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NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD): A NEW CARDIOVASCULAR RISK FACTOR

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Abstract

Non alcoholic fatty liver disease (NAFLD) affects nearly one-third of the world population and may increase the cardiometabolic risk, having cardiovascular consequences independently of traditional cardiovascular risk factors and of insulin resistance syndrome. NAFLD is a marker of ectopic accumulation of fat combined with a chronic inflammatory status. This leads to modification of physiological processes, such as abnormal glucose metabolism, changes in the fatty acids and lipoproteins, increased oxidative stress, changing the profile of adipokines, endothelial dysfunction and accelerated progression of atherosclerosis. It eventually leads to cardiometabolic dysfunction with cardiovascular mortality, representing the most important way of premature death in NAFLD. This review aims to introduce the notion of NAFLD to cardiologist clinicians, highlighting the link between NAFLD and cardiovascular risk, and the possible mechanisms underlying this association.

key words: *non-alcoholic fatty liver disease; cardiovascular risk factor, liver fat, cardiovascular disease*

Definition of NAFLD

Non alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver injury in the general population and occurs when the accumulation of triglycerides in hepatocytes exceeds 5%, in the presence of an alcohol intake of less than 20 g per day, without any other causes of liver disease [1]. It can be considered a benign condition, defined clinically, imagistically and biochemically. NAFLD is a slowly progressive disorder, presenting a wide spectrum in terms of the severity of liver damage, ranging from simple steatosis, inflammation with cell ballooning and necrosis, different degrees of fibrosis, to cirrhosis and risk of hepatocellular carcinoma [2]. Non alcoholic steatohepatitis (NASH) is the next stage of the disease, with the addition of the inflammatory component (lobular inflammation and hepatocellular ballooning). Simple steatosis is associated with a relatively low risk of progression to cirrhosis, unlike NASH (7% of patients develop cirrhosis within 3 years) [3]. The essential elements in the metabolic syndrome, insulin resistance and obesity, are closely associated with the progression of NAFLD. The prevalence of NAFLD in patients with metabolic syndrome is four times higher and 30% of the patients with NAFLD show metabolic syndrome. Despite the fact that the metabolic syndrome doubles the cardiovascular

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risk, there is evidence that NAFLD "per se" independently accelerates the atherogenesis process [4].

Epidemiology of cardiovascular disease in NAFLD

Numerous epidemiological studies report an increased incidence of cardiovascular events in patients with NAFLD, compared to the general population. Given that NAFLD is the most common cause of liver enzymes changes in developed countries [5], several epidemiological studies have taken them as surrogates for NAFLD. Other studies have shown a significant link between the gamma-glutamyltransferase (GGT) level and cardiovascular mortality over a 12 year period. Recently, the moderate increase in transaminases has been shown to be independently associated with an increased occurrence of atrial fibrillation (AF) [6]. It also has been proven that patients with type 2 diabetes (T2DM) and NAFLD show a higher risk of developing AF compared to those without NAFLD, and those diagnosed with NAFLD by ultrasound show a risk of AF episodes five times higher, independently of the metabolic syndrome and other risk factors [7]. Alanine aminotransferase (ALT) has been proven to be more related to liver fat content than GGT [8]. The correlation between elevated ALT and GGT with cardiovascular disease may simply reflect the association with insulin resistance [9], which is rather an important cardiovascular risk factor than a marker for the presence or the severity of NAFLD. The cohort studies are important to mention regarding the use of the ultrasound as a specific diagnosis for NAFLD in relation to liver enzymes [10,11]. Through various analyses, the association between NAFLD and future cardiovascular events was found to be independent of metabolic syndrome, as well as traditional cardiovascular risk factors or predictors of cardiovascular disease [12].

Cardiovascular risk assessment scores in NAFLD

Given that cardiovascular risk factors are common among subjects with NAFLD, a variety of scores have been used to assess the cardiovascular risk among patients with fatty liver. Most of these studies have shown that NAFLD determines independently an increased cardiovascular risk [13,14]. In addition, a strong association between histological severity of NAFLD and calculated cardiovascular risk (both QRISK2, and Framingham risk score - FRS), independent of glycemic control and obesity, has been recently shown [15].

It is known that some major determinants of NAFLD, such as insulin resistance, obesity, hypertriglyceridemia, which also increase the cardiovascular risk, are not always included in the risk assessment models. Indeed, FRS score underestimates the cardiovascular risk in metabolic syndrome which has many features in common with NAFLD. Thus, it is considered that the cardiovascular risk in patients with NAFLD cannot be graded exclusively with these scoring systems. Further investigations are needed to determine simple and cheap biomarkers for NAFLD status, including the cardiometabolic effects. Cardiovascular disease is the main cause of complications in NAFLD, while chronic liver disease is responsible for morbidity and mortality in non-alcoholic steatohepatitis (NASH) [16].

