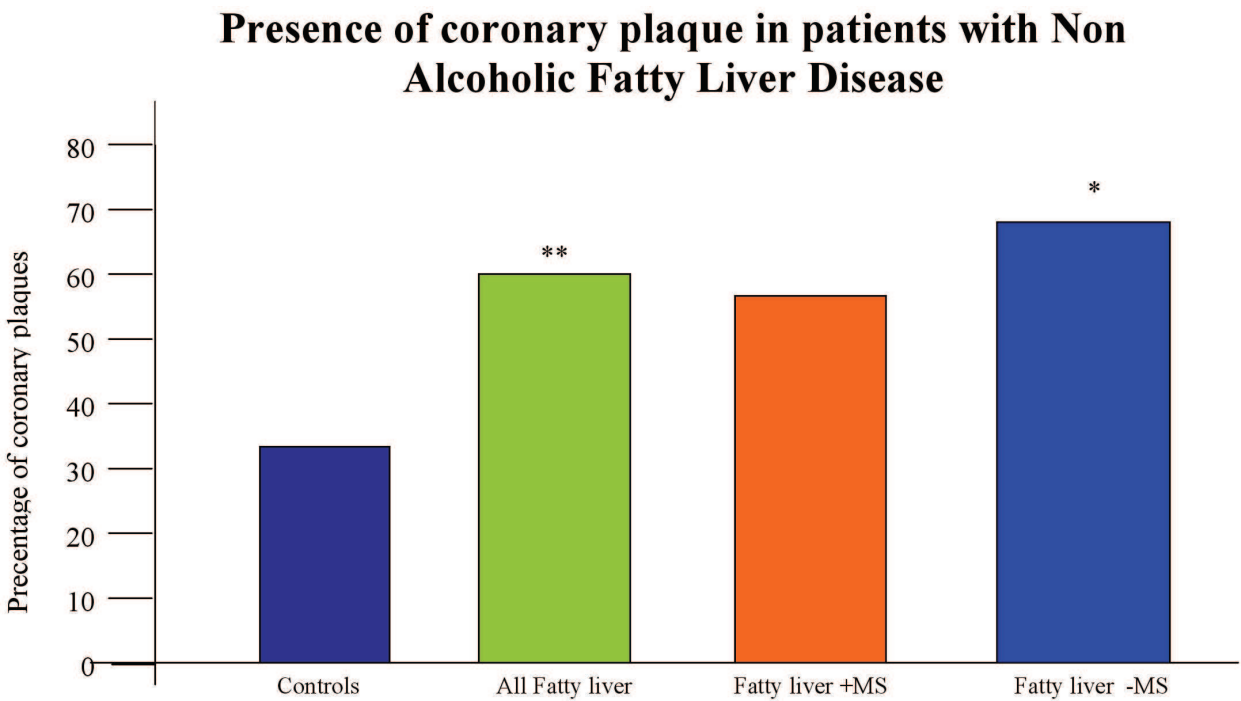
Most studies show that MetS is associated with a two-fold increase in CAD risk and a 5-fold increased risk for incidences of T2DM [7-12]. The importance of NAFLD component within the MetS is now increasingly recognized, and this has stimulated an interest in the possible relationship between NAFLD and cardiovascular disease (CVD). This review focuses on the relationship between NAFLD and CAD, the Biological mechanisms linking NAFLD and CAD and a proposed new treatment approach for patients with NAFLD.

2. The relationship between NAFLD and CAD

Prevalence: NAFLD affects 15-30% of the general population [13]. The prevalence is also high in overweight and obese children [14]. Factors contributing to NAFLD include sedentary life style, and increased consumption of foods with high fat and high fructose corn syrup content (soft drinks). Steatosis is associated with an increased prevalence and incidence of CAD and cardiovascular mortality. [15- 16].

