Review paper

The influence of NAFLD on the risk of atherosclerosis and cardiovascular diseases

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Abstract
Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in developed countries and is associated with obesity, dyslipidaemia, diabetes, and metabolic syndrome. Atherosclerosis and cardiovascular diseases are also highly prevalent in this group of patients, due to the presence of shared risk factors. The incidences of coronary artery calcification, hypertension, aortic valve sclerosis, diastolic dysfunction, atherosclerotic plaques, and increased carotid intima-media thickness were more common in patients with NAFLD than in those without. The present paper reviews the medical literature concerning the association between NAFLD and cardiovascular events.

Key words: non-alcoholic fatty liver disease, ischaemic heart disease, atherosclerosis.

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Introduction
Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in developed countries, with a prevalence ranging from 20% to 30% of the population of Europe. However, experts estimate that NAFLD affects from 25% to 90% of obese patients and 70% of patients with diabetes mellitus [1, 2]. The histologic spectrum of NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis (NASH) with the presence of fibrosis. Simple steatosis tends to be a stable condition, but steatohepatitis may progress to liver cirrhosis [3]. Liver failure in the course of NAFLD is the second most common indication for liver transplantation in the USA [4].

NAFLD is diagnosed mostly in patients between the ages of 40 and 60 years. Although the prevalence of NAFLD is higher in men, faster progression to cirrhosis is noted in women [5]. NAFLD is regarded as an isolated disease or as a spectrum of metabolic syndrome, and is associated with diabetes, obesity, dyslipidaemia, and hypertension [6]. NAFLD is found in 30% to 75% of patients with type 2 diabetes, depending on age and ethnicity [7]. Types of dyslipidaemia have a significant impact on the prevalence of NAFLD. Mixed hyperlipidaemia is reported in 50% of patients with NAFLD. Isolated hypertriglyceridaemia is reported in 27% of subjects with NAFLD, and hypercholesterolaemia in 17% [8]. An analysis of lipid fractions in patients with NAFLD revealed a tendency towards elevated triglyceride levels and low HDL levels in the atherogenic lipid profile [9].

Insulin resistance contributes to the development of NAFLD. Subclinical inflammation plays also an important role in the pathogenesis of NAFLD. High-sensitivity C-reactive protein (Hs-CRP) is elevated in patients suffering with NAFLD, even in young age; hs-CRP may be a marker of NAFLD [10-12]. Hs-CRP is not associated with severity of NAFLD or NASH [11, 12]. Subclinical inflammation also plays the principal role in the pathophysiology of atherosclerosis. Hs-CRP is a stronger cardiovascular risk predictor than LDL-C (low-density lipoprotein) [13]. However, many other studies have shown that oxidant stress and chronic inflammation associated with the production of cytokines including interleukin (IL) 6, tumour necrosis factor α...
(TNF-α), pro-coagulant factors, and adipocytokines are also involved in NAFLD pathogenesis [14, 15]. These risk factors are also strongly related to atherosclerosis. Patients with NAFLD exhibit a range of non-traditional risk factors of cardiovascular disease, including hyperuricaemia and hypovitaminosis D [16]. In addition, shared genetic factors exist between NAFLD and coronary artery heart disease, for instance: gene polymorphisms of adiponectin-encoding gene (ADIPOQ), leptin receptor (LEPR), apolipoprotein C3 (APOC3), peroxisome proliferator-activated receptors (PPAR), sterol regulatory element binding proteins (SREBP), transmembrane 6 superfamily member 2 (TM6SF2), microsomal triglyceride transfer protein (MTTP), TNF-α, and manganese superoxide dismutase (MnSOD) [17].

**Association between cardiovascular risk and NAFLD**

The individuals with NAFLD had a higher risk of 10-year cardiovascular events than healthy individuals. In subjects with and without NAFLD, the mean respective cardiovascular risks according to Framingham scoring were 16.0% and 12.7% in men and 6.7% and 4.6%, in women [18].

