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Chapter

Nonalcoholic Fatty Liver Disease

Marco Antonio López Hernández

Abstract

The nonalcoholic fatty liver disease (NAFLD) is the liver disorder that is most common in Western countries; has a global prevalence of approximately 25%; and is strongly associated to obesity and metabolic syndrome. According to the Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of NAFLD is more common in obese individuals with a prevalence of 39.4% than in lean individuals with a prevalence of 7.7%. Nonalcoholic fatty liver disease is the hepatic manifestation of the metabolic syndrome and is defined as the accumulation of fat in the liver. The NAFLD is defined by an accumulation of fat in liver with >5% of steatosis by histologic examination or by proton density fat fraction >5.6%. The diagnosis of NAFLD implies the exclusion of secondary causes like alcohol consumption. The NAFLD includes two different pathological conditions with different prognosis: the nonalcoholic fatty liver (NAFL) and the nonalcoholic steatohepatitis (NASH), the last one has a wide spectrum of severity.

Keywords: NAFLD, NAFL, NASH, liver disease, fatty liver disease

1. Introduction

The nonalcoholic fatty liver disease is the most common liver alteration in the Western countries, with an incidence from the 17–46% of the adult patients [1]. Analysis of the Third National Health and Nutrition Examination Survey presented in the 2018 Annual Meeting of the American Association for the Study of Liver Diseases [2] demonstrated nonalcoholic fatty liver disease prevalence of 7.7% among lean individuals vs. 39.4% among obese individuals. The prevalence of NAFLD among lean individuals without any components of metabolic syndrome was 2.2%, and no evidence of increased overall or cardiovascular-related mortality among this subgroup was found. The presence of diabetes mellitus (DM) was identified as independent risk factor for NAFLD in both lean and obese individuals in multivariate logistic regression analysis (**Table 1**).

The nonalcoholic fatty liver disease is defined as the accumulation of fat in the liver and can be considered a hepatic manifestation of the metabolic syndrome. The prevalence of NAFLD is 20–30% in adults and is higher in industrialized countries [3].

The screening for NAFLD in the community has been questioned for high costs of testing, but the progressive form of NAFLD, particularly when associated with advanced fibrosis, should be identified in patients at risk, because of its prognostic implications.

2. Definition of NAFLD

The NAFLD is characterized by an excessive liver fat accumulation and insulin resistance. Liver biopsy is the standard for diagnosis of NALFD, and it is defined by

NAFLD prevalence, %	Lean subjects (n = 3242)		Obese subjects (n = 2592)	
	Male	Female	Male	Female
Total	7.32	7.54	50.48*	35.2
Metabolically normal	4.39	7.12	23.89	15.14
DM + hypertension/hyperlipidemia	15.32	23.65	65.61	49.34
Hypertension + hyperlipidemia, only	12.76*	0.92	32.26	25.7
DM, only	15.01	6.50	5.32	57.96*
Hypertension, only	5.17	1.54	29.76	33.48
Hyperlipidemia, only	7.47	9.28	43.91*	20.75

**P < .05 for difference in men vs. women within lean or obese subsets.*

Table 1.
Prevalence of NAFLD according to features of metabolic syndrome in lean and obese subjects in NANHES III.

NAFL	NASH
Pure steatosis	Early NASH (F0–F1) no or mild fibrosis
Steatosis with mild lobular inflammation	Fibrotic NASH (F2–F3) significant or advanced fibrosis
	NASH cirrhosis (F4)
	Hepatocellular carcinoma

Table 2.
Classification of NAFLD.

the presence of more than 5% of steatosis of the hepatocytes by histologic examination or more than 5.6% assessed by proton magnetic resonance spectroscopy or quantitative fat/water selective magnetic resonance imaging.

The diagnosis of NAFLD implies the differentiation of two different liver disorders associated to the liver fat accumulation: the nonalcoholic fatty liver and the nonalcoholic steatohepatitis. NAFL can be subdivided in pure steatosis and steatosis with mild lobular inflammation. The spectrum of the NASH has includes a wide range of stages from: early NASH: no or mild fibrosis (stages F0-F1), fibrotic NASH; that includes significant (F2) or advanced (F3) fibrosis, NASH-cirrhosis (F4), and hepatocellular carcinoma (**Table 2**).

