Non Alcoholic Fatty Liver Disease, NAFLD: General Overview of a Multifactorial Disease

Corresponding Author:
Dr. Pamela Romanque,
Assistant Professor, Faculty of Medicine, Faculties of Medicine, University of Chile & University Diego Portales,
Ricardo Lyon 2256, aptm 901. Providencia, Santiago, 7111084 - Chile

Submitting Author:
Dr. Pamela Romanque,
Assistant Professor, Faculty of Medicine, Faculties of Medicine, University of Chile & University Diego Portales,
Ricardo Lyon 2256, aptm 901. Providencia, Santiago, 7111084 - Chile

Article ID: WMC004208
Article Type: Review articles
Submitted on: 17-Apr-2013, 08:25:42 PM GMT    Published on: 18-Apr-2013, 05:30:42 AM GMT
Article URL: http://www.webmedcentral.com/article_view/4208
Subject Categories: HEPATOLOGY
Keywords: Non alcoholic fatty liver disease, Non alcoholic steatohepatitis

How to cite the article: Macias-carballo M, Romanque P. Non Alcoholic Fatty Liver Disease, NAFLD: General Overview of a Multifactorial Disease . WebmedCentral HEPATOLOGY 2013;4(4):WMC004208

Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC-BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Source(s) of Funding:
This work has been supported by Fondecyt Projects N°11090240 and N° 1130274 granted to Dr. Pamela Romanque by CONICYT, Comisión Nacional de Investigación Científica y Tecnológica de Chile.

Competing Interests:
We have nothing to disclosed
Non Alcoholic Fatty Liver Disease, NAFLD: General Overview of a Multifactorial Disease

Author(s): Macias-carballo M, Romanque P

Abstract

Non alcoholic fatty liver disease (NAFLD) and non alcoholic steatohepatitis (NASH) correspond to frequent causes of liver disease nowadays. Changes in lifestyle, including unhealthy feeding and sedentarism, among others, have promote the increasing prevalence of the mentioned, associated with its risk factors, obesity, metabolic syndrome, insuline resistance and dianetes.

The increasing burden for the social and economic systems makes urgent to find solutions, early diagnosis, promp treatment and prevention of progression.

Scientific research, public policies, education are require to work together in this problem.

In this review we present an overview of the disease, mechanisms involved, risk factors, diagnostic and treatment available, along with a critic analysis of the current knowledge.

Introduction

The last decades, changes in people lifestyle, particularly but no exclusively in Western countries, including access to processed highly caloric food, unhealthy eating habits and lack of physical activity, have had a negative impact on health, promoting an increasing prevalence of diseases such as hypertension, diabetes mellitus, insulin resistance and obesity, among others. Either individually or grouped these diseases favored the appearance of non alcoholic fatty liver disease (NAFLD).

NAFLD is one of the most common types of chronic liver injury (1), is considered a metabolic disorder, characterized by excessive accumulation of fat inside the hepatocytes, mainly triglycerides, that exceeds the range considered normal in an histopathology evaluation: 5% to 10% in a high power field (HPF) (2, 3). Currently, this disease is a public health problem worldwide, due to the high prevalence, high level of disability associated and high cost for the health system (4, 5). NAFLD diagnosis requires exclusion of other liver diseases such as viral or autoimmune hepatitis, toxic hepatitis, more than 14 or 28 units per week (40 g/day for men and 20 g/day in women) alcohol consumption (6-8). Initially, NAFLD is characterized by fat deposition exclusively, and according to the patient and treatment characteristics, may progress to other clinical manifestations such as hepatitis, fibrosis, cirrhosis and sometimes hepatocellular carcinoma (9). Two phases may be recognized in this pathological process, while in the first phase fat infiltration is observed without other alterations, in the second phase appears evidence of inflammation and other nonspecific histological alterations, are identified (10).

NAFLD was first described by Westwater and Fainer in 1958, in a study in obese patients, in whom the first evidence of this disease was described (8). In 1980, Ludwig first used the term non-alcoholic steatohepatitis, after observing samples with histopathological changes similar to those presented in alcoholic hepatitis, i.e. inflammation, necrosis and fibrosis in obese patients with no history of alcohol consumption (11).

Based on previous studies, Day and James proposed in 1998 the “two hits” hypothesis. This theory states that the first hit is due to an accumulation of lipids in the hepatocytes, in part promoted by insulin resistance, which sensitizes the liver to produce a necroinflammatory response, and favors the occurrence of the second hit where oxidative stress is involved, causing the lipid peroxidation (10-12).