Clinical studies: Targher et al showed a significant increase of carotid intima-media thickness (IMT) in the presence of NAFLD [17]. Brea et al showed that patients with NAFLD had increased intima-media thickness (IMT), independently by the MetS [18]. Lin et al

showed that patients with NAFLD were more likely to have CAD compared to patients without NAFLD, independent of obesity and other risk factors [19]. Villanova et al showed that NAFLD patients have a significant decrease in brachial artery flow- mediated vasodilatation, which correlates with the extent of liver disease. Furthermore, the 10-year probability of coronary heart disease (as calculated according to the Framingham risk score) was moderately increased in NAFLD patients, and particularly in patients with NASH [20]. This study and others provide evidence of severe endothelial dysfunction and increased risk of cardiovascular events in NAFLD [21]. Targher et al showed an increased prevalence of CAD in patients with T2DM and NAFLD as compared with diabetic patients without NAFLD [22] and that the severity of liver histology among NAFLD patients is strongly associated with early carotid atherosclerosis, independent of classical risk factors, insulin resistance, and the presence of MetS [23]. Akabame et al showed that NAFLD is a novel risk factor for vulnerable plaques, using a multislice computed tomography (MSCT) [24]. Recently, we showed that patients with NAFLD, even without MetS, have more vulnerable coronary soft plaques than healthy controls. [25] (Figure 1). Pacifico et al demonstrated that obese children with NAFLD have a marked increase in carotid IMT in comparison with control healthy children, and that the carotid IMT was higher for obese children with NAFLD than obese children without liver involvement but with similar body mass index (BMI) [26].



Graph of coronary plaque in NAFLD patients with or without metabolic syndrome (MS) and in controls * $P<0.07$; fatty liver without metabolic syndrome versus fatty liver with metabolic syndrome. ** $P<0.001$;all fatty liver versus controls.(reference 25)

Fig. 1. Presence of coronary plaque in patients with Non Alcoholic Fatty Liver Disease

3. Cause of death in patients with NAFLD

The mortality rate among patients with NAFLD followed for 8 years was higher than in the general population, [27]. In another study consisting of biopsy-proven, NAFLD patients

who were followed for 18 years, CVD was among the common causes of death after all of the cancers combined [28]. In the Valpolicella Heart Diabetes Study, Targher et al showed that NAFLD patients have been associated with an increased incidence of major CVD events after excluding classical risk factors, diabetes duration, glycemic control, medication use, and components of the metabolic syndrome [29-30]. Dunn et al showed that NAFLD patients had significantly increased all-cause mortality and cardiovascular mortality, especially in the 45-54 years age group [31]. A strong association between mildly elevated serum liver enzymes as a surrogate marker of NAFLD and increased risk for CVD mortality and morbidity was reported in several population-based cohort studies [21, 32, 33]. A Swedish study consisting of 129 patients with NAFLD showed that patients with NASH had higher incidences of cardiovascular mortality compared to the reference population [34]. Recently, other studies with 28 years follow up showed that CAD was the leading cause of death in patients with NAFLD, followed by hepatic and extra hepatic malignancy and finally by cirrhosis and its complications [35, 36, Table 1].

Cause of death	Number of patients	%
CAD	15	35.0
Extra hepatic cancer	12	28.0
Liver cancer, cirrhosis	8	18.6
Diabetes mellitus	3	7.0
Poisoning	3	6.8
Intestinal Perforation	1	2.3
Alcohol abuse	1	2.3

Table 1. Causes of Death in 143 patients with NAFLD (death= 43)

4. Classical and emerging risk factors for atherosclerosis

The new risk factors for CAD include markers for inflammation (e.g. CRP, lipoprotein A), homocystine, markers of fibrinolytic and homeostatic function (e.g. fibrinogen, tissue plasminogen activator, and plasminogen activator inhibitor-1). These markers are also associated with NAFLD [37-41]. The classic common risk factors for NAFLD and CAD are age and gender [42, 43], physical inactivity [44- 47], T2 DM [48-52], hyperlipidemia [53- 56], obesity [57-63], and hypertension [64- 66]. These risk factors are well known and beyond the scope of this review.