Studies evaluating coronary artery disease in NAFLD

The coronary arteries calcium scoring (CAC) is a well established marker for subclinical coronary disease and helps predict the cardiovascular risk among asymptomatic patients. It also represents an independent risk factor for stroke [17].

There are data showing that patients with NAFLD have elevated serum markers for oxidative stress and inflammation, which are partly due to liver disease, thus causing an inflammatory and prothrombotic status [18].

A strong association between NAFLD and the prevalence of coronary heart disease, evidenced by coronary angiography, was frequently reported [19-21]. Although these studies indicate an independent association between NAFLD and increased coronary disease relative to the angiographic aspect, none have evaluated the functional significance of these coronary lesions. Given that the presence of ischemia, more than the coronary anatomy, dictates the therapeutic plan, the significance of these results in conjunction with NAFLD should not be overestimated.

Studies evaluating carotid disease in NAFLD

Carotid intima-media thickness (CIMT) is a marker for atherosclerosis and is a validated screening method for cardiovascular risk prediction in asymptomatic patients. NAFLD can be independently associated with carotid disease, and the patients must be evaluated in terms of cardiovascular risk [22]. A systematic review of seven studies published (a total of 3497 subjects) reported a significant association between NAFLD and CIMT, showing an increase estimated at 13% of CIMT in patients with NAFLD, compared with the control group. The prevalence of carotid atherosclerotic plaque was also more common in patients with NAFLD [23]. The association between NAFLD and increased CIMT was independent of metabolic syndrome in four studies [24-26]. Thus, people with risk factors such as hypertension, T2DM and obesity are likely to develop carotid atherosclerosis. The presence of NAFLD should be considered an independent factor for atherosclerosis [27].

Studies evaluating cardiac function in NAFLD

NAFLD is associated with diastolic dysfunction, abnormal left ventricular geometry and reduction of myocardial perfusion [28]. Only few studies have focused mainly on subjects with NAFLD, finding abnormal left ventricular geometry and diastolic dysfunction. One study also demonstrated a strong correlation between the degree of diastolic dysfunction and liver fat quantity with diastolic dysfunction and insulin resistance, being the single independent parameters associated with NAFLD [29].

Studies evaluating endothelial dysfunction and myocardial metabolism in NAFLD

Endothelial dysfunction is now recognized as the earliest detectable component in the development of atherosclerosis. In cohorts conducted among diabetic patients, as well as those made on non-diabetics, studies have shown an independent association between impaired endothelial-dependent flow-mediated dilation (FMD) and NAFLD [30].

The excess of free fatty acids also leads to cardiac lipotoxicity by causing intracellular lipid accumulation and reducing the oxidative capacity of normal cardiomyocytes, resulting in increased oxidative stress, and cardiac apoptosis and dysfunction [31].

Visceral fat (visceral adipose tissue-VAT)

Studies show that increased VAT mass is independently associated with impaired glucose tolerance, insulin resistance and dyslipidemia, giving an increased cardiovascular risk, regardless of diabetic status [32]. Considered to be a pro-inflammatory status, obesity is associated with metabolic and cardiovascular complications [33].

Furthermore, the portal hypothesis suggests that increased VAT lipolysis secondary to insulin resistance leads to an elevated flux of

free fatty acids into the portal vein for direct transport to the liver, resulting in increased hepatic fatty load, which raises the hypothesis that visceral adipose tissue is an important mediator of liver fat content [34]. In fact, one study shows that elevated fatty acids levels lead to a doubling of the risk of ischemic heart disease, regardless of the presence of diabetes [35]. However, Stefan et al. have identified a form of benign obesity in which obese people who are insulin sensitive show a smaller percentage of hepatic fat accumulation compared with those who are insulin resistant [36].

Epicardial fat

The epicardial fat is considered a true visceral fat and the best representation of cardiac fat load [37]. It is a source of proinflammatory and proatherogenic cytokines that may influence the cardiac function [38]. Imaging studies have already shown that epicardial thickness or pericardial adipose tissue correlates with the amount of visceral fat, in both obese and non-obese subjects.

Epicardial fat has been shown to correlate with more cardiac comorbidities, including coronary disease, left ventricular dysfunction and atrial fibrillation [39]. Moreover, epicardial adipose tissue thickness is directly associated with the presence and severity of coronary disease, documented by angiography, while increased epicardial or pericardial adipose tissue, measured by CT, is independently associated with the CAC (coronary artery calcium) score [40].

