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Endothelial dysfunction in adolescents and young adults with nonalcoholic liver disease

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Review

Endothelial dysfunction in adolescents and young adults with nonalcoholic liver disease

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Abstract

Nonalcoholic liver disease is a global public health problem that increases cardiovascular morbidity and mortality in these patients. This paper discusses endothelial dysfunction among patients (adolescents and young adults) with nonalcoholic liver disease.

On the one hand, evidence suggests that cardiovascular disease is the leading cause of mortality in patients with advanced nonalcoholic liver disease and that nonalcoholic fatty liver is associated with an increased risk of cardiovascular disease independent of the presence of cardiovascular risk factors and metabolic syndrome components.

On the other hand, nonalcoholic liver disease, especially the non-inflammatory form of nonalcoholic steatohepatitis, may not only be a marker of cardiovascular damage but also a factor involved in its pathogenesis. Such patients are candidates not only for the treatment of liver disease but also for the early treatment of cardiovascular risk factors because many of them, especially those with severe nonalcoholic liver disease, will develop major cardiovascular events and may eventually die of cardiovascular disease before the advanced liver disease occurs.

Keywords : nonalcoholic liver disease, cardiovascular disease, endothelial dysfunction, intima-media thickness

Highlights

- ✓ Nonalcoholic fatty liver disease is commonly associated with obesity, type-2 diabetes, hypertension and dyslipidemia.
- ✓ These patients are candidates not only for the treatment of liver disease, but also for the early treatment of cardiovascular risk factors.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a pathological condition with an increasing incidence, being a major cause of morbidity and mortality in both adults and children (1). Over the past 30 years, the interest in studying NAFLD has increased progressively, with the condition being partly already known, but certainly underestimated, especially among adolescents. With the increasing prevalence of obesity and diabetes among the general population, non-alcoholic fatty liver disease has become an important public health issue (1). In Europe, in well-developed countries, it is estimated that 20-30% of adults and 3-10% of children are affected by NAFLD (2). The latest data estimate that 6 million people in the United States suffer from nonalcoholic steatohepatitis (NASH), about 600,000 individuals developed NASH post-cirrhosis, and 13-14% of children have NAFLD (3). Moreover, the World Health Organization (WHO) warns that underdeveloped and developing countries will experience in the next 10 to 20 years the "double burden" of the co-existence of undernutrition and obesity in the same population, thus favoring the emergence of NAFLD (4). Children exposed to malnutrition are more susceptible to the harmful effects of "cheap" diets (which are hyperlipidic, hyperglucidic, rich in sodium, hypercaloric and nutrient-rich), thus favoring fat accumulation at the visceral level (5).

NAFLD includes a wide range of liver disorders, from simple steatosis to steatohepatitis, associated with necro-inflammation and/ or fibrosis. The disease, in its more severe forms, can lead to cirrhosis, for which the only existing therapeutic strategy is liver transplantation (6). The effects of specific risk factors such as obesity and a sedentary lifestyle associated with genetic predispositions lead to the development of NAFLD in children (7). However, despite the high prevalence and the increased morbidity, the pathogenesis and the consequences of this condition have not yet been fully elucidated.

Discussions

Nonalcoholic fatty liver disease is commonly associated with obesity, type-2 diabetes, hypertension, and dyslipidemia, most patients presenting central obesity and evidence of insulin resistance (1, 8). These associations support the idea that this disorder may be the hepatic expression of the metabolic syndrome. The relationship between nonalcoholic liver disease and metabolic syndrome has suggested a possible role for nonalcoholic liver disease in the pathogenesis of cardiovascular disease. In addition, there have been studies showing that patients with nonalcoholic liver disease have an increased prevalence and incidence of cardiovascular diseases (9, 10). At the same time, it is not surprising that cardiovascular diseases are the leading cause of death in patients with nonalcoholic liver disease, being responsible for about 30% of all deaths (11, 12). Instead, only a few of the NAFLD patients develop cirrhosis or die due to liver disease complications. Although cardiovascular disease is the leading cause of death in NAFLD patients, it is less clear whether NAFLD increases morbidity and mortality independently of the presence of traditional cardiovascular risk factors (13, 14). In the literature, some studies have shown that the magnitude of the association between NAFLD and cardiovascular disease is diminished after adjusting for metabolic factors (15), although several studies suggest that NAFLD remains an independent risk factor for cardiovascular disease (14, 16).

Since the prevalence of NAFLD in adolescents and young adults has reached alarming levels, it is important to determine whether liver disease independently increases the risk of cardiovascular disease in these individuals. It is well known that atherosclerosis begins at birth, the reason young individuals with NAFLD may have a potentially increased cardiovascular risk from early ages (16, 17).

Although an association between nonalcoholic liver disease and atherosclerotic risk factors has been described in adult patients, possible relationships between them in youngsters still remain to be elucidated. The pathological findings of a study based on the association between fatty liver and atherosclerosis, performed on 817 pediatric patients who died from external causes (accident, suicide), showed that fatty liver was present in 15% of them, mild atherosclerosis in 21%, and moderate to severe atherosclerosis in 2%. Atherosclerosis was significantly more frequent ($p < 0.0001$) in patients with fatty liver (30%) than in those without fatty liver (19%) (18).

