



SYSTEMIC REVIEW OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) IS AN ALARMING SIGN TO THIS GENERATION

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ABSTRACT

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) is the most common chronic liver condition in the Western world. It occurs when excess fat accumulates in liver cells in people who consume little or no alcohol. NAFLD is associated with various metabolic risk factors, such as obesity and diabetes type 2, triglycerides, Polycystic ovary syndrome, Sleep apnea, hypothyroidism, hypopituitarism. It is associated with insulin resistance and frequently occurs with features of the metabolic syndrome. Disease presents from asymptomatic elevated liver enzyme levels to cirrhosis with complications of liver failure and hepatocellular carcinoma. Current recommended treatments are limited to weight loss and exercise, although several promising medications too. In this review we will discuss the epidemiology, risk factors, sign & symptoms diagnosis & finally draw a conclusion of nonalcoholic fatty liver disease.

Keywords: Non-alcoholic fatty liver disease (NAFLD), Non-alcoholic steatohepatitis (NASH) Insulin Resistance (IR) Metabolic syndrome (MS)

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) occurs when there's excess fat builds up in the liver (hepatocytes) due to causes other than alcohol use.¹ There are two known main types, non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH).^{1/2/3} Non-alcoholic fatty liver often doesn't progress to liver damage or NASH.¹ Both fatty liver and liver inflammation are included in NASH.² It can lead to a couple of complications such as cirrhosis, liver cancer (HCC), liver failure, or cardiovascular disease.^{1/4} Risk factors contain diabetes, obesity, fructose rich diet and older age.³ Together with alcoholic liver disease NAFLD is a type of fatty liver disease.³ It is related to insulin resistance (IR) and metabolic syndrome (MS). It can be diagnosed by a liver biopsy.

Weight loss by dietary modifications and exercise is the general treatment.^{2/5} Tentative evidence are available for pioglitazone and vitamin E.^{6/7/1} NASH having 2.6% risk of dying each year.²

Epidemiology:

NAFLD is the most common hepatic disorder in developed countries. It affected 75 to 100 million Americans in 2017.^{8/9/10} 80% of obese people as well as up to 20% normal weight people might also develop it.¹¹ According to an estimation value 24% of the worldwide population is affected in 2017.¹¹ It is the leading cause of chronic liver disease as of 2017.¹¹ In United States about 12 to 25% of people have NAFLD,¹² while NASH affects in between 2 and 12%.¹² In 2016 the US annual economic burden was estimated at US\$103 billion.¹¹ Around 8-19% of Asians with body mass indexes (BMI) less than 25kg/m² are also found to have NAFLD, a condition often described as "lean" or "non-obese" NAFLD. It is also increasing alarmingly in South Asia, where it has reached by an epidemic proportion of 30 percent and the main reasons behind of it were epidemic of obesity and Metabolic Syndrome (MS) in younger south Asians since last 2 decades.

Sign and Symptoms:

According to the American Association for the Study of Liver Diseases (AASLD) NAFLD defined as follows: an evidence of hepatic steatosis, and absence of some other factors that could explain the fat accumulation in the liver, such as alcohol (over 21 g/week for men and 14 g/week for women) on priority, heredity drug induced steatosis, or by parenteral nutrition deficiencies such as choline.² The National Institute for health and Care Excellence (NICE) and The European Association for the Study of Liver (EASL) considered excessive alcohol use (over 30g for men and 20g for women), hepatitis C, drug-induced steatosis, and endocrinal conditions are as alternative causes of fatty liver unrelated to NAFLD.^{6/13}

NAFL, and the more aggressive form NASH are two separated histological categories of NAFLD. According to AASLD, at least 5% presence of hepatic steatosis should be there for both NAFL and NASH, but for NAFL there shouldn't be any evidence of (hepatocellular injury in form of hepatocyte ballooning), while NASH is characterized by the presence of inflammation with hepatocyte injury such as ballooning, with or without any fibrosis.²