The NAFLD also called primary NALFD is associated with risk factors and components of metabolic syndrome, like waist circumference >94 cm in men or >80 in women, arterial pressure >130/85 mmHg or treated for hypertension, serum triacylglycerols >150 mg/dL, and HDL cholesterol <40 mg/dL in men or <50 mg/dL in women.

The screening for metabolic syndrome independent of liver enzymes in all the patients with liver steatosis is recommended, and, because the nonalcoholic fatty liver disease is the main reason of unexpected elevated liver enzymes, the patients with persistently high elevation of liver enzymes must be screened. The screening of NAFLD with liver enzymes and USG in the patients with obesity or metabolic syndrome is also recommended.

3. Pathogenesis

The high-calorie diet with an excess of saturated fats and refined carbohydrates has been associated with weight gain and obesity and more recently with NAFLD [4, 5]. The "multiple hit" hypothesis considers multiple insults acting together on

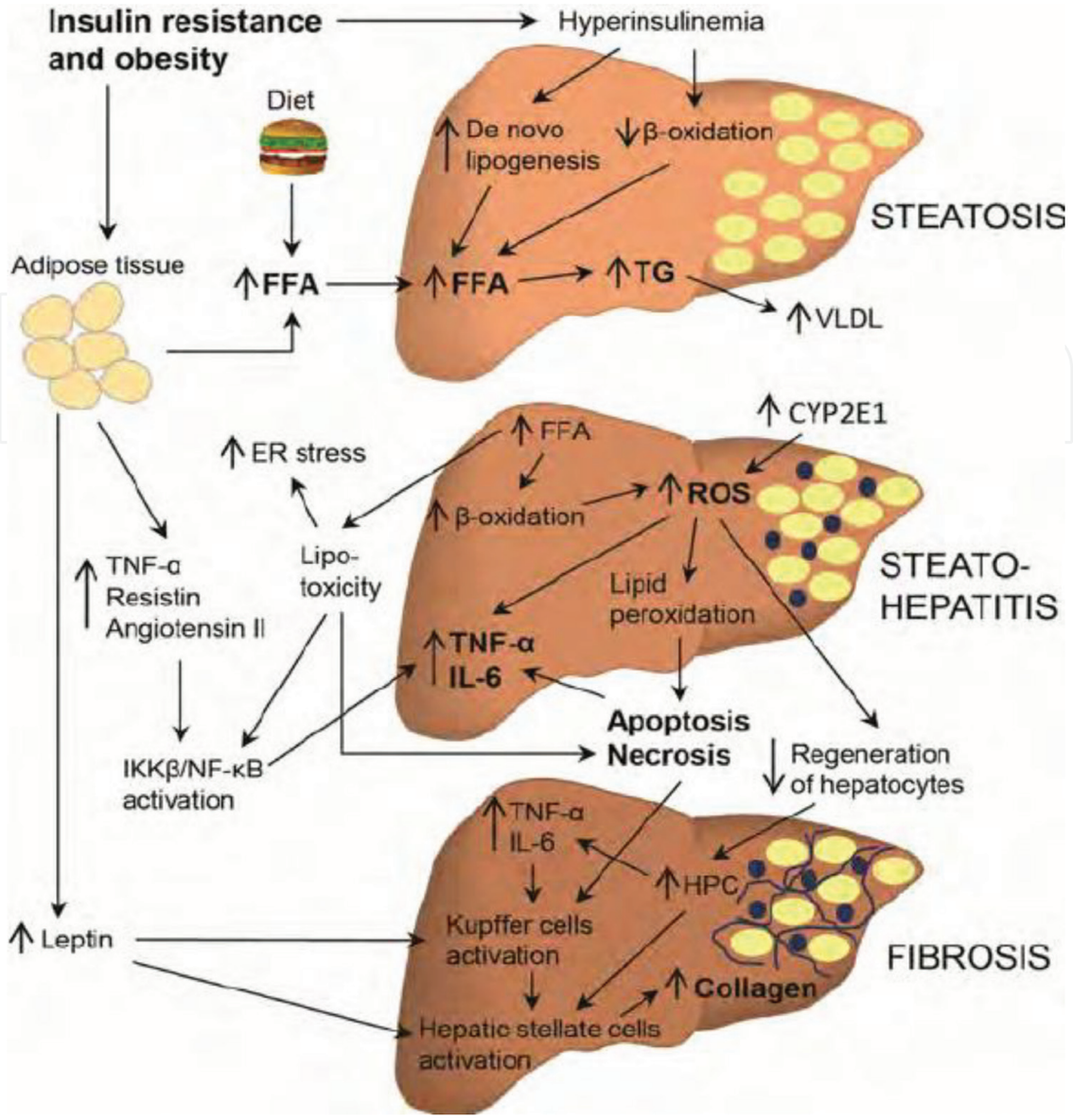

Figure 1.
Multiple hit theory of pathogenesis of NAFLD.

genetically predisposed subjects to induce NAFLD and provide a more accurate explanation of NAFLD pathogenesis [6].

Dietary habits and genetic and environmental factors can lead to insulin resistance, obesity with adipocyte proliferation, and changes in the gut microbiota. The insulin resistance is a key factor in the pathogenesis of NAFLD; the insulin resistance results in a hepatic de novo lipogenesis and impaired inhibition of adipose tissue lipolysis, with consequent increased flux of fatty acids to the liver [7]. Insulin resistance also promotes adipose tissue dysfunction that results in an impaired secretion of adipokines and inflammatory cytokines [8] (**Figure 1**).

Genetic factors and epigenetic changes, in predisposed individuals, affect hepatocyte fat content and contribute to create an inflammatory environment in the liver with possible progression to hepatocellular death mediated for both direct toxicity and apoptosis activating mechanisms, activation of hepatic stellate cells, and deposition of fibrous matrix.

Altered microbiota in the gut leads to the fatty acid accumulation in the small bowel, increased permeability and absorption of fatty acids, and raised circulating levels of molecules which contribute to the activation of inflammatory pathways and release of proinflammatory cytokines [9].

