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Non-alcoholic Fatty Liver Disease Associated With Metabolic Syndrome, a Major Risk Factor for Atherosclerotic Disease

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REVIEW

Abstract

In the current review we summarize the relationships between the non-alcoholic fatty liver disease, metabolic syndrome, and atherosclerotic disease. We have shown the markers of subclinical atherosclerosis, carotid atheromatous lesions, coronary atheromatous lesions, and their impact on the cardiac function. Finally, we discuss the risk of the data already mentioned on acute myocardial infarction and stroke, and the impact on cardiovascular mortality.

Keywords: non-alcoholic fatty liver disease, metabolic syndrome, atherosclerosis

I. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a vast chapter of liver pathology in medical practice [1,2]. Prevalence in the general population is approximately 10-30%, being higher in developed and current countries` development [3]. There is an association between NAFLD with insulin resistance and metabolic syndrome. A possible explanation of this association would be that the NAFLD patients often present abnormalities in carbohydrate metabolism, are overweight or obese, and hypertensive [4]. Other mechanisms that would explain this association are the increased oxidative stress, the altered adipokine profile, and the state of hypercoagulability [5]. However, the clinical and epidemiological significance of a NAFLD is not fully elucidated. The fact that NAFLD is associated with traditional cardiovascular risk factors (hypertension, dyslipidemia, obesity, sedentary lifestyle, insulin resistance, endothelial dysfunction, and inflammation) placed patients with NAFLD in a risk category increased for cardiovascular events. In support of this statement comes the fact that a number of studies have shown an increased prevalence of surrogate markers in patients with NAFLD, such as subclinical atheromatosis [6], atheromatous plaques in the carotid arteries [7], acute myocardial infarction, or stroke [5]. The severity of coronary lesions found angiographically is also higher in patients with NAFLD [8]. In fact, cardiovascular disease is the main cause of death in these patients. However, it is not clear whether NAFLD is an independent marker or risk factor for atherosclerotic cardiovascular diseases [9].

II. NAFLD AND CARDIOVASCULAR RISK FACTORS

A. Markers of subclinical atherosclerosis

Patients with NAFLD, adults, and children that meet the diagnostic criteria for metabolic syndrome (abdominal obesity, hypertension, dyslipidemia, and carbohydrate metabolism disorders), also present numerous risk factors of atherosclerotic cardiovascular disease [10]. When compared to control subjects (without hepatic steatosis), those with NAFLD show impaired vasodilation mediated arterial flow [11] and carotid intima-media thickening (CIMT) [12,13]. These parameters are proven markers for subclinical atherosclerosis and are independently associated with obesity and other cardiovascular risk factors.

B. Carotid atheromatous lesions

Carotid intima-media thickness (CIMT) measurement by vascular ultrasonography is a validated and accepted method for screening for atherosclerotic cardiovascular disease in asymptomatic subjects [14]. A meta-analysis that included seven clinical trials, summing up 3,497 subjects with NAFLD diagnosed by ultrasonography, demonstrated a strong association between CIMT and the increased prevalence of carotid atheromatous plaques. Some studies have reported an independent association between NAFLD and atherosclerotic carotid disease, but the power of this association diminished after statistical adjustment for the components of the metabolic syndrome. The severity of hepatic histological lesions is independently correlated with the value of CIMT, this being on average 13% higher in subjects with NAFLD

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compared to control subjects [15]. In a study from 2006, the CIMT index had the highest values in patients with nonalcoholic steatohepatitis (NASH), was intermediate in those with simple hepatic steatosis, and lowest in the control subjects of the same age and the same sex [16].