This theory is widely accepted to describe pathogenesis of the disease; still, mechanisms of pathogenesis are still on study. Within these mechanisms, microarrays have been used to study...
genetic pathways associated with liver fat accumulation and inflammation in patients with NAFLD, a number of enzymes, \(\Delta^5\) and \(\Delta^6\), which controls processing and availability of fatty \(\omega-6\) and \(\omega-3\) have been identified. These fatty acids serve as precursors for either pro-inflammatory (\(\omega-6\)) or antiinflammatory (\(\omega-3\)) lipid biosynthesis, therefore imbalance \(\omega-6/\omega-3\) contributes to the pathogenesis of NAFLD (13). Phosphatidylinositol-3 kinase (PI3K) and the serine-threonine protein kinase (AKT) pathways activate immune cells by inflammatory cytokines, and are related to NAFLD, which may point out a potential therapeutic target (14). Additionally, the accumulation of cholesterol damage the hepatocytes, by disrupting the mitochondrial and the endoplasmic reticulum membranes integrity, mitochondrial oxidative injury causes endoplasmic reticulum stress, oxidizing Kupffer cells and activating stellate cells, thereby promoting inflammation and fibrogenesis in the liver (15).

Growth hormone (GH) and insulin-like growth factor 1 (IGF-I) play important roles in childhood NAFLD. The deficiency of growth hormone in adult is characterized by accumulation of visceral fat, abnormal lipid profile, premature atherosclerosis and increased mortality. Current reports suggest that growth hormone deficiency is associated with increased prevalence of NAFLD and NASH and faster progression of the disease (16). Tumor necrosis factor (TNF)-alpha produced by Kupffer cells may also be involved by triggering NASH development through increased production of the chemokine Interferon gamma induced protein (IP)-10 and MCP-1. TNF-alpha silencing prevents cells producing these chemokines avoiding the development of NASH. Therefore blocking TNF could be an attractive therapeutic target in NASH, avoiding severe progression of liver disease (17).

**Epidemiology**

The prevalence of NAFLD is not easy to estimate, because of the difficulty of establishing the diagnosis, often subclinical course and variety of risk factors that can be related to it. These data can also vary according to the population studied. For example, the prevalence of NAFLD in patients with diabetes mellitus is 63%, with changes in liver enzymes in 66% to 90% of them; whereas in obese subjects, fatty liver has an estimated prevalence of 72% to 93% (8).

Overall, the prevalence of NAFLD is higher in Western (14% -40%) and lowest in Asian countries (9% -30%) (2). Mexico has reported a prevalence of 10.3% to 17.05% (18, 19), while in other Latin American countries, such as Brazil and Chile, the prevalence range from 20% to 35% (11). About 74% to 90% of patients who undergo liver biopsy have abnormal deposits of triglycerides (20).

**Risk Factors**

Nonalcoholic fatty liver disease is a multifactor disease, with risk factors including obesity, insulin resistance and metabolic syndrome. Obesity is itself a multifactor syndrome, a nutritional disorder, of complex development which is influenced by genetic, behavioral and environmental elements. It is the most common form of malnutrition in developed countries and in many developing countries, and it can compromise patients since pediatric age, constituting a heavy burden for the health system (21). Obesity is regarded as one of the diseases part of the metabolic syndrome, and is currently considered as the main risk factor for the development of NAFLD, (22).

Risk factors for NAFLD are difficult to estimate, because many times are simultaneous, for example, many obese patients are also diabetic or dyslipidemic. Among the factors associated with lifestyle, which may occur concomitantly with the above, is the sedentary lifestyle. Studies have shown a close link between the decline in physical activity and the incidence of NAFLD (23). Exercise is a protective factor as it can prevent diseases related to the metabolic syndrome (24).

Consumption of low fat or low processed carbohydrates foods, intake of calories according to individual needs, adding vegetable fiber to the diet, help maintain an ideal weight with a normal body mass and other parameters of body composition assessment, avoiding overweight and obesity.

NAFLD has a genetic predisposition; related genes are currently under study. Underlying this predisposition are cases that occur in families And the ethnic background suggest a higher in Hispanic and Caucasian, compared to Asian and Afroamericans (2, 25). Prevalence is also higher in adults and women, who are in higher risk to evolve to advanced stages in the disease. (8).

Within the studied genes, are those related to lipid metabolism, proteins like microsomal triglyceride transfer (MTTP) inhibited in hypercholesterolaemic families (26) and apolipoprotein C3 (APOC3) with two polymorphisms (C-482T and T-455C) have been linked with NAFLD. Also a variation in the gene PNPLA3 (patatin-like phospholipase domain-containing 3), a lipase that participates in the hydrolysis of triglycerides, has been associated with hepatic steatosis (27).

The metabolic syndrome, which may include hypertension, central obesity, fasting hyperglycemia, hypertriglyceridemia, among others; has an important
role in the development of diabetes mellitus (28,29). The available evidence suggests that metabolic syndrome is a strong risk factor for developing NAFLD and insulin resistance. Hepatic fat accumulation would be the consequence of a combination of increased peripheral lipolysis and increasing visceral fat stores. The accumulation of free fatty acids (FFA) and their metabolites in hepatocytes leads to the development of insulin resistance (30). Insulin resistance promotes disruption of lipid metabolism, with the increased availability of FFA in the liver, resulting in the development of fatty liver (31).