NAFLD can also cause symptoms which are related to liver dysfunction. By performing a liver biopsy NAFLD can be diagnosed, and is often incidentally diagnosed by following abnormal liver function tests on

routine blood tests or after a hepatic steatosis which is detected on biopsy. Indeed, in cases of signs or symptoms attributable to liver disease or when related tests show abnormal liver chemistries on lab findings, NAFLD should be suspected as well as investigated. However, in case when no signs or symptoms attributable to liver disease are reported or when the tests show normal liver chemistries, but a hepatic steatosis is detected, other metabolic risk factors (e.g... diabetes mellitus, obesity, dyslipidemia) and alternate causes such as alcohol should be investigated to rule out the cause.² Patients may complain of malaise, fatigue and dull right upper quadrant abdominal discomfort. Although the rare but mild jaundice may be noticed too.¹⁵

RISK FACTORS:

Comorbidities:

Insulin resistance (IR) and metabolic syndrome (MS) such as (obesity, combined hyperlipidemia, diabetes mellitus (type II), and high blood pressure), as well as insulin resistance, persistently elevated transaminases, panhypopituitarism and hypoxia caused by obstructive sleep apnea, increasing age and BMI, all associated with NAFLD with some of them being strong predictors of disease progression.^{4/8/11/16/7}

Being the consequence of a decreased capacity for storing fat and reduced mitochondrial function in adipose tissues, non-obese people affected by NAFLD (lean NAFLD) in particular, have been found to have impaired insulin sensitivity, to be frequently sedentary, to have increased cardiovascular risk and increased liver lipid levels, and increased hepatic de novo lipogenesis.¹¹

Although some controversies are there, such as NAFLD is observed to be twice as prevalent in men as compared to women,² which might be related to and explained by estrogen deficiencies.¹⁷

Genetics:

NAFLD has sort of relation with individual genetics too. It is reported that more than one family member having NAFLD in those families where history of diabetes type 2 is 66.67%. For those family members where someone was diagnosed with NASH, there's a higher risk of fibrosis.¹⁴ In addition, Hispanic people are in higher prevalence of NAFLD than white individuals, whereas in black individuals the lowest susceptibility is observed.

Two genetic mutations have been identified for susceptibility for NAFLD and validated in large cohorts: [the non-synonymous single-nucleotide polymorphisms (SNPs) in PNPLA3 and TM6SF2], as they have been shown to correlate with NAFLD presence and severity, but their role for patient diagnosis remain unclear.^{11/18} NAFLD has a genetic component, the AASLD does not recommend screening of family members as there isn't enough confirmation of heritability,² although there's some evidence available from familial aggregation and twin studies.¹¹

Dysbiosis:

NAFLD links, in particular, have been documented in between dysbiosis of the gut microbiota and liver diseases. NASH patients can have increased levels of blood ethanol. More aggressive NAFLD patients were found to have a choline depletion which linked to an increased choline metabolism.^{19/20/21/22}

Diet:

Diet composition and quantity, particular in omega-6 fatty acids lipids and fructose sugar, play an important role in disease progression from NAFL to NASH and fibrosis.^{23/24}

Choline deficiency can lead to the development of NAFLD.²⁵ There is a complex which indeed interplay between the environment, particularly the diet, genetics and gut microbiota dysbiosis that can impact the development and progression of NAFLD.²⁴ Being overweight and dietary habits who played a role in building up hepatic fat all are associated with NAFLD. Carbohydrates and sugars rich diets for instance can be a contributing factor for metabolic diseases including NAFLD.^{26/27}

Pathophysiology:

Steatosis alone, a steatosis concurrent with lobular or portal inflammation without ballooning; or a steatosis with ballooning but without inflammation all can include in NAFLD. In NASH, other histological features such as portal inflammation, polymorphonuclear infiltrates, Mallory bodies, apoptotic bodies, clear vacuolated nuclei, microvacuolar steatosis, megamitochondria and perisinusoidal fibrosis can appear, but they are not necessary for diagnosis.¹³ As compared with simple steatosis, in NASH hepatocyte death via apoptosis or necroptosis is increased, and inflammation is one of NASH hallmarks.¹⁸