C. Coronary atheromatous lesions

Patients with ultrasonographically highlighted NAFLD have a higher prevalence of the clinical manifest cardiovascular disease when compared to the control subjects [17]. Among the patients with type 2 diabetes, the prevalence of coronary, cerebral, and peripheral vascular atherosclerotic disease was significantly higher than in those with NAFLD, regardless of the presence of the traditional risk factors, the components of the metabolic syndrome, the duration of diabetes, the values blood glucose, or the treatment with statins, hypotensive drugs, antiplatelet agents or antidiabetic drugs [18]. A similar result was found in another study that enrolled adults with type 1 diabetes [19].

Ischemic heart disease has an increased prevalence in patients with ultrasonographically demonstrated NAFLD [20]. Coronary angiography showed that this category of patients has more severe coronary lesions, regardless of the presence of traditional cardiovascular risk factors [21]. Moreover, necropsy studies performed on children have shown that the prevalence of atherosclerotic coronary heart disease was double in those with NAFLD [22]. The calcium score of the carotid arteries, determined by computed tomography, represents a sensitive method that demonstrates the presence and severity of coronary atheromatosis, allowing better quantification of cardiovascular risk in asymptomatic subjects [23]. A series of studies showed a significant increase in the prevalence of atherosclerotic coronary heart disease in the presence of NAFLD. This is in accord with the increase in the plasma markers of oxidative stress and inflammation, partially due to liver dysfunction that causes a systemic inflammatory condition, and a prothrombotic state [24, 25]. Several studies proved the independent association between NAFLD and angiographically confirmed ischemic heart disease. The results of the Framingham Heart Study did not confirm the association between hepatic steatosis established by computed tomography (CT), and clinically manifest atherosclerotic cardiovascular disease, but they proved a significant association between NAFLD and carotid calcium score [27].

D. Cardiac function

Patients with metabolic syndrome present, when compared to control subjects, a significantly higher left ventricular mass index, as well as an impairment in cardiac diastolic fu

nction. These are side effects of insulin resistance, obesity, hypertension [28]. Unfortunately, only a few echocardiographic studies included subjects with NAFLD, but the results regarding left ventricular hypertrophy and diastolic dysfunction were similar to those found in the presence of the syndrome metabolic [29]. Fallo showed a strong correlation between diastolic dysfunction and the severity of hepatic steatosis, the only independent parameters associated with NAFLD being ventricular diastolic dysfunction and insulin resistance [30]. Another study showed that the echocardiographically determined coronary reserve function was significantly lower in subjects with NAFLD compared to the control group, even after the adjustments for obesity, the traditional cardiovascular risk factors, and the components of the metabolic syndrome were done. The histologically demonstrated liver fibrosis was the only independent predictive factor for impaired coronary functional reserve, which reflects coronary endothelial dysfunction [31].

The finding of a subclinical (asymptomatic) cardiac dysfunction in patients with NAFLD is not surprising if we consider the fact that left ventricle hypertrophy and diastolic dysfunction are closely correlated with insulin resistance [32]. Endothelial dysfunction is recognized as an early sign of atherosclerosis, both in diabetics and in non-diabetics. There is an independent association between the alteration of the vasodilation mediated flow and the presence of NAFLD. Endothelial dysfunction was more severe in those with NAFLD compared to those with simple hepatic steatosis, confirming the possibility of correlating cardiovascular risk with the severity of NAFLD [11]. To explain the causes of subclinical cardiac dysfunction in patients with NAFLD, the effects of hepatic steatosis on cardiac metabolism were evaluated [33]. A positive correlation was found between the degree of hepatic steatosis and the insulin resistance of the myocardium. The more severe the hepatic steatosis, the more severe the systemic insulin resistance was found, and this was associated with a reduction in myocardial glucose uptake and extraction, with a decrease in coronary reserve function, and with increased plasma levels of inflammation markers and molecules of vascular adhesion. These abnormalities in myocardial metabolism in subjects with hepatic steatosis precede functional and structural cardiac changes that lead to left ventricle hypertrophy and diastolic dysfunction. The trigger seems to be systemic, hepatic insulin resistance leading to hyperinsulinemia and to increased free fatty acids and insulin resistance in the myocardium. The cardiomyocyte metabolism becomes energy inefficient, so it goes from glycolysis to lipolysis and produces less ATP. The stress to which the myocardium is subjected causes cardiac dysfunction, with activation of the adaptive remodeling mechanisms and the occurrence of myocardium lesions. The excess free fatty acids induces cardiac lipotoxicity, causing intracellular accumulation of lipids, and exceeding the oxidative capacity of the myocardial cells. The increased oxidative stress has as consequences apoptosis and cardiac dysfunction [33].