**Symptoms**

Patients with NAFLD are usually asymptomatic. Some may refer diffuse symptoms such as fatigue, weakness, and vague pain in the right upper quadrant (10, 18). Because of this, it is difficult to diagnose the disease in early stages and is essential to suspect NAFLD and carry out laboratory tests in the presence of risk factors.

**Diagnosis**

The diagnosis of NAFLD is made based on three elements: physical examination, laboratory and imaging tests, however, the definite diagnosis is achieved only through liver biopsy confirming the presence of fat over the normal percentage, and this test remain the gold standard for diagnosis.

Physical examination may be normal or found signs of chronic liver disease or portal hypertension, depending on the stage at the consultation, the most common finding is painless hepatomegaly, splenomegaly or chronic liver disease stigmata.

The tests to be performed include complete liver profile, complete blood count, prothrombin time, antibodies against hepatitis C virus, hepatitis surface antigen B, iron tests, ceruloplasmin in young patients, antinuclear antibodies, α1-antitrypsin and anti-mitochondrial antibodies (19). In these tests it is possible to find elevated transaminase levels, elevated alkaline phosphatase levels, coagulation altered. 65% of the patients show increased levels of ferritin and transferrin saturation (18).

Most authors agree that liver ultrasound is the most reliable image for NAFLD suspicion, considering also that is an affordable, standardized and widely available test in health services (10). The use computed tomography can detect intrahepatic fat content at a threshold of 30% (19), and magnetic resonance imaging can detect moderate to severe changes in liver fat. The latter is a more accurate and rapid method to measure liver fat, the problem of this study is its high cost and availability (19). Transient elastography (FibroScan), is a non-invasive method to detect fibrosis, and relies on the measurement of the stiffness or elasticity of the tissue, using a mechanical vibration pulse and an ultrasound wave (32). It has a good correlation to histological findings in patients with chronic liver disease, but it is not routinely used for NAFLD (33).

Liver biopsy observing accumulation of lipids vacuoles inside the hepatocytes, is the conclusive diagnostic element, although it is not a routinely applied procedure due to the risk associated with an invasive procedure. The majority of patients with NAFLD are not biopsied, although the decision remains in the physician, more frequently, a hepatologist.

**Treatment**

The treatment of patients with NAFLD is unspecific and is centered in modifying risk factors, including weight management, exercise and pharmacological treatment of associated pathologies. Together, dietary changes and physical activity are effective for weight reduction. Within the pharmacological treatment, alternatives have reported to be effective and beneficial in people with NAFLD, although they are not routinely used. Among these are orlistat, which reduce fatty infiltration of the liver and liver fibrosis (34); metformin (10), which reduced insulin levels, C-peptide, necroinflammatory activity, hepatomegaly and steatosis (35); and statins, which have proved to be hepatoprotective in addition to its role in the treatment of dyslipidemias (17, 36). Ursodeoxycholic acid is an antiapoptotic agent, cytoprotective and immunomodulator used in multiple liver diseases and vitamin E, as an antioxidant is effective against lipid peroxidation of membrane, preventing the activation of stellate cells (33, 37).

**Conclusion**

Nonalcoholic fatty liver disease has a high prevalence worldwide, is a multifactor disease which requires thorough diagnostic techniques to be identified. Currently this disease is associated with obesity and metabolic syndrome, without excluding other etiologic factors. Various treatments have been described that are integral, combining changes in lifestyle, diet and exercise. Pharmacological treatment of proven benefit in patients with NAFLD is not routinely used due to lack of evidence of benefits in all patients. Finally it is essential to conduct further studies to explore the mechanisms involved in NAFLD, as well as associated risk factors and elements that determine a worse prognosis. These elements will, in the future, allow an earlier diagnosis, timely and effective treatment and awareness of the population for public prevention policies, in order to reduce a disease named as the
new century epidemia with its tremendous social and economic impact.

References

33. Carrillo R, Muciño J. Fatty liver and nonalcoholic steatohepatitis. Journal of the Faculty of Medicine of the UNAM. 2011, 54 (3).
Disclaimer

This article has been downloaded from WebmedCentral. With our unique author driven post publication peer review, contents posted on this web portal do not undergo any prepublication peer or editorial review. It is completely the responsibility of the authors to ensure not only scientific and ethical standards of the manuscript but also its grammatical accuracy. Authors must ensure that they obtain all the necessary permissions before submitting any information that requires obtaining a consent or approval from a third party. Authors should also ensure not to submit any information which they do not have the copyright of or of which they have transferred the copyrights to a third party.

Contents on WebmedCentral are purely for biomedical researchers and scientists. They are not meant to cater to the needs of an individual patient. The web portal or any content(s) therein is neither designed to support, nor replace, the relationship that exists between a patient/site visitor and his/her physician. Your use of the WebmedCentral site and its contents is entirely at your own risk. We do not take any responsibility for any harm that you may suffer or inflict on a third person by following the contents of this website.