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Extrahepatic Outcomes of NAFLD: Cardiovascular Diseases

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Synopsis (100 words): Patients with Non-Alcoholic Fatty Liver Disease (NAFLD) are at high risk of Cardiovascular Disease, including carotid atherosclerosis, coronary artery disease, heart failure and arrhythmias. The risk is partially due to shared risk factors, but it may vary according to liver injury. A fatty liver may induce an atherogenic profile, the local necro-inflammatory changes of Non-Alcoholic-Steatohepatitis (NASH) may enhance systemic metabolic inflammation, fibrogenesis can run parallel in the liver and in the myocardium and precedes heart failure. The detrimental impact of a Western diet combines with polymorphisms in genes associated with atherogenic dyslipidemia. Shared clinical/diagnostic algorithms are needed to manage the CV risk in NAFLD.

Key words (3-8): NAFLD, cardiovascular disease, coronary artery disease, atherosclerosis, cardiac remodeling, heart failure, gene polymorphisms, gut dysbiosis

Key points (3-5)

- Non-Alcoholic Fatty Liver Disease (NAFLD) is associated with an increased prevalence of Cardiovascular Disease (CVD), including hypertension, arrhythmias, atherosclerosis, coronary artery disease, ventricular remodeling with potential evolution into diastolic dysfunction and heart failure;

- NAFLD is associated with increased incidence of fatal and non-fatal major adverse cardiovascular events and CVD represents the major cause of long-term mortality in NAFLD population even in advanced stages of liver fibrosis;
- The deposition of ectopic fat tissue in the epicardium runs parallel to fat deposition and it is linked to myocardial insulin resistance and altered energy metabolism;
- Polymorphisms in TM6SF2 gene, involved in the hepatic lipid metabolism, are linked to a worse cardiovascular phenotype due to an atherogenic lipid profile;
- Gut dysbiosis promoted by the Western Diet leads to alterations in the intestinal epithelial barrier and endotoxemia, favoring metabolic inflammation in both cardiac and hepatic districts.

1. Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) can be considered one of the protean manifestations of the metabolic syndrome (MetS). The close link and shared pathophysiology of NAFLD and visceral obesity, type 2 diabetes mellitus (T2DM), arterial hypertension and dyslipidemia, is mirrored in the association and incidence of common adverse outcomes, with cardiovascular disease (CVD) being a major cause of morbidity and mortality in the NAFLD population. Currently, it is difficult to prove an independent role for NAFLD in the development of CVD as this liver condition is often embedded in a complex setting of insulin resistance, adipose tissue dysfunction and gut microbiota alteration. Nevertheless, some evidence suggests a reciprocal influence of MetS and NAFLD and the relative risk of CVD may vary according to the features of liver injury (steatosis, necro-inflammation and fibrosis) and the degree of hepatic damage. Ectopic fat accumulation in the liver runs parallel to other ectopic fat depots, including the cardiac district, but a fatty liver may worsen the atherogenic profile of MetS. Local necro-inflammatory changes of Non-Alcoholic Steatohepatitis (NASH) may significantly enhance the systemic metabolic inflammation, thus increasing the risk of adverse cardiovascular outcomes. The fibrogenesis that marks the progressiveness of NAFLD can be also observed in the myocardium and precedes the development of heart failure in dysmetabolic conditions. It is crucial to investigate the effects of NAFLD on the development of cardiovascular events in order to organize an efficient health prevention and treatment program to identify the risk of CVD in patients with NAFLD. In this chapter, we will summarize the association between NAFLD and CVD, highlighting the liver-centered mechanism associated with CVD and the clinical implications.

1. Epidemiology of CVD in NAFLD individuals

1.1. NAFLD, atherosclerosis and ischemic heart disease

The increased risk of prevalent and incident cardiovascular events linked with NAFLD is well-documented across literature and mainly attributed to a reciprocal influence of NAFLD and MetS.