A meta-analysis of 34 studies (164,494 participants) published between 1965 and 2015 indicates an increased risk of cardiovascular disease in NAFLD patients, although the prevalence of NAFLD was not associated with mortality from cardiovascular events in this group. The results of this study suggest that NAFLD was an independent risk factor for the incidence of cardiovascular events [19]. However, Hamaguchi et al. report that NAFLD is strongly related to metabolic syndrome. Because it is important to note that it is extremely difficult to separate the components of metabolic syndrome in statistical analysis, Hamaguchi et al. suggest that high cardiovascular risk in patients with NAFLD is not a consequence of liver disease but of metabolic syndrome [20].

**Association between NAFLD, type 2 diabetes, and cardiovascular risk**

NAFLD is hepatic manifestation of metabolic syndrome and may predict the development of type 2 diabetes independently of obesity and age [21]. Insulin resistance is a key pathogenic factor for NAFLD and type 2 diabetes. The presence of NAFLD increases two-fold the risk of developing type 2 diabetes over a median period of five years [21]. Ekstedt et al. found that 78% of patients with NAFLD develop type 2 diabetes or impaired glucose tolerance [22]. Patients with NAFLD and diabetes have a 2.4-fold increased risk of cardiovascular diseases [23]. Of note, the meta-analysis published by Ballestri shows that NAFLD is also associated with an approximately twofold increased risk of incident of metabolic syndrome [24]. Again, Gami et al. in a meta-analysis of 37 studies comprising 172,573 patients with metabolic syndrome, found 1.78-fold higher relative risk of cardiovascular events in patients with metabolic syndrome compared to healthy subjects [25]. In another meta-analysis that incorporated 16 observational studies with 34,043 patients with NAFLD, the authors concluded that the presence of NAFLD conferred an OR of 1.64 for fatal and non-fatal incidence of cardiovascular events, and the risk appeared to increase with greater severity of NAFLD [26]. A large number of studies confirm the relationship between NAFLD and incidence of cardiovascular events and death (Table 1).

**NAFLD and coronary artery disease**

An increasing number of studies suggest the presence of a relationship between NAFLD and coronary artery heart disease [34, 35]. It is estimated that cancers and cardiovascular disease are the leading causes of death in patients with NAFLD [36]. NAFLD is observed in 51% of patients with mild and insignificant coronary stenosis and in as much as 100% of patients with three affected coronary arteries [37]. Perera et al. note the presence of NAFLD in 46.7% of patients with acute coronary syndrome [38]. Patients with NAFLD show a significantly higher prevalence of calcified and non-calcified coronary plaques than healthy subjects, independent of the incidence of metabolic syndrome [39]. Again, the coronary flow reserve (CFR), measured as the maximum increase in blood flow through the coronary arteries above the normal resting volume, is significantly lower in patients with NAFLD than in healthy subjects [40].

**NAFLD and arrhythmias**

NAFLD is associated with an increased risk of the incidence of arrhythmias, especially the atrial fibrillation or ventricular tachyarrhythmias typically observed in the course of left ventricular diastolic dysfunction [41].

**NAFLD and hypertension**

Hypertension is diagnosed in about 50% of patients with NAFLD [42]. Hypertension predisposes to the development of left ventricular hypertrophy and increases the risk of plaque rupture.
NAFLD and atherosclerosis

The greater intima-media thickness (IMT) of carotid arteries represents a marker of endothelial dysfunction, and subclinical atherosclerosis was found in patients with NAFLD [43]. NAFLD is associated with a high coronary artery calcification score, irrespective of the presence of traditional cardiovascular risk factors and metabolic syndrome [44]. Lower flow-mediated dilation (FMD)-indicated endothelial dysfunction is found in patients with NAFLD and is associated with an elevated risk of acute coronary syndrome and ischaemic stroke [45, 46].

Increased arterial stiffness, as a marker of cardiac hypertrophy and early atherosclerotic changes, was reported in patients with NAFLD [47]. Brachial-ankle pulse wave velocity is used as a simple index of assessing arterial stiffness [48]. Lee et al. reported elevated brachial-ankle pulse wave velocity in patients with NAFLD, independent of conventional cardiovascular risk factors and the presence of metabolic syndrome [49]. The increased arterial stiffness results from the degeneration of the extracellular matrix of elastic arteries, apoptosis of endothelial cells, and diffusion of macromolecules into the arterial wall [50]. The decrease in vascular susceptibility leads to an increase in cardiac afterload output and insufficient coronary flow [51].