Genetic variants, especially in the form of single nucleotide polymorphisms, influence hepatic fatty acids flux, oxidative stress, response to endotoxins, and cytokine production and activity and are determinants of NAFLD development and progression. Epigenetic modifications are defined as stable changes which do not alter the basic DNA sequences at transcriptional level, such as histone modifications, DNA methylation, and activity of microRNAs, and these changes contribute to a high degree of developmental and environmentally driven plasticity in the cell homeostasis [10, 11].

Genotyping may be considered in selected patients and clinical studies but is not recommended routinely. The carriers of the PNPLA3 I148M and the TM6SF2 E167K genotypes have a higher liver fat content and increased risk of NASH. The NAFLD due to these variants is not systematically associated with features of insulin resistance.

4. Diagnosis

The standard procedure for the diagnosis of NASH is the liver biopsy and is the only procedure that can differentiate the NAFL from NASH, despite limitations due to sampling variability [12].

The histologic NAFL features include steatosis alone, steatosis with lobular or portal inflammation, without ballooning, or steatosis with ballooning but without inflammation.

For evaluation of severity of the disease, the NAFLD Activity Score (NAS) scoring system can be used; this score should not be used for diagnosis. This score is correlated with homeostasis model assessment of insulin resistance (HOMA-IR) and the aminotransferase level [13].

Noninvasive diagnostic procedures must be considered in primary care settings; they identify the risk of NAFLD among individuals with increased metabolic risk; in secondary and tertiary care settings, they identify those with worse prognosis; monitor disease progression; and predict response to therapeutic interventions.

When NAFLD is suspected as the primary disease or as a coexisting condition, steatosis should be documented. The presence of NASFLD also predicts cardiovascular events, arterial hypertension, and diabetes mellitus. The quantification of fat content is not of interest, in clinical practice, except for the evaluation of treatment efficacy, and is therefore not generally recommended. Steatosis of the liver should be documented by ultrasonography, because it is a cheaper and more available method than MRI. US has limited sensitivity and does not reliably detect steatosis when <20% [14, 15].

