Review

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Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysiological mechanisms and implications

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Summary

Non-alcoholic fatty liver disease (NAFLD) has become one of the most frequent chronic liver diseases in the Western society and its prevalence is likely to rise even further. An increasing body of evidence shows that NAFLD is not only a potentially progressive liver disease, but also has systemic consequences. More specifically, evidence points out that NAFLD has to be considered as a significant independent risk factor for subclinical and clinical cardiovascular disease (CVD). Long-term follow-up studies demonstrate cardiovascular mortality to be the most important cause of death in NAFLD patients. Moreover, ample evidence associates NAFLD with endothelial dysfunction, increased pulse wave velocity, increased coronary arterial calcifications and increased carotid intima media thickness, all established markers for CVD.

Despite of all this evidence, the mechanisms by which NAFLD causally contributes to CVD are not fully elucidated. Furthermore, an extensive overview of all potential pathophysiological mechanisms and the corresponding current data are lacking. In this review we summarise current knowledge, originating from fundamental and clinical research, that mechanistically links NAFLD to CVD. Subsequently, the impact of CVD on current clinical practice and future research in the area of NALFD are discussed.

Keywords: NAFLD; Cardiovascular disease; Pathophysiology; Clinical implications.

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; CV, cardiovascular; CVD, cardiovascular disease; MetS, metabolic syndrome; AT, adipose tissue; TG, triglycerides; DM, diabetes mellitus; NASH, non-alcoholic steatohepatitis; CVRF, cardiovascular risk factor; cIMT, carotid intima media thickness; LV, left ventricle; ADMA, asymmetric dimethyl arginine; LDL, low-density lipoproteins; HDL, high-density lipoproteins,; VLDL, very low-density lipoproteins; NAFL, non-alcoholic fatty liver (also known as simple steatosis); VEGF, vascular endothelial growth factor; CAD, coronary artery disease; PAI-1, plasminogen inhibitor activator 1; hsCRP, high sensitive C-reactive protein; FetA, fetuine A; FGF21, fibroblast growth factor 21; SeP, selenoprotein P; ANGPTL, angiopoietin like protein; TMA, trimethylamine; TMAO, trimethylamine-n-oxide; PNPLA3, patatin-like phospholipase domain containing protein 3; TM6SF2, transmembrane 6 superfamily member 2; SNP, single nucleotide polymorphism.

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become a major cause of chronic liver disease in Western societies and will become the main underlying cause for liver transplantation within 10 years [1]. Although awareness amongst physicians has increased and the importance is recognised, levels of screening and referral to hepatologists in suspected NAFLD is low in primary care and non-hepatology specialties [2,3]. As a result, NAFLD is relatively underdiagnosed and long-term outcomes of hepatic and extrahepatic manifestations of NAFLD are compromised. Indeed, NAFLD is not only associated with increased liver-related morbidity and mortality, but also with increased mortality due to cardiovascular disease (CVD) and cancer [4,5].

The role of NAFLD as an independent cardiovascular risk factor is still debated. Several studies demonstrated unequivocally an increased cardiovascular (CV) mortality in NAFLD [4,6]. Nevertheless, some studies failed to confirm this association, including two large cohort studies with long-term follow-up [7,8]. However, the data should be interpreted with caution because of several methodological issues, including retrospective diagnosis based on recorded ultrasound imaging or on biochemistry [7], which is known to poorly correlate with histological NAFLD features [9]. Even in the absence of a significant relation with CV mortality, CVD was still undoubtedly increased in NALFD patients compared to controls [8], supporting the many convincing data that NAFLD independently contributes to (sub)clinical CVD.

Distillation of NAFLD as a separate risk factor is impeded by overlap with other well-established risk factors for CVD, as they are also risk factors for NAFLD itself [5]. Assuming that NAFLD is a contributor to CVD implies the need

Key point

Increased cardiovascular mortality and morbidity are observed in NAFLD.

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for knowledge on the underlying pathophysiological mechanisms that explain how NAFLD independently impacts on CVD. An extensive overview of potential mechanisms is currently lacking.

In this review we summarise knowledge, originating from animal research as well as translational and clinical research, about the underlying pathophysiological mechanisms that might link NAFLD to CVD. We subsequently discuss the potential implications of these findings for clinical management of patients with NAFLD and future research goals.