NAFLD and ischaemic stroke

NAFLD was found in 42.7% of ischaemic stroke patients and 22.7% of controls in a population from Iran. It is estimated that the risk of ischaemic stroke in NAFLD sufferers is 1.68-times higher than in the general population and is associated with the incidence of traditional cardiovascular risk factors [52].

NAFLD and left ventricular systolic and diastolic dysfunction

Morphological and functional changes in cardiac myocytes are observed in cases of NAFLD [53]. Myo-
cardiac steatosis is a well-known predictor of diastolic heart failure [54]. Diastolic dysfunction is three times more common in patients with NAFLD than in the general population, especially left ventricular relaxation correlating with NAFLD Activity Score (NAS) [55, 56]. Trovato et al. reported a higher left ventricular mass index in patients with NAFLD [57]. In these patients, there is a significantly greater left ventricular filling pressure (E/e’ ratio: mitral filling velocity [E]/early diastolic mitral annular velocity [E/e’] ratio) [55]. However, NAFLD patients with obesity, hypertension, or diabetes also display impaired left ventricular systolic function [58].

NAFLD patients tend to demonstrate the presence of epicardial adipose tissue [59], which acts as a source of pro-inflammatory cytokines and increases the risk of cardiovascular diseases [60]. In addition, NAFLD is strongly associated with an increased risk of aortic valve sclerosis, which is an independent indicator of atherosclerosis [61]. Aortic stenosis is the most common valvular heart disease and increases the risk of cardiovascular death [62].

**Histological severity of NAFLD and incidence of cardiovascular diseases**

Byrne et al. reported a correlation between the risk for cardiovascular mortality and the progression of NAFLD [63]. Many studies found the stage of liver fibrosis and steatosis in NAFLD to be related to the incidence of cardiovascular diseases [64]. Targher et al. identified increased carotid IMT levels in advanced stages of hepatic steatosis, necroinflammation, and fibrosis in NAFLD, independent of the presence of traditional risk factors, insulin resistance, and metabolic syndrome [65]. Individuals with NAFLD and advanced fibrosis had a 3.5-fold greater risk of left ventricular hypertrophy [66]. In patients with NAFLD, increased arterial stiffness and epicardial fat thickness, impaired left ventricular function, and higher coronary calcification score correlate with the progression of fibrosis in NAFLD [67].

**Treatment of NAFLD could decrease cardiovascular risk**

Statin therapy in patients with NAFLD decreases fat accumulation in the liver and even decreases fibrosis in some NAFLD patients [68]. It has been known for many years that statins decrease coronary heart disease risk [69]. This cardiovascular disease benefit is significantly greater in patients with elevated liver enzymes due to NAFLD than it is in patients with normal liver tests [70]. We could explain an excellent protection of statin treatment against cardiovascular risk in NAFLD patients not only with reduction of fat accumulation in atheromatous plaques but also with reduction of subclinical inflammation and with decrease of pro-coagulant factors production in the cardiovascular system, especially in coronary arteries [71]. Statin hepatotoxicity is minimal in patients with elevated liver tests [70]. Study published by Ruscica et al. showed that liver fat accumulation is associated with increased circulating PCSK9 (proprotein convertase subtilisin/kexin type 9) [72]. PCSK9 inhibitors have significant cardiovascular benefit in high-risk patients, but the effect of PCSK9 inhibition on liver fat accumulation and liver fibrosis is still unknown [73]. The cardiovascular benefit of other promising NAFLD treatment options must also be studied in the future.

Patients with NAFLD possess a high risk of developing acute or chronic cardiovascular diseases with shared pathogenic factors. Therefore, it is necessary to estimate the cardiovascular risk in patients with NAFLD and to determine the potential benefits of early cardiovascular prevention strategies.

**Disclosure**

Authors report no conflict of interest.

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