Studies that used carotid ultrasound to measure the intima-media thickness showed that it was increased in children with family hypercholesterolemia, diabetes mellitus, hypertension, and obesity (18, 19).

Obesity in children and adolescents is a predictive factor for a wide range of conditions that occur later on, and obesity likely increases the risk of cardiovascular morbidity and mortality, functional and morphological changes of the vascular wall being found in obese youngsters (20). A prospective study published in 2001, performed on children and youngsters suffering from

morbid obesity, reported the presence of endothelial dysfunction and an increase in arterial wall resistance though without significant thickening of the intima-media thickness (20). However, more recent studies have compared obese children with non-obese ones and have shown a significant increase in the intima-media thickness in obese patients (21, 22). At the same time, the reduction of the intima-media thickness measured at the carotid level in obese subjects after exercise and diet suggests a certain degree of reversibility of early changes in atherosclerosis (23-25).

The biological mechanisms by which nonalcoholic liver disease contributes to the acceleration of atherosclerosis, independent of other risk factors, have not yet been thoroughly understood. Many studies have shown that insulin resistance plays an essential role in the occurrence of cardiovascular clinical events in patients with nonalcoholic liver disease (26-28). There has been an association between insulin resistance and the intima-media thickness at the carotid level (29), but hepatic steatosis may be atherogenic despite the association with insulin resistance. The concentration of adiponectin, acytokine with antiatherogenic properties, may be another basic mechanism that links nonalcoholic liver disease with atherosclerosis (30, 31). Prospective studies have shown a connection between low adiponectin levels and cardiovascular disease. Patients with nonalcoholic liver disease also have a significant decrease in the adiponectin level, and this decrease is associated with the histological severity of liver disease, independent of abdominal obesity and other components of the metabolic syndrome (31).

Studies have investigated the interaction between adiponectin, nonalcoholic liver disease, and atherosclerosis by using the pulse wave velocity measured in the ankle and arm (32, 33), but a statistically significant correlation between the adiponectin values and the velocity of the pulse wave did not occur. Thus, other atherogenic mechanisms may be involved in patients with nonalcoholic liver disease, including oxidative stress and subclinical inflammation (18).

Obese subjects, as well as patients with nonalcoholic liver disease, frequently have elevated levels of inflammatory markers, atherosclerosis being systematically associated with inflammation (18). Studies have, for example, shown an increased level of interferon-secreting T-CD4-positive cells in obese children, a pro-inflammatory factor (34) which lowers collagen production and activates macrophages, effects that favor the breakdown of the atheromatous plaque. Additional studies are required to evaluate the role of pro-inflammatory cytokines and their interposition between hepatic disease and systemic atherosclerosis in children and adolescents.

In recent years, a theory has been proposed to explain the development of fatty liver in obese children and adolescents, called the "two-stroke theory" (35). Hepatosteatosis and hyperlipidemia cause the first stroke, respectively resistance to insulin, followed by the second stroke of cytokine release and oxidative stress producing inflammation, fibrosis and cirrhosis in the liver (35-37).

The first signs of atherosclerosis are fat streaks which appear in childhood; recent studies identified the presence of fat streaks in fetuses of mothers who suffer from hypercholesterolemia (38). The progression of fat streaks is accelerated by hyperlipidemia, smoking, arterial hypertension, obesity, and diabetes. Early detection and elimination of risk factors slow down the progression and even the regression of the lesions (39, 40). In recent years, the interest in the early detection of atherosclerotic lesions that can lead to asymptomatic lethality has increased (32). Nowadays, the development of imaging studies leads to the observation of the early vascular changes by using non-invasive ultrasonography (40). These early changes include the thickening of the arterial wall, arterial stiffness, and impaired vasodilator function (32).

Studies have revealed an increase in hepatosteatosis with increasing body mass index (BMI) and abdominal obesity in children. An Italian study on 75 obese children reported an important association between the degree of hepatosteatosis determined by ultrasonography, the body mass index, and the level of transaminases (41). Hepatosteatosis is accompanied by an inflammatory process; the increase of the transaminases is common after the occurrence of steatohepatitis (42-45). Therefore, screening by using liver enzymes may not be sufficient in order to detect liver disease in obese patients, and therefore other diagnostic methods should be used.

Conclusions

Nonalcoholic liver disease is a global public health problem that takes into account the increasing cardiovascular morbidity and mortality in these patients. So far, evidence suggests that cardiovascular diseases are the leading cause of mortality in patients with advanced nonalcoholic liver disease and that nonalcoholic fatty liver is associated with an increased risk of cardiovascular disease independent of the presence of cardiovascular risk factors and metabolic syndrome components. Although additional research is needed to draw a final conclusion,

there is still the possibility that nonalcoholic liver disease, especially the non-inflammatory form of nonalcoholic steatohepatitis, may not only be a marker of cardiovascular damage but also a factor involved in its pathogenesis. This process can occur through the systematic release of proatherogenic factors from the fatty liver or through its contribution to insulin resistance and atherogenic dyslipidemia.

These patients are candidates not only for the treatment of liver disease but also for the early treatment of cardiovascular risk factors, because many of them, especially those with severe nonalcoholic liver disease, will develop major cardiovascular events and will eventually die of cardiovascular disease before the advanced liver disease occurs.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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