5. Mechanisms linking NAFLD and CAD

The biological mechanisms potentially responsible for accelerated atherogenesis in NAFLD 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 factors for CAD, and the common pathways of both diseases (Figure 2)

A) Oxidative stress

Oxidative stress plays an important role in the progression from simple steatosis to steatohepatitis [67]. The role of oxidative stress is supported by different animal models of

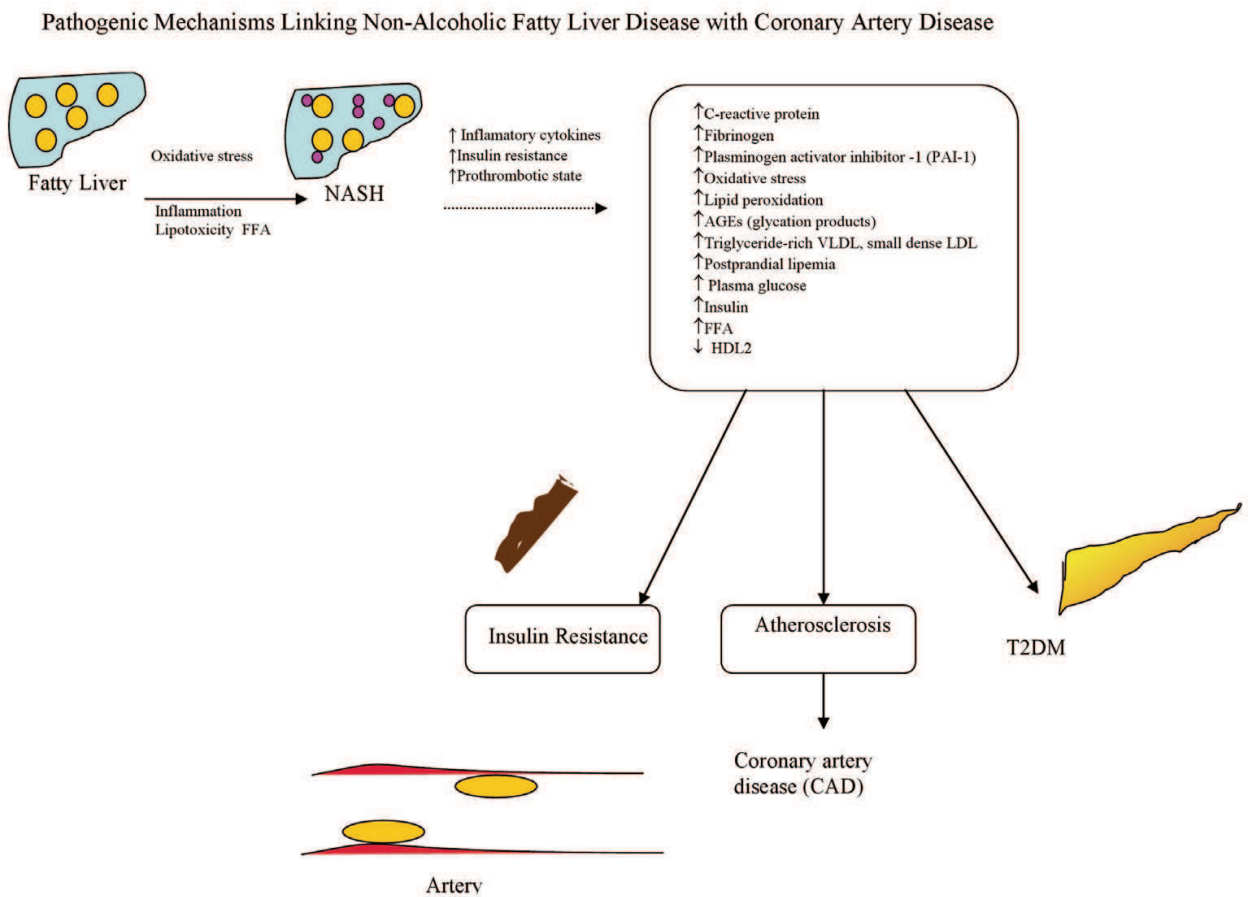


Fig. 2. Biological mechanism of accelerated atherosclerosis in patients with NAFLD. Fat accumulation in the liver induces hyperglycemia, sub clinical inflammation, atherogenic dyslipidemia, lipotoxicity, and the secretion of cytokines. Thereby inducing insulin resistance, atherosclerosis, and diabetes mellitus. All contributes to coronary artery diseases.

NAFLD which show either increased reactive oxygen species (ROS) formation or evidence of extensive lipid peroxidation [68,69]. The association between oxidative stress and NAFLD in humans is supported by the immunohistochemical detection of lipid peroxidation products and 8-hydroxy-deoxyguanosine in the plasma and liver biopsies from patients with NAFLD [70, 71]. The earliest events in the pathogenesis of atherosclerosis are thought to be changes in endothelial functions, in turn triggered by oxidative modification of low-density lipoproteins (LDL), leading to the formation of oxidized LDL in the subintimal space [72]. The expression of chemotactic factors such as monocyte chemoattractant protein-1 (MCP-1) is enhanced by oxidative stress and oxidized LDL. Endothelial expression of vascular cell adhesion molecule-1 (VCAM-1), which is regulated through a redox-sensitive mechanism, promotes the adhesion of monocytes to the endothelium. The release of macrophage colony-stimulating factor (M-CSF) is also stimulated by modified LDL. Expression of these factors results in the attraction and adhesion of monocytes to the arterial wall and the promotion of their differentiation into tissue macrophages. Exposure to the superoxide ion, a ROS, activates the nuclear factor kappa-B (NF-kappa B) regulatory complex and triggers the transcription of several atherosclerosis-related genes (VCAM-1, MCP-1, tumor necrosis factor (TNF), matrix metalloproteinase (MMP)-9 and procoagulant