Further injury, or one debated mechanism proposes a second hit, which is enough to cause change that leads from hepatic steatosis to hepatic inflammation. Hormonal imbalances, oxidative stress, and mitochondrial abnormalities all are potential causes for this "second hit" phenomenon.¹⁴ To predict the impact of lifestyle changes and genetics for the evolution of the NAFLD pathology, a further nutrigenomics model which named "multiple hit" extends the second hit model by integration with multiple disease biomarkers and factors such as nutrition and genes.²⁸ NAFLD indeed, other than the liver, can be considered a multisystem disease, as it impacts and is influenced by organs and regulatory pathways.^{29/30/31}

NAFLD and alcoholic fatty liver disease they both do share similar histological features, which elaborates that they might share common pathogenic pathways too. Indeed, NASH patients can have elevated levels of blood ethanol and proteobacteria (which produce alcohol), with dysbiosis which proposed as a mechanism for this elevation.¹⁹ Unlike glucose, by using similar metabolic pathways, a refined sugar, fructose, can cause inflammation and addiction similar to ethanol, which prompts some researchers to argue that NAFLD and alcoholic fatty liver disease are similar diseases.^{23/32} Excessive macronutrients intake shows contribution to tissue inflammation and perturbation of homeostasis, and micronutrients might also be involved.³³ In addition to reducing weight and risk factors, lifestyle modifications might also prompt changes in the gut microbiota.³⁴

Diagnosis:

To distinguish NAFLD (including NAFL and NASH) from other forms of liver disease a liver biopsy (tissue examination) is the only gold standard test widely accepted and that can be used to assess the severity of the inflammation and resultant fibrosis. However, most of people affected by NAFLD are likely to be asymptomatic, hence liver biopsy presents too high risk for routine diagnosis, so others less risk containing

methods such as liver ultrasonography might be preferred. For the children and young people, liver ultrasonography is advised, but biopsy still remains the best evidence.^{6/2/15} To detect NAFLD routine liver function blood tests aren't sensitive enough, and the biopsy only procedure that can reliably differentiate NAFLD from NASH.¹³ Elevated liver enzymes and a liver ultrasound showing steatosis are common findings. To exclude gallstone problems (cholelithiasis) an ultrasound may also be used. To rule out NAFLD, it is dis advised to test enzymes levels, because they are often within the normal range even in advanced disease too, according to NICE guidelines.^{4/11/6} But according to EASL screening is recommended for a steatosis, whenever a NAFLD is suspected as this is a key predictor of the disease evolution and predicts future diabetes type II, cardiovascular events and hypertension.¹³

Other tests included such as erythrocyte sedimentation rate (ESR), glucose, albumin, and kidney functions are useful blood tests to rule out or to confirm the diagnosis. Because the liver is important for making proteins which are used in blood clotting coagulation related studies, and are often carried out especially the INR (international normalized ratio). Blood tests are usually used to rule out viral hepatitis (hepatitis A, B, C and herpesviruses such as Epstein-Barr virus or cytomegalovirus), rubella, and autoimmune diseases in those people having fatty liver and associated inflammatory injury (steatohepatitis). In NASH patients, low thyroid activity is more prevalent, which would be detected by determining the thyroid stimulating hormone (TSH).³⁵

CONCLUSION

NAFLD is common, and with the rising incidence of obesity and diabetes its prevalence is increased in Europe as well as in Asia too. A minority of patients with NAFLD, particularly those with NASH and diabetes, are at risk of liver-related complications such as cirrhosis and hepatocellular carcinoma. Current, treatment is limited to weight loss, exercise and the control of metabolic risk factors. Effective pharmacotherapies are still awaited. Furthermore, studies should be conducted on it as of risk factors among young generation are increasing.

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