Data extrapolated from the Framingham Heart Study showed that patients with baseline NAFLD had an increased incidence of arterial hypertension and T2DM than those without NAFLD, and that in those with metabolic co-morbidities, including arterial hypertension, incident NAFLD was more prone to occur[1]. While it is difficult to disentangle the independent contribution of each risk factor, an important clue is the increased sub-clinical atheromatous plaque formation in several vascular districts occurring in NAFLD subjects. A meta-analysis of 27 cross-sectional studies reported a strong association between NAFLD detected either by imaging or biopsy and markers of sub-clinical atherosclerosis (i.e. impaired flow-mediated vasodilatation and increased carotid-artery intimal medial thickness) independent of classical cardiovascular risk factors and MetS features, although this finding has been not universally confirmed[2]. In a large cross-sectional study in South Korean population, subjects with a fatty liver at ultrasound had a higher coronary calcium score (detected by coronary computed tomography angiography) than those without and the risk for any atherosclerotic plaque was increased by 20% in NAFLD after adjustment for traditional cardiovascular risk factors (age, sex, obesity, diabetes mellitus, hypertension, hyperlipidaemia, current smoking, family history of CAD, and hs-CRP)[3]. The RISC (Relationship between Insulin Sensitivity and Cardiovascular disease) study showed that even healthy subjects are more prone to early carotid atherosclerosis in the presence of a fatty liver[4]. On the other hand, in high-risk groups such as diabetic subjects, the prevalence of coronary, cerebrovascular, and peripheral vascular disease is again remarkably higher in patients with NAFLD than those without, independent of traditional risk factors[5]. The impact of NAFLD in atherosclerosis is corroborated by the evidence that long-term regression of NAFLD bears a lower risk of carotid atherosclerosis development[6].

The higher prevalence of atherosclerosis in patients with NAFLD translates into an increased risk of cardiovascular events, roughly two-fold higher than the general population. In a large prospective study of NAFLD individuals and matched population controls, CVD represented the most frequent cause of death, accounting for 36% of the total[7]. In particular, high-risk, non-calcified coronary plaques seem more frequent in NAFLD and linked to more adverse outcomes[8]. In a meta-analysis of

more than 30.000 patients with a median follow up of 7 years, the risk of incident fatal and non-fatal (myocardial infarction, stroke, angina pectoris) CVD events was increased by 64% in NAFLD compared to non-NAFLD individuals[9]. In the heterogeneous population bearing NAFLD, the presence of T2DM leads to a twofold increased risk of CVD[10]. Another meta-analysis of 34 studies found that NAFLD patients were more prone to develop coronary artery disease and hypertension (HR 2.3 and 1.16 respectively), and that the presence of NASH increased the risk of incident CVD (HR 2.97)[11]. Indeed, the histological severity of NAFLD appears to have an impact on cardiovascular risk. While cirrhosis is the strongest determinant for liver-related death, advanced fibrosis is associated with strongest hazards for CVD[12]. NAFLD is significantly associated with increased CVD incidence over 14 years of follow-up, but only NAFLD with advanced hepatic fibrosis (assessed by non-invasive scores) has a 70% increased risk of mortality due to CVD[13]. The above mentioned meta-analysis[9] reported a higher incidence of cardiovascular events as well as a higher mortality due to CVD (OR 3.28) in a subgroup of patients with severe NAFLD (defined as altered liver biochemistry, increased non-invasive scores of fibrosis or advanced fibrosis at histology). A large Swedish population-based cohort study assessed the risk for incident major adverse cardiovascular events (MACE) (including ischemic heart disease, stroke, congestive heart failure or cardiovascular mortality) in about 10.000 patients with histologically confirmed NAFLD compared to matched population controls without NAFLD by age, sex, calendar year and country (n = 46.517)[14]. Over a median of 13.6 years, patients with NAFLD had higher incidence of MACE than controls (aHR 1.63), including higher rates of ischemic heart disease (aHR 1.64), congestive heart failure (aHR 1.75), stroke (aHR 1.58) and cardiovascular mortality (aHR 1.37). Rates of incident MACE increased progressively with worsening NAFLD severity, with the highest incidence observed in cirrhosis. While the parallel increase of CV risk and liver fibrosis has been confirmed in other studies, the association with cirrhosis has not been universally confirmed and might be biased by International Classification of Disease (ICD) codes. In a multi-center prospective study of biopsied patients,

incidence of CVD was more pronounced in pre-cirrhosis (fibrosis stage F3), while in cirrhosis a major incidence of liver-related events was observed[15].