tissue factor). This series of events leads to the accumulation of macrophages in the arterial wall, which then avidly incorporate oxidized LDL to form foam cells. Oxidized LDL, in turn, stimulates the release of interleukin-1 from macrophages. The activity of MMPs is also regulated by oxidative stress and appears to be closely linked to smooth muscle cell activation and migration. MMPs have also been implicated in the physiopathology of plaque rupture. Furthermore, ROS can lead to platelet activation and thrombus formation. Therefore, oxidative stress appears to be important in both the early and later stages of the atherosclerotic process [73, 74].

B) Insulin resistance

NAFLD is strongly associated with hepatic and adipose tissue insulin resistance (IR), as well as reduced whole-body insulin sensitivity [75]. Previous studies have documented a reduction of 45-50% in glucose disposal, and an impaired ability of insulin to suppress endogenous glucose production (hepatic IR) in subjects with NAFLD [76]. The spectrum of metabolic disturbances associated with IR extends beyond hyperglycemia and includes dyslipidemia, obesity, hypercoagulability, and inflammation. In long-term follow-up of patients with T2DM, IR was independently predictive of CAD, with a 1-unit increase in IR assessed by the homeostasis model assessment (HOMA) associated with a 5.4% increased risk for CAD [77]. Increased levels of fatty acids, (NEFA), lipotoxicity and disturbances in adipokine secretion, are believed to be related to insulin resistance. Increased levels of NEFA might affect the endothelial nitric oxide production, thereby impairing endothelium-dependent vasodilatation. They may increase myocardial oxygen requirements and, therefore, ischemia. Recent evidence in older men with CAD has shown that NEFAs are independently associated with cardiovascular mortality [78]. The Insulin Resistance and Atherosclerosis Study (IRAS) also confirmed the relation between IR and atherosclerosis in the carotid artery [79]. Overall, growing evidence suggests that hepatic insulin resistance is sufficient to induce several components of the metabolic syndrome and promote progression to cardiovascular disease