The cardiovascular risk associated with NAFLD

General considerations

The specific contribution of NAFLD to increased CVD risk is, especially in clinical studies, difficult to dissect from the combination of risk factors that are shared by both NAFLD and CVD. The population of NAFLD patients is furthermore probably heterogeneous, in some of whom NAFLD is just part of and victim of the global metabolic derangement whilst in others, the liver is particularly involved in the pathophysiology of the Metabolic Syndrome (MetS) itself, and in the emergence of CVD and other complications [10,11]. Many patients will be somewhere in between, with the liver being diseased because of some metabolic abnormalities, and, once diseased, also contributing significantly to disease progression in terms of MetS, CVD and malignancies. This concept is fundamental in our understanding of NAFLD as part of a systemic disease.

The mechanisms by which the liver might contribute are also complex and heterogeneous. The liver plays a crucial role in lipid and glucose homeostasis and is hence in the center of cardiometabolic disease. There is a very complex interplay between the gut, visceral and subcutaneous adipose tissues (AT), muscle tissues, the cardiovascular system and the liver [12].

One of the starting points is most probably an imbalance in calorie-intake and expenditure, exceeding the storing-capacity of AT leading to deposition of ectopic fat, including the liver [13].

Once these mechanisms are initiated, a vicious circle starts, after which interplay between the different players is so complex that simple cause-effect relations become extremely difficult to assess (Fig. 1). As the liver is centrally positioned between different players, it is surprising that the mechanisms contribution to diabetes mellitus (DM) and CVD have gained so little attention. If it can be demonstrated that non-alcoholic steatohepatitis (NASH) livers play a pivotal role in that vicious circle, targeting the liver becomes attractive to break through the circle and halt metabolic and CVD progression.

Determinants of outcomes in NAFLD: subclinical and clinical CVD data

NAFLD encompasses a spectrum of liver diseases, ranging from non-alcoholic fatty liver (NAFL, also known as simple steatosis) over NASH and might lead to advanced fibrosis or cirrhosis and hepatocellular carcinoma (HCC). NAFLD is characterized by excessive fat accumulation in the hepatocytes (steatosis). When steatosis is accompanied by both hepatocellular ballooning degeneration and lobular inflammation, a diagnosis of NASH is made [14]. The natural history of NAFLD and its different subtypes is not so well described, in part because the gold standard for the accurate diagnosis of NASH is liver biopsy, and large long-term follow data with repeated biopsies are scarce and should be interpreted with caution because, amongst others, of potential selection bias. Nevertheless, NAFLD is generally considered to run a benign course, with a low (but not completely absent) risk of fibrosis progression, whereas NASH has a significantly higher risk of progressive liver disease [15].

This dichotomous concept has recently been challenged [16]. Singh *et al.* [17] systematically reviewed and performed a meta-analysis on 11 paired biopsy cohort studies. Although the majority of the patients had stable disease, it was shown that fibrosis progression occurred in both patients with NASH as well as NAFL (annually increase 0.14 and 0.07 fibrosis stage respectively). Moreover, a subset of patients was identified with considerable rapid fibrosis progression. Of note, progressors with baseline NAFL frequently had mild lobular inflammation or ballooning compared to non-progressors and although insufficient for the diagnosis of NASH, these subtle differences might explain their progression and are still in line with the concept of necro-inflammation being the driving force of disease progression [17]. Another recent paired biopsy study also showed that 44% of the patients with NAFL progressed to NASH, and 37% to fibrosis (including some with progression to stage 3 fibrosis). Of note, at baseline NAFL patients were significantly younger compared to NASH patients, and most of the progressors out of the NAFL group had NASH at follow-up, and frequently had mild lobular inflammation at baseline. Development of type 2 DM was also an important determinant of progression [18].

NAFLD is unambiguously related to increased liver-related and all-cause mortality [4,6]. Importantly, CVD is the main cause of death in NAFLD patients (38% of all causes [19]), with baseline fibrosis being the strongest predictor [4,19]. Earlier studies suggested that the risk was higher in patients with NASH compared to NAFLD [20]. In

Key point

NAFLD is not only associated with, but also contributes to the pathogenesis of cardiovascular diseases.

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