Review

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NAFLD: A multisystem disease

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Summary

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in Western countries that is predicted to become also the most frequent indication for liver transplantation by 2030. Over the last decade, it has been shown that the clinical burden of NAFLD is not only confined to liver-related morbidity and mortality, but there is now growing evidence that NAFLD is a multisystem disease, affecting extra-hepatic organs and regulatory pathways. For example, NAFLD increases risk of type 2 diabetes mellitus (T2DM), cardiovascular (CVD) and cardiac diseases, and chronic kidney disease (CKD). Although the primary liver pathology in NAFLD affects hepatic structure and function to cause morbidity and mortality from cirrhosis, liver failure and hepatocellular carcinoma, the majority of deaths among NAFLD patients are attributable to CVD. This narrative review focuses on the rapidly expanding body of clinical evidence that supports the concept of NAFLD as a multisystem disease. The review discusses the factors involved in the progression of liver disease in NAFLD and the factors linking NAFLD with other extra-hepatic chronic diseases, such as T2DM, CVD, cardiac diseases and CKD. The review will not discuss NAFLD treatments as these are discussed elsewhere in this issue of the Journal. For this review, PubMed was searched for articles using the keywords "non-alcoholic fatty liver disease" or "fatty liver" combined with "diabetes", "cardiovascular (or cardiac) disease", "cardiovascular mortality" or "chronic kidney disease" between 1990 and 2014. Articles published in languages other than English were excluded.

Keywords: Non-alcoholic fatty liver disease; Hepatocellular carcinoma; Type 2 diabetes; Insulin resistance; Cardiovascular disease; Cardiac disease; Cardiac arrhythmias; Chronic kidney disease.
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Abbreviations: AF, atrial fibrillation; ATGL, Adipose triglyceride lipase; AST/ALT, aspartate aminotransferase to alanine aminotransferase ratio; APRI, aspartate to platelet ratio index; CRP, C-reactive protein; CVD, cardiovascular disease; CGI-58, Comparative Gene Identification-58; CKD, chronic kidney disease; DAG, di-acyl glycerol; Di-P PA, di-palmitoyl phosphatidic acid; ELF, Enhanced Liver Fibrosis panel; FGF-21, fibroblast growth factor-21; FIB4, Fibrosis-4 Score; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; HF, heart failure; HR, hazard ratio; IRS-1, insulin receptor substrate-1; IL-6, interleukin 6; LCFAs, long chain fatty acids; LPA, lysophosphatidic acid; LV, left ventricular; MetS, metabolic syndrome; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; NHANES, National Health and Examination Survey; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor-kappa B; OR, odds ratio; PTEN, phosphatase and tensin homolog; PA, phosphatidic acid; PAI-1, plasminogen activator inhibitor-1; PKCε, protein kinase Cε; T2DM, type 2 diabetes mellitus; TAG, triacylglycerol; TLR-4, toll-like receptor-4; TNF-α, tumour necrosis factor-α; VLDL, very-low-density lipoprotein.

Introduction

Over the last decade, it has been shown that the clinical burden of non-alcoholic fatty liver disease (NAFLD) is not only confined to liver-related morbidity and mortality, but there is now growing evidence that NAFLD is a multisystem disease, affecting several extra-hepatic organs and regulatory pathways [1]. Since NAFLD has become the predominant cause of chronic liver disease in many parts of the world [2], NAFLD is also potentially contributing to an important burden of extra-hepatic chronic complications. For reasons that are not completely clear, NAFLD is more common in men than women and although precise estimates of incidence rates for NAFLD are uncertain (because of difficulties with establishing a precise diagnosis during sequential follow-up), current incidence rates are approximately 20/10,000 person-years, peaking in the sixth decade of life [3]. Current population-based prevalence of NAFLD is approximately 30–40% in men and 15–20% in women [4] and is even higher in people with type 2 diabetes mellitus (T2DM), occurring in up to 70% of this group of patients [5].

A major focus of the NAFLD-related chronic diseases during the last 10 years has involved chronic liver disease, cardiovascular disease (CVD) and T2DM; e.g., a recent meta-analysis showed that NAFLD increased overall mortality by 57% mainly from liver-related and CVD causes, and increased risk of incident T2DM by approximately twofold [6]. Additionally, and even more recently, increasing attention has also focused on NAFLD-related chronic kidney disease (CKD) and a further recent meta-analysis reported that NAFLD was associated with an approximate twofold increased risk of CKD [7]. Although there is also emerging evidence that NAFLD is linked to other chronic diseases, such as sleep apnea, colorectal cancers, osteoporosis, psoriasis and various endocrinopathies (e.g., polycystic ovary syndrome) [8], because of the limitations on space, this review will focus only

on NAFLD-related extra-hepatic diseases where there is strongest evidence for a possible causal link between NAFLD and pathology in extra-hepatic organs (namely T2DM, CVD and CKD).

This narrative review will discuss NAFLD and: a) liver disease that is relevant to the development of extra-hepatic complications, b) T2DM, c) CVD and cardiac diseases, and d) CKD. The aetiology and pathogenesis of each of these hepatic and extra-hepatic chronic complications will also be briefly discussed.