C) Sub clinical inflammation

Targher et al showed that in healthy non-smoking volunteers, plasma CRP, fibrinogen, von Willebrand factor (v-WF) and plasminogen activator inhibitor-1 (PAI-1) activity levels were markedly higher in subjects with hepatic steatosis than in those without, even after controlling for other confounders such as age, BMI, blood pressure, insulin resistance and triglyceride levels [80]. Recently, IL-6 and CRP have been shown to correlate with higher degrees of fibrosis and inflammation (i.e. NASH) in patients with NAFLD [81]. Thus, NAFLD/NASH should be considered a chronic inflammatory condition. Recent advances in basic science have established a fundamental role for inflammation in mediating all stages of atherosclerosis from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis.

Prospective epidemiological studies have found increased vascular risk in association with increased inflammatory markers such as, IL-6, TNF- α , CRP and fibrinogen [82-85]. Elevated values of circulating inflammatory markers commonly accompany acute coronary syndrome (ACS). Such elevations correlate with in-hospital and short-term prognosis [85, 86]. Chronic subclinical inflammation is a common finding in NAFLD and in atherosclerosis. Moreover, chronic sub clinical inflammation is strongly involved in IR and MetS, as mainly demonstrated by mechanistic studies in animal models [87]. Ectopic fat deposition in visceral adipose depots, heart and other depots increases the expression of visceral

proinflammatory mediators such as monocyte chemotactic protein-1 and IL-6, leading to local macrophage infiltration and associated systemic chronic inflammation [88].

Hepatic steatosis is associated with increased production of pro-inflammatory cytokines by hepatocytes and non-parenchymal cells, including Kupffer cells and hepatic stellate cells. Increased intra-hepatic cytokine expression results from local NF- κ B activation, mediated by hepatocellular damage and fat-derived factors, and is likely to play a major role in NAFLD progression and CVD pathogenesis [81, 88-90].

An atherogenic role of liver inflammation is supported by the observation that CAD risk is greater in NASH than in simple hepatic steatosis [27, 28].

D) Adiponectin

Liver fat accumulation, NEFAs, adiponectin, low-grade inflammation in the context of insulin resistance patient with fatty liver, might explain the development of endothelial dysfunction and early cardiovascular disease. Mature adipocytes act as an active endocrine and paracrine organ, secreting an increasing number of growth factors that participate in diverse metabolic processes, particularly IR. Patients with NAFLD exhibit reduced levels of adiponectin, which are inversely correlated with the severity of NAFLD histology [91-93]. The reduced production of adiponectin associated with obesity may contribute to the progression of NAFLD [89]. Adiponectin increases the expression of messenger RNA and protein production of tissue inhibitor of metalloproteinase in macrophages through the induction of IL-10 synthesis and selectively suppresses endothelial cell apoptosis [94, 95]. This suggests that adiponectin protects plaque rupture by the inhibition of matrix metalloproteinase function. Endothelium-dependent vasoreactivity is impaired in people with hypoadiponectinaemia, which might be at least one cause of hypertension in visceral obesity [96]. The protein inhibits the expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), ICAM-1 and E-selectin, through the inhibition of NF- κ B activation; it also suppresses foam-cell formation. From this, it is clear that adipokines are capable of contributing to remodeling of the myocardial extracellular matrix [96]