Overall, the main message delivered by the above data is that, whatever the reason might be, a subject with NAFLD has an increased risk of CV events and should be managed accordingly.

1.2. NAFLD, cardiac dysfunction and arrhythmias.

NAFLD is associated with abnormalities in cardiac function, both in diabetic and non-diabetic populations. In a community-based cohort of 1.886 Korean adults, ultrasound-diagnosed NAFLD was associated with left ventricular diastolic dysfunction, independently of established cardiovascular risk factors[16]. In diabetic patients with known coronary artery disease, the presence of ultrasound-proven NAFLD was associated with reduced coronary functional capacity[17]. Diastolic dysfunction, an early predictive sign of heart failure with preserved ejection fraction, has been linked to impaired myocardial energy metabolism. Perseghin et al. showed that otherwise healthy individuals with fatty liver have an increased amount of fat in the epicardial area and display an abnormal cardiac energy metabolism despite of normal left ventricle morphological features and systolic/diastolic functions[18]. Similar findings have been confirmed also in pediatric NAFLD, where overweight or obese children with NAFLD had echocardiographic features of early left ventricular dysfunction independent of multiple CVD risk factors; some functional cardiac alterations were more pronounced in subjects with NASH[19]. Moreover, recent evidence links NAFLD to cardiac valve disease, including aortic valve sclerosis and mitral annulus calcifications, which contributes to of left ventricular hypertrophy and the development heart failure[20].

Finally, an increased prevalence of arrhythmias, such as atrial fibrillation and atrioventricular blocks, further links NAFLD to cardiac complications. A meta-analysis of 9 cross-sectional studies found an association between NAFLD and persistent atrial fibrillation in middle-aged and elderly individuals with T2DM[21]. In a prospective study of 400 diabetic patients with a 10-year follow up, atrial fibrillation occurred more frequently in patients with concomitant NAFLD[22]. In a retrospective study

based on 24-hour Holter monitoring, NAFLD resulted also significantly associated with ventricular arrhythmias (non-sustained ventricular tachycardia and premature ventricular complexes), independent of multiple risk factors and comorbidities[23]. These additional CV complications of NAFLD are less documented and certainly require additional evidence.

2. Pathophysiology

2.1. The deposition of ectopic fat tissue as key driver of metabolic dysfunctions.

The accumulation of adipose tissue in ectopic sites is linked to most adverse cardiometabolic outcomes of MetS (**Figure 1**). The accumulation of ectopic fat in the epicardium shapes the epicardial adipocytes into a pro-inflammatory, pro-thrombotic phenotype and modulates the heart function through its anatomical proximity and shared microcirculation with the myocardium[24,25]. The reduction in the adiponectin synthesis, the infiltration of pro-inflammatory macrophages, and the increased synthesis of tumor necrosis-alpha, interleukin-1b and interleukin-6 promote a chronic, low-grade inflammation that alter the microvascular system and activate fibrogenesis processes. The effect of this metabolically altered microenvironment upon the myocardium translates into coronary artery disease, chronic ischemic heart disease, and cardiac dysfunction due to the ventricular fibrosis, which ultimately leads to heart failure[26]. Insulin resistance in the cardiac muscle largely contributes to deranged myocardial energy metabolism and perfusion. In uncomplicated T2DM, Rijzewijk et al. showed a positive association between intramyocardial and intrahepatic fat contents detected by proton magnetic resonance spectroscopy, but liver steatosis was the strongest predictor of myocardial insulin sensitivity and perfusion[27]. In this complex picture of “metabolic” inflammation, the interconnection between different affected tissues exerts pleiotropic effects and may leads to synergic effects than deserve to be better investigated.