Key Points

- Liver fat accumulation in NAFLD increases risk of type 2 diabetes mellitus approximately twofold
- Hepatic lipid accumulation (e.g., di-acyl glycerol) in NAFLD impairs insulin signaling (insulin resistance) that contributes to abnormal hepatic metabolism
- Increasing evidence suggests more severe forms of NAFLD further increase risk of type 2 diabetes mellitus
- Both NASH and type 2 diabetes mellitus increase risk of hepatocellular carcinoma
- Mechanisms contributing to the pathogenesis of hepatocellular carcinoma also occur with obesity and insulin resistance (i.e., two common risk factors for type 2 diabetes mellitus)
- Increasing evidence indicates that the presence and severity of NAFLD is associated with an increased prevalence and incidence of cardiovascular disease, independently of established cardiovascular risk factors
- Some evidence also indicates that the presence and severity of NAFLD is associated with an increased prevalence and incidence of chronic kidney disease, independently of multiple cardio-renal risk factors
- It is now becoming increasingly evident that NAFLD is not simply a marker of cardiovascular disease and chronic kidney disease, but also may play a part in the pathogenesis of these extra-hepatic chronic complications
- The clinical implication for these findings is that NAFLD patients may benefit from more intensive surveillance and early treatment interventions to decrease the risk for cardiovascular and kidney complications

NAFLD: diagnosis, development, and progression of liver disease

In clinical practice, an initial diagnosis of NAFLD is usually established with radiological imaging techniques, by the presence of $\geqslant$5% hepatic fat accumulation in the absence of other recognized causes of fatty liver, e.g., alcohol, virus, drugs, autoimmunity.

Because of the limitations of space, this review will not discuss the use of the various techniques for diagnosing NAFLD. However, for a detailed recent review of the radiological imaging modalities available for the assessment of NAFLD see [9]; for more details regarding the sensitivity and specificity of ultrasonography to detect liver fat, the reader is referred to the following [10–12]; and for information, regarding the sensitivity and reproducibility of magnetic resonance techniques to assess liver fat [13,14]. For a discussion of the utility of histological characterization of the liver, using a designated scoring system, see [11,15].

NAFLD is fast becoming one of the most common causes of chronic liver disease worldwide, and is now a major cause of liver-related morbidity and mortality [16]. NAFLD begins with liver lipid accumulation, and marked hepatic fat accumulation is a risk factor for disease progression. Although the major risk factors for hepatic fat and hepatic fibrosis development in NAFLD are well established (e.g., age >50 years, obesity, insulin resistance, T2DM, increased ferritin levels and the patatin-like phospholipase domain-containing 3 (*PNPLA3*) I148M polymorphism) [17–19], the pathological mechanisms by which each of these risk factors (particularly *PNPLA3* genotype) cause NAFLD progression are less well understood. It has been shown that when associated with the I148M gene variant, NAFLD has a lower plasma triacylglycerol profile. This supports the notion that the I148M gene variant inhibits intra-hepatocellular lipolysis rather than stimulates hepatic triacylglycerol synthesis [20]. However, further work is required to establish the precise function of PNPLA3 in the pathogenesis of liver disease progression in NAFLD, as it has also been highlighted in response to this work that a contribution of PNPLA3 lysophosphatidic acid acyltransferase activity could also contribute to altered plasma triacylglycerol composition and concentration [21]. Where there is evidence of advanced hepatic fibrosis, which is easier to establish with some of the newer non-invasive imaging modalities [9,22], complications such as cirrhosis and hepatocellular carcinoma (HCC) are not uncommon. Development of hepatic fibrosis occurs in 40–50% of patients with non-alcoholic steatohepatitis (NASH) and current estimates are that approximately 30–40% of people with NAFLD develop NASH [23]. From a meta-analysis of 40 studies, it has been estimated that NASH increases the risk of liver-related mortality by ~5–10 fold (mainly depending on the degree of hepatic fibrosis present) [6]. With regard to this, Ekstedt *et al.* recently confirmed that hepatic fibrosis stage was the strongest predictor for all-cause and disease-specific mortality in patients with histologically confirmed NAFLD, who were followed-up for a mean period of 26.4 years [24]. In 2009, patients with NASH accounted for ~10% of patients undergoing liver transplantation in the United States; NASH is the third most common indication for liver transplantation in the United States, and considering the spectrum of disease encapsulated within NAFLD, NAFLD is on a trajectory to become the most common indication for liver transplantation [25].

It has been known for many years that obesity and T2DM increase the risk of HCC [26] but the biological explanation for this link remains uncertain. NASH is common in patients with obesity, insulin resistance and T2DM and NASH increases the risk of HCC [27]. That said, it is uncertain whether there is a diabetes/obesity-specific factor that increases risk of HCC or whether there are common pathological mechanisms that occur both in HCC and in T2DM/obesity. For HCC, it has been recently shown that incidence and mortality rates have increased approximately twofold in men and women between 1968 and 2008 [28,29]. Although it is less certain whether simple steatosis increases risk of HCC, it is now becoming clear that NASH is a risk factor for HCC, even in people without cirrhosis [30–32].