US is the preferred first-line diagnostic procedure for imaging of NAFLD, as it provides additional diagnostic information. A quantitative estimation of liver fat can only be obtained by 1H-MRS. This technique is of value in clinical trials and experimental studies but is expensive and not recommended in the clinical setting.

The diagnosis of NASH implicates closer follow-up, provides important prognostic information, and indicates an increased risk of fibrosis progression, cirrhosis, and possibly hepatic comorbidities. It may also prompt possibly a greater need for more intensive therapy. Clinical, biochemical, or imaging measures cannot distinguish NASH from steatosis [16, 17].

NASH must be diagnosed by a liver biopsy showing steatosis, hepatocyte ballooning, and lobular inflammation. Biomarkers and scores of fibrosis, as well as transient elastography, are acceptable noninvasive procedures for the identification of cases at low risk of advanced fibrosis/cirrhosis.

5. Metabolic disorders linked to NAFLD

5.1 Obesity

Insulin resistance has been associated with NAFLD, not only in the liver but also in adipose tissues and muscle and also with the metabolic syndrome. The metabolic syndrome is defined as the cluster of any three of the following five features: impaired fasting glucose or type 2 diabetes mellitus, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, increased waist circumference, and high blood pressure [18].

Obesity is the major phenotype and risk condition for NAFLD, driven by insulin resistance, and increases the risk of advanced disease. Most lean persons with NAFLD display insulin resistance and altered body fat distribution even though they have less severe metabolic disturbance than overweight NAFLD.

5.2 Diabetes mellitus

Type 2 diabetes mellitus patients are insulin resistant, often obese, dyslipidemic, display increased liver enzymes, and tend to accumulate hepatic fat, without relation with the body mass index [19–21].

In persons with NAFLD, screening for diabetes is mandatory, and in patients with type 2 diabetes mellitus, the presence of NAFLD should be looked for irrespective of liver enzyme levels, since those patients are at high risk of disease progression.

5.3 Cardiovascular disease

Atherogenic lesions such as increased carotid intima-media thickness, coronary artery and abdominal aortic and aortic valve calcifications, and endothelial dysfunction are more common in NAFLD. The prevalence and incidence of cardiovascular disease is higher in NAFLD than in matched controls and driven by the association between NAFLD and metabolic syndrome components. In most studies, biochemical markers of atherosclerosis or inflammation and increased levels of procoagulant/prothrombotic factors are more common in NAFLD than in persons without steatosis. They are largely independent of traditional risk factors, duration of diabetes, glycemic control, drug treatment, and metabolic syndrome components. The consensus is that cardiovascular disease should be identified in NAFLD regardless of the presence of traditional risk factors. Conversely NAFLD screening should be performed in persons at high CVD risk [22–24].

5.4 Natural history

In general, NAFLD is a slowly progressive disease, but in 20% of cases fibrosis rapidly progresses. The rate of progression corresponds to one fibrosis stage every 14 years in NAFL and every 7 years in NASH and is doubled by arterial hypertension. Compared with the general population, NASH is associated with an increased standardized mortality ratio. US-diagnosed NAFLD is not associated with increased mortality, presumably because progression to NASH and fibrosis is rare for steatosis alone (**Figure 2**) [25–27].

Metabolic reprogramming for adaptation to the local environment has been recognized as a hallmark of cancer. Although alterations in fatty acid metabolism in cancer cells have received less attention compared to other metabolic alterations such as glucose or glutamine metabolism, recent studies have uncovered the importance of lipid metabolic reprogramming in carcinogenesis.