2.2. Hepatic insulin resistance and altered metabolism

The hepatic insulin resistance arising in a fatty liver can affect the heart function through impaired lipid and glucose metabolism. The excessive fat accumulation in the liver enhances the synthesis of very low-density lipoproteins (VLDL) through activation of lipogenic transcription factors (including the sterol regulatory element-binding protein 1c), inducing a systemic condition of atherogenic dyslipidemia, characterized by high triglycerides and low high-density lipoprotein (HDL) cholesterol. The apolipoprotein-B in these particles undergoes oxidative processes and acts as damage-associated molecular patterns (DAMPs) in the subendothelial vascular space. In parallel, both increased intake of sugars, particularly fructose, and increased gluconeogenesis foster *de novo* lipogenesis. The activation of the innate immune system promotes intravascular inflammation via toll-like receptors[28-30]. The increased synthesis of plasminogen activator inhibitor-1 by the liver affects fibrinolysis and increases susceptibility to microvascular thrombosis[31]. Moreover, steatotic hepatocytes can secrete extracellular vesicles containing specific miRNA (including miR-1) which promotes a proinflammatory phenotype of the endothelium via activation of Nuclear Factor kappa-B[32]. All these processes induce the formation of vulnerable atherosclerotic plaques, which are key drivers of cardiovascular outcomes.

2.3.Genetic determinants of CVD susceptibility in NAFLD.

Mutations of targeted genes associated with a more aggressive course of liver disease, including PNPLA3 (Patatin-like phospholipase domain-containing protein 3) or TM6SF2 (Transmembrane 6 Superfamily Member 2), are mainly involved in the regulation of lipid metabolism. Carriage of single nucleotide polymorphisms in these genes causes impaired lipid export and lipid-derived oxidative stress in the liver. In contrast, this might translate into a lower circulating lipid burden that reduces the risk factors of CVD. However, PNPLA3 polymorphisms has no proven effect on CVD[33,34], while TM6SF2 polymorphisms has a differential impact on liver disease and CVD. Carriage of the TM6SF2 T allele is linked to more severe hepatic inflammation and fibrosis, while carriage of the more common C allele leads to enhanced VLDL excretion, dyslipidemia and a higher risk for CVD[35,36].

Finally, variants in the glucokinase regulatory protein (GCKR) may predispose to CVD risk through a more atherogenic lipid profile[37].

2.4. The role of nutrition and gut microbiota

The Western Diet is the most relevant environmental factor for the development of NAFLD and metabolic co-morbidities[38]. High consumption of saturated fats, sucrose-sweetened beverages, high glycemic index nutrients and processed meats, shape the gut microbiota into a less favorable profile (including reduced diversity and rise in Gram-negative strains) and affect the integrity of the epithelial intestinal barrier. The rise in Gram-negative strains induced by a high-fat diet is linked to enhanced synthesis of lipopolysaccharide (LPS), which is responsible for the endotoxemia that contributes to the systemic inflammation observed in NAFLD patients[39]. A specific gut microbiome signature has been suggested for NAFLD[40]. For instance, individuals with coronary artery disease and additional NAFLD showed a significant increase in the abundance of *Coprococcus* and *Veillonella*, and reduction in the abundance of *Parabacteroides*, *Bacteroides* and *Ruminococcus*, which was well-distinguished from individuals without NAFLD[41]. A diet rich in red meats and dairy products has a more pronounced impact on CVD outcomes via gut microbiota. This type of diet is particularly rich in L-carnitine, which is converted by gut commensals into trimethylamine (TMA) and then metabolized in the liver to TMA N-oxide (TMAO)[42]. Circulating levels of TMAO have been associated with incident fatal and non-fatal CVD events, with markedly increased levels in patients with ischemic stroke[43]. In particular, TMAO seems to upregulate Nuclear Factor kappa-B, inducing endothelial dysfunction and vascular calcifications[44]. In addition, pre-clinical models have shown a pro-thrombotic effect of TMAO through modulation of calcium signaling pathways in platelets[45]. However, the association between NAFLD and TMAO is less clear, since only one study conducted on 61 biopsy-based NAFLD reported higher levels of TMAO in individuals with severe liver injury[46]. This complex crosstalk between diet, microbiome shaping and inflammatory pathways may contribute to the interconnection between liver and cardiac affections.