E) Myocardial Lipotoxicity

Increasing plasma free fatty acids for few hours causes endothelial dysfunction and induces the production of systemic inflammation, and pro coagulants in vitro, in animal models and in humans. Of interest, free fatty acid impairs nitric oxide production by endothelial cells through the activation of an IKK β - mediated response. For instance, subjects with either glucose intolerance or T2DM have a significant increase in myocardial triglyceride content. There is a significant correlation between the development of fatty liver and abnormalities in left ventricular energy metabolism. [97]. In Diabetic patients with NAFLD, fatty liver and elevated aminotransferases coexist with myocardial insulin resistance and coronary dysfunction [97]

F) Atherogenic dyslipidemia

Liver fat accumulation originate from peripheral fats stored in adipose tissue that flow to the liver via the plasma nonesterified fatty acid (NEFA, 60%) pool, fatty acids newly made within the liver through de novo lipogenesis (DNL, 30%), and from dietary fatty acid uptake (10%). The fat of lipids entering the liver may be secreted as very low-density lipoprotein (VLDL) triglycerides, oxidized or stored. The major component of dyslipidemia in NAFLD patients is an elevation of serum triglycerides (TG) which comes mainly from increased concentration of VLDL. In addition to increased synthesis of VLDL, there is also decreased clearance of triacylglycerol-rich lipoprotein (TRLs) induced by a decrease in lipoprotein lipase activity [98]. Other components of dyslipidemia, such as formation of small dense low-density lipoprotein (LDL), are closely associated with IR and hypertriglyceridemia [99].

VLDL1 triglyceride is a major predictor of LDL size. It seems that stimulated hepatic lipase activity favors the formation of small dense LDL particles. The increased activity of hepatic lipase in IR conditions such as in NAFLD and obesity produces smaller HDL particles, leading to increased HDL elimination [100]. In addition, increased levels of VLDL1 alter the composition of HDL, leading finally to an increased catabolism of these particles, which explains the inverse correlation of HDL and liver fat [101]. In summary, patients with NAFLD have increased levels of VLDL, TG, and small dense LDL particles and decreased levels of HDL. The presence of small dense LDL particles is associated with increased CVD risk [102]. Small dense LDL particles can move through endothelial fenestrations, entering the subendothelial space where inflammation and transformation into plaque can occur, and leading finally to coronary artery diseases [103]. Further, alterations in smooth muscle ion channels, Ca^{2+} handling, and cell signaling may be important mechanisms leading to coronary micro vascular dysfunction [103].

G) *Postprandial lipemia*

Exaggerated postprandial lipemia is an established CVD risk in T2DM [104]. Studies comparing the postprandial response of TG and FFA to a fat rich meal in nondiabetic subjects with biopsy proven NASH to control subjects showed that patients with NASH had significantly higher postprandial TG levels than healthy control subjects [105]. Other studies support a close relationship between dietary habits, postprandial lipemia and CAD [106]. The atherosclerotic risk of postprandial hyperlipidemia is derived from an increase of remnant lipoproteins (RLPs) [107]. In patients with IR, an increase of postprandial RLP values usually occurs and becomes a coronary risk factor. The RLP is easily taken into the macrophage in the arterial wall via the apolipoprotein B48 receptor, promoting foam cell formation of macrophages and performing the atherosclerotic lesion as is oxidized LDL [108]. Stanhope et al showed that consumption of fructose-sweetened but not glucose-sweetened beverages for 10 weeks increases de novo lipid synthesis and the 24-hour postprandial TG including increased levels of apoB, LDL, oxidized LDL, RLP triglyceride, and the apoB / apoA1 ratio (all biomarkers of increased for CAD) [109].

Dietary habits and genetic determinants, including microsomal transfer protein (MTP) polymorphisms, may promote NASH and atherogenesis via hypoadiponectinaemia [110,111]. Recently, Musso et al reported that the risk of adiponectin single-nucleotide polymorphisms (SNPs) 45TT and 276 GT are significantly more prevalent in NAFLD than in the general population and are associated with the severity of liver disease. In addition, an association with an atherogenic postprandial lipoprotein profile in NASH was detected independently of fasting adipokine and lipid levels [112].