E. The risk of acute myocardial infarction and stroke

In a meta-analysis performed by Lu [35], it was found that NAFLD doubles the risk of major cardiovascular events. After adjusting for age, sex, and duration control of diabetes, smoking, dyslipidemia, and medication followed, the relative risk dropped to 1.5 but remained statistically significant ($P < 0.001$). For most subjects with NAFLD being asymptomatic, a careful evaluation of their cardiovascular risk is recommended. Other meta-analyses performed in recent years

also draw attention to the fact that people with NAFLD are at increased risk to develop acute myocardial infarction or stoke, their risk approaching that of patients with type 2 diabetes [18]. As demonstrated by a meta-analysis published in 2016 [36], that included 86 studies in 22 states, the patients with NAFLD have an increased prevalence of associated comorbidities, such as obesity (51%), diabetes mellitus 2 (22%), arterial hypertension (39%). This explains the increased cardiovascular risk in this category of patients.

A longitudinal analysis of over 120,000 adult subjects with a confirmed diagnosis of NAFLD, coming from four European states that were included in the European Health Information Network, assessed the risk of acute myocardial infarction (AMI) or stroke. The average follow-up period was of 2 years. The relative risk was modest, about 1.2. The predictive value of NAFLD for the risk of heart attack or stroke was lower compared to classical risk factors for cardiovascular disease, after adjusting for their presence.

These results suggest that the risk patients with NAFLD should be systematically evaluated, by means of the common risk scores used for the general population, but with particular attention to detect yet undiagnosed diabetes. The association of NAFLD with diabetes, arterial hypertension, or dyslipidemia increases the cardiovascular risk of the patient, but NAFLD does not act as a risk enhancer. The diagnosis of NAFLD is useful for risk stratification of liver damage. It also justifies the change of the lifestyle, as this measure will bring benefits not only in reducing hepatic steatosis but also in body weight. The latter will reduce the risk for AMI and stroke, including dyslipidemia, systolic blood pressure, and type 2 diabetes [5].

F. Cardiovascular mortality

In general, the published studies show that NAFLD patients have higher mortality than the general population, most of the deaths being due to the association between cardiovascular disease and liver dysfunction. The magnitude of the death risk was different, depending on diagnosing method of the liver disease.

In a retrospective study of 420 patients with NAFLD diagnosed by liver biopsy, followed-up over an average period of 13 years, the deaths from cardiovascular disease were the most common cause of death [38]. Ekstedt found that the risk of cardiovascular death was double in subjects with nonalcoholic steatohepatitis compared to the general population over a period of 14 years. This was not the case for patients with simple steatosis [39.40]. In the case of ultrasonographically diagnosed NAFLD, Hamaguchi found that this was associated with an increased risk of cardiovascular events, independent of the cardiometabolic risk factors, including the presence of or absence of type 2 diabetes [41].

III. CONCLUSION

In conclusion, the data published so far suggest that the patients with NAFLD have multiple cardiovascular risk factors and that in these patients, cardiovascular deaths are more common than those caused by the liver. NAFLD is associated with an increased risk of cardiovascular disease events in both diabetics and non-diabetics. So far, it is not known whether NAFLD amelioration could prevent or slow down the onset or worsening of atherosclerotic cardiovascular disease. The prognostic value of NAFLD in the stratification of cardiovascular risk is still controversial.

Conflict of interest: none to declare.

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