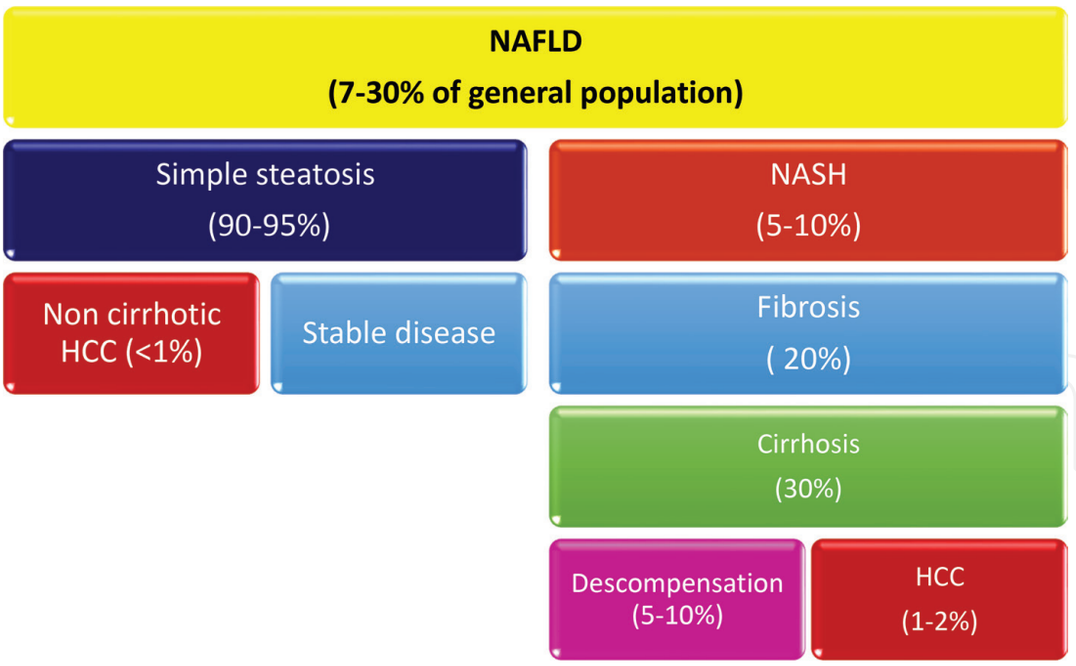

Figure 2.
Natural history of NAFLD. HCC denotes hepatocellular carcinoma.

Obesity and nonalcoholic steatohepatitis (NASH) are well-known risk factors of hepatocellular carcinoma (HCC), and individuals with these conditions exhibit an increased intake of dietary FAs accompanied by enhanced lipolysis of visceral adipose tissue due to insulin resistance, resulting in enormous exogenous fatty acid supplies to hepatocytes via the portal vein and lymph vessels. However, the way in which HCC cells adapt to such a condition and exploit it to aid their progression is not understood. In addition, accumulating evidence supports the importance of lipid metabolic reprogramming in various situations of hepatocarcinogenesis.

5.5 Treatment

Successful treatment of NASH should improve outcomes. The resolution of the histological lesions defining NASH is now accepted as a surrogate end point, particularly in clinical trials. Few well-designed randomized controlled trials are available, with improvement/regression of hepatic necroinflammation and/or fibrosis as primary outcomes.

5.6 Diet and lifestyle changes

Epidemiological evidence suggests a tight relationship between unhealthy lifestyle and NAFLD, which makes lifestyle correction mandatory in all patients. Relatively small amounts of weight loss reduce liver fat and improve hepatic insulin resistance [28].

For the patients with NAFLD, structured programs for lifestyle changes toward healthy diet and habitual physical exercise are recommended. The counseling for healthy diet and physical activity is the election therapy in patients without NASH or fibrosis and with no pharmacotherapy for their liver condition. In overweight or obese NAFLD, weight loss, with a target of 7–10% of the basal weight, is recommended; this results in histology and liver enzyme improvement. Dietary recommendations should consider the caloric restriction and the exclusion of processed food and food and beverages high in added fructose which are NAFLD-promoting components. A macronutrient composition is recommended according to the

Mediterranean diet. Both resistance training and aerobic exercise effectively reduce the amount of fat in the liver. The training must be maintained in the long-term and then is recommended that the choice of training should be tailored based on patients' preferences.

5.7 Drug therapy

Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression, could also be candidates to prevent disease progression.

While no firm recommendations can be made, pioglitazone or vitamin E or their combination could be used for NASH.