Insulin resistance

Insulin resistance is the main factor involved in the development of fatty liver. The majority of the above mentioned studies show an independent link between NAFLD and increased cardiovascular risk. However, there is considerable heterogeneity in terms of results, regarding the diagnostic methods of NAFLD and quantification of severity of NAFLD. This seems to be of paramount importance due to the physiological and metabolic consequences of the various stages of simple steatosis and NASH, but closely related to hepatic and peripheral insulin resistance [41]. In fact, hepatic fat content seems to be the best independent predictor of insulin resistance in skeletal muscle, adipose tissue and liver [42]. Although NAFLD is associated with obesity, insulin resistance and T2DM, many people with NAFLD are not obese and many people with NAFLD do not have T2DM [43].

Patients with NAFLD often consume large amounts of fructose, a common component in most sweeteners, which promotes hepatic de novo lipogenesis and intrahepatic lipid storage [44,45].

An essential point is the bidirectional relationship between insulin resistance and NAFLD, each predicting the subsequent development of the other. This is partly based on the finding that increased levels of liver enzymes such as alanine aminotransferase (ALT) predicts the decreasing in hepatic insulin sensitivity. Elevated concentrations of GGT also seem to predict impaired glucose tolerance, leading to T2DM. The link between liver enzymes and cardiometabolic parameters obtained from lifestyle modification has been reported recently [46].

Adverse cardiovascular effects are likely to be associated with liver fat / inflammation, being in a progressive increase with more advanced stages of NAFLD [29]. It is important to highlight the progressive relationship between glucose levels and cardiovascular disease long before the threshold of diabetes [47].

Ultimately, the development and progression of insulin resistance seems to be the key mediator in the initiation and propagation of NAFLD, primarily through changes in glucose,

fatty acids, and lipoprotein metabolism, both conditions working in a synergistic manner. Alterations in cellular transport of free fatty acids, possibly through hyperinsulinemia, are involved in the pathogenesis of ectopic fat distribution by redirecting the accumulation of triglyceride towards other metabolic organs such as skeletal muscle and liver. This leads to an alteration of insulin sensitivity in these tissues, thus exacerbating insulin resistance and the cascade of cardio-metabolic dysfunctions [48]. These processes are also exacerbated by the association of subclinical inflammation, modified adipokines and increased fat accumulation in other organs such as the heart, ultimately contributing to increased cardiovascular risk. Patients with NAFLD show more frequently extrahepatic complications (mainly cardiovascular) than the liver disease itself and, clearly, with the epidemic of obesity and T2DM, the prevalence of NAFLD will significantly increase [49].

Conclusions and future directions

NAFLD is a marker of ectopic fat accumulation combined with a chronic inflammatory status, and characterized, almost always, by insulin resistance. This leads to pathophysiological processes, including abnormal glucose, fatty acids and lipoprotein metabolism, increased oxidative stress, changes in the profile of adipokines, subclinical inflammation, hypercoagulability, endothelial dysfunction, progression of atherosclerosis, and eventually cardiometabolic phenotype with adverse cardiovascular events. Moreover, current evidence suggests that NAFLD, although considered a hepatic manifestation of the metabolic syndrome, develops as an independent risk factor for the occurrence and progression of cardiovascular disease [50].

Recent data suggest that patients with NAFLD show low survival rates compared to the general population, and that cardiovascular risk plays a more important role than the progression of liver disease does. Although future studies will quantify liver fat by using spectroscopy as the gold standard, there remains a problem in terms of non-invasive measurements of inflammation and fibrosis, to document NAFLD (or NASH).

Importantly, when steatohepatitis is more advanced, a reduction in hepatic fat tissue is frequently seen, this being replaced with necrotic tissue and fibrosis, making the measurements for the severity of NAFLD inaccurate. Therefore it is necessary that future therapeutic trials include validated cardiac, metabolic and inflammatory measurements, to serve as indicators in the change of status of the NAFLD and the cardiometabolic risk associated with it. The present studies tend to evaluate the clinical and biochemical algorithms to grade the severity of liver disease, ignoring cardiometabolic effects, which are often the main cause of clinical events in these patients. Moreover, cardiometabolic consequences of NAFLD are heterogeneous in terms of their interaction with visceral adiposity, insulin resistance and subclinical inflammation and, given that a quarter of the general population shows this condition, a pharmacologic intervention strategy would be a challenge.

Thus, future studies in this area are needed to determine ways to prevent cardiovascular risk and to identify new treatments, to improve cardiovascular risk associated with NAFLD.

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