3. Clinical implications and management

The current evidence supports a strong relationship between NAFLD and both prevalent and incident CVD thorough shared pathophysiology and risk factors and suggests an independent role of NAFLD on the risk of multiple cardiac complications. It is still unclear whether the inclusion of NAFLD-based parameters would help improve the prediction ability for future CVD events. The Framingham risk equation has been validated for patients with NAFLD, but it includes only the traditional risk factors for CVD[47]. Current guidelines for NAFLD management remark the importance of treating the underlying metabolic co-factors (including T2DM, arterial hypertension, dyslipidemia), which help improving both liver and cardiovascular health[48]. No clear referral pathways or strong diagnostic pathways have been developed to help clinicians in a comprehensive metabolic evaluation of patients with NAFLD. The same dialogue that currently exists between diabetologists and cardiologists is not established yet for the hepatology setting.

Whatever the reason might be, the strong association between NAFLD and CVD poses the attention to a careful screening for early, pre-clinical signs of the cardiovascular involvement in NAFLD patients, followed by management according to current CVD guidelines (**Figure 2**). NAFL (Non-Alcoholic Fatty Liver) does not seem to affect significantly the cardiovascular compartment, but the presence of NASH and fibrosis are clearly linked to adverse cardiovascular outcomes. In this perspective, the identification of liver fibrosis through invasive or non-invasive modalities could improve the screening for subclinical cardiac and vascular dysfunction.

In the follow up of patients with NAFLD, a comprehensive assessment of the glucose and lipid profile is warranted, in order to detect early signs of insulin resistance and atherogenic dyslipidemia. A regular domiciliary monitoring of arterial blood pressure, followed by management according to current CV guidelines, would prevent systemic and organ complications of arterial hypertension. Carotid artery ultrasound is a useful tool to detect early carotid plaques and their calcification rate.

Echocardiography is a strong tool to detect early signs of diastolic dysfunctions, which predispose to heart failure with preserved ejection fraction.

The advice for a healthy lifestyle including dietary changes and physical exercise represents the cornerstone of NAFLD management, aiming at weight loss and improvement of metabolic dysregulations. The American Heart Association stated that replacing saturated fat with polyunsaturated vegetable oil reduces the incidence of CVD by 30%[49]. Importantly, this shift towards more unsaturated fats occurs when a Westernized diet containing processed foods is replaced by the Mediterranean diet. It is beyond the scope of this chapter to discuss the many potential mechanisms of benefit by which a Mediterranean Diet may benefit NAFLD and CVD, but a reduction in saturated fats and red meat consumptions may also help preventing the intestinal dysbiosis and improve an altered liver-gut axis with important cardiovascular implications.

Finally, since NAFLD is associated with extra-hepatic complications such as T2DM and chronic kidney disease that also increase risk of CVD, effective treatment strategies are urgently required. Crucially, similar proportions of people with NAFLD die from CVD as from liver disease and when patients with NAFLD develop T2DM, the presence of diabetes further increases risk of CVD, creating a vicious spiral of ill-health. Consequently, an ideal treatment for NAFLD might be expected not only to reduce the risk of chronic liver disease-related complications but also to decrease the risk of T2DM and CVD. As a matter of fact, statins are known to be safe in patients with NAFLD and should be prescribed for the increased cardiovascular risk. Further, statin use is probably associated with lower risk of hepatic decompensation and mortality, and might reduce portal hypertension, in patients with advanced chronic liver disease[50].

Conclusions

In conclusion, the strong association between NAFLD and CVD demands a comprehensive evaluation of metabolic dysfunctions at multiple districts. The cardiovascular health represents the main targets of screening strategies to prevent adverse outcomes in the NAFLD population. Improved

referral policies and development of shared pathways of management will help reduce the burden of cardiovascular mortality in this population.

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Figure Legends.

Figure 1. Pathophysiology pathways and clinical manifestations of cardiovascular dysfunctions in Non-Alcoholic Fatty Liver Disease (NAFLD). Abbreviations: EV: extracellular vesicles; HDL: high density lipoproteins; IL: interleukin; NF-kB: Nucelar Factor-kB; PAI-1:

plasminogen activator inhibitor-1; TNF: tumor necrosis factor; VLDL: Very-Low Density Lipoproteins.

Figure 2. Suggested clinical management for cardiovascular risk in Non-Alcoholic Fatty Liver Disease (NAFLD). Abbreviations: ECG: electrocardiogram; NASH: Non-Alcoholic Steatohepatitis.