The optimal duration of therapy is unknown; in patients with increased ALT at baseline, after 6 months of therapy, treatment should be stopped if there is no reduction in aminotransferases; no recommendations can be made in patients with normal ALT at baseline.

The statins have not been showed benefit in liver harm in patients with NAFLD, but may be confidently used to reduce LD cholesterol and prevent cardiovascular risk. There is not data to support the use of n-3 polyunsaturated fatty acids specifically for NASH, but reduce both liver and plasma lipids [29].

By improving obesity and diabetes, bariatric surgery reduces liver fat and is likely to reduce NASH progression; prospective data have shown an improvement in all histological lesions of NASH, including fibrosis [29].

5.8 Drugs in study

In the 2018 Annual Meeting of the American Association for the Study of Liver Diseases, phase II data in therapies with drugs for NAFLD and NASH were presented (**Table 3**).

5.9 Farnesoid X receptor agonists

Farnesoid X receptors (FXRs) are nuclear hormone receptors expressed in high amounts in body tissues that participate in bilirubin metabolism including the liver,

Agent	MOA	N	Study population
GS-9674	FXR agonist	140	NASH
Obeticholic acid	FXR agonist	84	NASH, fibrosis
Tropifexor	FXR agonist	198	NASH
NGM282	FGF19 analogue	38, 85	NASH
MGL-3196	THR-β agonist	125	NASH, hepatic fat fraction ≥10%
VK2809	THR-β agonist	35	NAFLD, liver fat >8%, elevated LDL-C and TG
GS-0976	ACC inhibitor	75	NASH, no cirrhosis
Aramchol	SCD1 inhibitor	247	NASH, overweight or obesity, prediabetes or diabetes
Semaglutide	GLP-1 receptor agonist	957	Obesity, no diabetes

Table 3.
Phase II Data on Investigational NAFLD/NASH Therapies Presented at AASLD 2018.

intestines, and kidneys. Bile acids are the natural ligands of the FXRs. XRs play a critical role in carbohydrate and lipid metabolism and regulation of insulin sensitivity. FXRs also modulate live growth and regeneration during liver injury.

The farnesoid X receptor agonist GSK-9674 was compared with placebo at doses of 30 and 100 mg and showed ≥30% relative reduction in liver fat, and markers of fibrosis also improved [30].

Obeticholic acid (OCA) is a semisynthetic bile acid analogue which has the chemical structure 6α-ethyl-chenodeoxycholic acid. The natural bile acid, chenodeoxycholic acid, was identified in 1999 as the most active physiological ligand for the farnesoid X receptor, which is involved in many physiological and pathological processes. In a double-blind, placebo-controlled, phase II study, the OCA was compared with placebo; at week 16, patients with vs. without cirrhosis (F4 vs. F1–F3) showed no trend for differences in ALT, bilirubin, platelets, and INR [31].

The FLIGHT study on tropifexor (TXR), a three-part randomized, placebo-controlled, double-blind, dose-ranging phase IIb study in adults with NASH, weighing 40–150 kg with liver fat ≥10%, showed reduction in liver fat, ALT, and GGT compared with placebo [32].

5.10 Fibroblast growth factor (FGF) analogues

NGM282 is a non-tumorigenic analogue of human FGF19 demonstrating significant reductions in hepatic steatosis, liver transaminases, and fibrosis markers after 12 weeks of treatment at doses of 3 and 6 mg. The use of NGM282 for 12 weeks at doses of 1 and 3 mg showed clinically meaningful improvements in fibrosis in NASH patients and in all components of the NASH, and this was preceded by rapid and significant improvements in liver transaminases and imaging-based parameters [33].

5.11 Tyroid hormone receptor beta (THR-β)

In a randomized, multicenter, placebo-controlled phase IIa study, at Week 12 a higher proportion of patients with liver fat >30% compared with placebo is shown [34].

MGL-3196 is a liver-directed, orally active, highly selective THR-β agonist which may reduce lipotoxicity in NASH by increasing hepatic fat metabolism. At Week 36, MGL-3196 treatment compared with placebo resulted in significant and sustained reductions in hepatic fat on MRI-PDFF, liver enzymes, fibrosis biomarkers, atherogenic lipids, and improvement in NASH on liver biopsy. In the patients treated with MGL-3193 was observed ≥30% fat reduction (MRI-PDFF) at Week 12 and improved NASH histologic response at Week 36 were predicted [35].