H) *Pro-coagulation and hypofibrinolysis*

The prothrombotic state in the atherosclerosis process encompasses platelets hyperaggregability, hypercoagulability and hyperfibrinolysis. Markers of fibrinolytic and hemostatic function (e.g. fibrinogen, tissue plasminogen activator, and plasminogen activator inhibitor 1-antigens), are strongly associated with NAFLD. Plasminogen activator inhibitor-1(PAI-1) is expressed in visceral adipose tissue. It is mainly expressed in stromal cells including monocytes, smooth muscle cells and pre-adipocytes [113]. Plasma PAI-1 levels are more closely related to fat accumulation and PAI-1 expression in the liver than in adipose tissue, suggesting that, among insulin-resistant individuals, the fatty liver is an important site of PAI-1 production [114]. We showed also that there is an association between the thrombotic risk factors and the extent of fibrosis in patients with NAFLD [40]. This confirms the central role of the liver in these processes. Fibrinogen, von

Willebrand factor (vWF) and PAI-1 are also considered markers of the acute-phase reaction of inflammation and thrombosis, and has been closely linked to CAD and diabetes mellitus [115]. CRP increases PAI-1 expression and activity in human aortic endothelial cells [116].

6. Clinical implications

It is evident that patients with NASH are more prone to develop CAD (Increase mortality by 86%) than patients with simple steatosis (increase mortality by 55%, 117); however, it has not been clear until now whether the treatment of NAFLD patients will prevent CAD development. We suggest adding a new modality of approaching patients with NAFLD. Once the diagnosis of NAFLD was made, the first step will be a lifestyle intervention using a combination of diet, active walking, and behavior modification [118], with a goal of >10% weight reduction [119]. Mediterranean diet derived mainly from olive oil (rich in omega-9) is recommended [120,121]. We advise to reduce or discontinue the consumption of fast foods and regular soft drinks, which contain fructose [122]. Recently Dunn et al showed that modest wine drinking (20-30 gram/daily) offers protection against suspected NAFLD [123]. The second step is to assess the risk of hepatic fibrosis: There are two modalities of assessment of fibrosis in NAFLD: The noninvasive methods of fibrosis include BARD score or Angulo score [124,125]. The invasive methods (liver biopsy) remains the only reliable means to determine prognosis based on the severity of fibrosis.

The third step will include the assessment of cardiovascular risk stratification: We suggest the use of the Framingham score with effort test and/or measurements of the carotids arteries (IMT) as well as biomarkers of inflammation (CRP, fibrinogen), oxidative stress, (MDA, Paraoxonase), Insulin Resistance, (HOMA), lipotoxicity (TG, HDL, LDL, TC), OGTT, and microalbumin/creatinin ratio [126].

The fourth step includes the assessment of malignancy: For patients older than > 45. Colonoscopy, mammography, chest X-ray, gynecology consultation, and tumor markers (CEA, AFP, PSA, and CA19-9, and CA125, stool blood) are recommended since malignancy is the second most common cause of death in patients with NAFLD [127]. The final step is to initiate an appropriate therapy according to the comorbidities, and the clinical status of each patient. A combination therapy is favored.

A) Patients with metabolic syndrome

The most effective antidiabetic agent is metformin especially in obese T2DM or pioglitazone in non-obese patients [128,129]. We advice to delay early insulin therapy because it may increase fibrosis and weight [130]. Whether insulin increases the risk of HCC or not is still under debate. Exenatide induces significant weight loss, which may lead to an insulin-sensitizing effect [131]. Gliptins are a group of drugs, which increase incretin levels by inhibiting the enzyme DPP-4. These agents are relatively new and, as for the GLP-1 analogues, improve insulin resistance in prediabetic individuals and patients with T2DM after weight loss [132]. Lipid-lower agents are mandatory treatment in diabetic patients with NAFLD, statins and fibrates for dyslipidemic and diabetic patients [133-135] are recommended. Renin-angiotensin system (RAS) inhibitors or alpha-blockers for hypertensive patients [136,137]. However, these types of medicines are not approved solely for fatty liver. Low dose aspirin is reasonable for patients with 10 years cardiovascular disease risk >10% and no risk factors for bleeding.