5.12 Acetyl-CoA carboxylase (ACC) inhibitor

Elevated plasma levels of medium- and long-chain acylcarnitines are markers of impaired mitochondrial beta oxidation of fatty acids. GS-0976 inhibits cytoplasmic ACC1 and mitochondrial ACC2 thereby reducing fatty acid synthesis and augmenting beta oxidation, respectively. NASH patients who responded to GS-0976 demonstrated a reduction in plasma acylcarnitine species with reduction of liver fat by MRI-PDFF also. This effect is consistent with an improvement in the efficiency of mitochondrial beta oxidation. The reductions in plasma acylcarnitine species provide further evidence to support, in patients with NASH for the therapeutic targeting of ACC1 and ACC2 [36].

5.13 Stearoyl-coenzyme A desaturase 1 (SCD-1) modulator

Aramchol (arachidyl amido cholanoic acid) is a novel fatty acid bile acid conjugate, inducing beneficial modulation of intrahepatic lipid metabolism. The ARREST study enrolled 247 NASH patients who were overweight/obese and had prediabetes or diabetes with HbA1C at baseline of 6.6%. More than 50% were hypertensive and had dyslipidemia. Baseline histology demonstrated a population with advanced disease, with 60% having stage 2 and 3 fibrosis and 70% having NAS ≥ 5.

The study ARREST, is a randomized, global phase IIb study with aramchol in patients with NASH and diabetes or prediabetes, compared aramchol at doses of 400 and 600 mg versus placebo, in the aramchol patients the proportion with >5% of reduction in liver fat by MRI, the resolution of NASH than in the placebo group [37].

5.14 Glucagon-like peptide type 1 (GLP-1) receptor agonist

The glucagon-like peptide 1 analogues semaglutide and liraglutide improve glycemic control and reduce elevated liver enzymes in subjects with type 2 diabetes and reduce body weight in subjects with or without diabetes. Semaglutide at doses of 0.2–0.4 mg daily reduced ALT in subjects with obesity and high ALT to an extent that was broadly comparable across weight loss categories and resulted after 52 weeks in dose-related ALT normalization in up to 46% of subjects. These data suggest a potential role for semaglutide in the treatment of NAFLD with elevated liver enzymes [38].

5.15 Bariatric surgery

Medical therapy, including the newly available drugs, has only limited effects and does neither influence survival or the development of complications or the progression of NASH to liver cirrhosis or the development of hepatocellular carcinomas in NASH. Importantly, even existing diabetic complications such as nephropathy as well as the features of NASH can be reversed by metabolic surgery.

Metabolic surgery is a very effective treatment for NAFLD in general, but in particular for NASH, the beneficial and significant changes in steatosis and NAS after metabolic surgery have been shown with steatosis decreased from 60 to 10% after surgical treatment, and the NASH diminished from 5 to 1, essentially normalizing the liver histology in patients with NASH. Metabolic surgery has even shown to reduce liver fibrosis. A meta-analysis also demonstrated this effect: each of the 16 studies included demonstrated a diminution of steatosis after metabolic surgery [39, 40].

6. Conclusions

The nonalcoholic fatty liver disease is the liver disorder most common in Western countries, has a global prevalence of approximately 25%, and is strongly associated to obesity and metabolic syndrome. Successful treatment of NASH should improve outcomes. Lifestyle changes are the foundation of any treatment plan and weight loss ≥3–10% associated with histologic improvement in NAFLD. In the guides of the European Association for Study of Liver disease (EASLD) and the American Association for the Study of Liver Disease (AASLD) is cited recommendations for the use of vitamin E (NASH without diabetes), pioglitazone (NASH with or without diabetes), and bariatric surgery.

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Author details

Marco Antonio López Hernández
Internal Medicine Division, Ecatepec General Hospital, Mexico

*Address all correspondence to: niklaus2003@yahoo.com.mx

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