B) *Patients without metabolic syndrome*

Best evidence for metformin or pioglitazone for 1-2 year in treating NAFLD patients without MetS. However, routine prescription of this drug (pioglitazone) needs further clarification. Vitamin E (400 IU/day) and omega-3 may be recommended [138,139]. However, vitamin E is not approved yet and high dosage may increase all cause mortality (140). Ursodeoxycholic acid has no benefit for NASH patients as compared to placebo (141). Statins for dyslipidemic patients. Aspirin to prevent CAD according to Framingham score (142). Diagnosis of NAFLD may be a clear indication for diabetes screening, and cardiovascular risk screening and should be performed with the use of existing risk calculators and should be guided by established cardiovascular risk factors.

- a. For patients with metabolic syndrome: tailored therapy
 - Metformin/ Pioglitazon/Insulin for T2DM.
 - However, routine prescription needs further clarification
 - Statins /Fibrates for atherogenic dyslipidemia
 - Renin angiotensin system inhibitors/ α - blockers for hypertension
- b. For patients without metabolic syndrome:
 - Best evidence for metformin/ pioglitazone or vitamin E.
 - However, high dose vitamin E (>400 IU/ day) may increase mortality
 - Currently, high dose ursodeoxycholic acid has no benefit for NASH patients
 - Omega-3 and vitamin D (2000 IU/day) may be beneficial.
- c. For the future:
 - Promising agents awaiting randomized controlled trials (Fatostatin,
 - (Aramchol, DPP-4 inhibitors, GLP-1 agonists and combination therapy)

Table 2. Pharmacologic treatment of patients with NAFLD

7. Conclusion

NAFLD is a growing public health problem worldwide. The clinical impact of NAFLD on CAD risk deserves particular attention in view of the implications for screening and surveillance strategies in the growing number of NAFLD patients. NAFLD is associated with increased biomarkers level of chronic inflammation and atherosclerosis. Pharmacotherapy should be given for patients at high risk for complications (NASH, T2DM, obesity, atherogenic dyslipidemia). However, it is not currently known whether improving NAFLD will prevent the development and progression of CAD. Moreover, the prognostic value of NAFLD in CAD risk stratification has yet to be determined. NAFLD patients should be candidate not only for aggressive treatment of their liver disease , but also for aggressive treatment of underlying CAD risk factors, because many patients with NAFLD will have major CAD events and die prior to the development of advanced liver disease.

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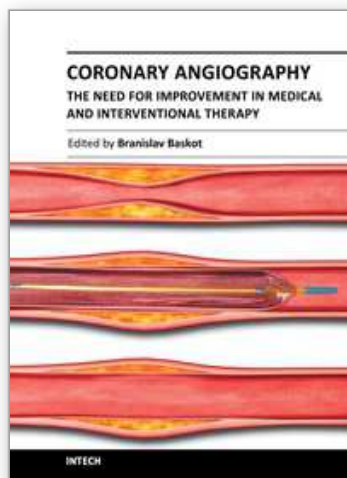
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In this book we examined a periprocedural complication of coronary angiography, and coronary intervention. That includes related to cardiac catheterization and diagnostic coronary angiography, and those that occur as a consequence of the specific equipment. However, improvements in devices, the use of stents, and aggressive antiplatelet therapy have significantly reduced the incident of major periprocedural complications. This book giving knowledge and experiences many of interventional cardiologists from all over the world, and provide possibility to recognize new approach in this domain. Book gives lecture on how we image and how we decide on what to treat, how to treat it, and then results of that treatment. They offer many answers to what we have today and what we will have tomorrow.

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