

WJG 20th Anniversary Special Issues (12): Nonalcoholic fatty liver disease

Non-alcoholic fatty liver disease: What the clinician needs to know

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Author contributions: Machado MV wrote the manuscript; Cortez-Pinto H reviewed the manuscript.

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Received: February 24, 2014 Revised: April 21, 2014

Accepted: May 25, 2014

Published online: September 28, 2014

esis; Genetics; Diagnosis; Prognosis; Management

Core tip: This is a review in non-alcoholic fatty liver disease (NAFLD) that puts the disease into context, highlights the recent advances in pathology, and gives special focus to the diagnosis and management of those patients. We present NAFLD patients in a holistic view, understanding that in many cases thinking outside the liver, namely in the cardiovascular and neoplastic risk, may have a bigger impact in the prognosis. In the era of genomics and high-throughput approaches, we also summarized the latest breakthroughs regarding the genetic associations with NAFLD.

Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most frequent cause of liver disease in the Western world. Furthermore, it is increasing worldwide, paralleling the obesity pandemic. Though highly frequent, only about one fifth of affected subjects are at risk of developing the progressive form of the disease, non-alcoholic steatohepatitis with fibrosis. Even in the latter, liver disease is slowly progressive, though, since it is so prevalent, it is already the third cause of liver transplantation in the United States, and it is predicted to get to the top of the ranking in few years. Of relevance, fatty liver is also associated with increased overall mortality and particularly increased cardiovascular mortality. The literature and amount of published papers on NAFLD is increasing as fast as its prevalence, which makes it difficult to keep updated in this topic. This review aims to summarize the latest knowledge on NAFLD, in order to help clinicians understanding its pathogenesis and advances on diagnosis and treatment.

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Key words: Non-alcoholic fatty liver disease; Metabolic syndrome; Insulin resistance; Epidemiology; Pathogen-

Machado MV, Cortez-Pinto H. Non-alcoholic fatty liver disease: What the clinician needs to know. *World J Gastroenterol* 2014; 20(36): 12956-12980 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i36/12956.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i36.12956>

EPIDEMIOLOGY

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease characterized by the presence of ectopic fat in the liver, steatosis, which cannot be explained by alcohol consumption. It ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) that can have different degrees of fibrosis and progress to liver cirrhosis and end-stage liver disease, with its associated complications, including hepatocellular carcinoma (HCC).

NAFLD is the pandemic liver disease from the twenty-first century. It has been estimated that about one billion individuals worldwide have NAFLD^[1]. In fact, it is the number one cause of altered aminotransferases in the Western world^[2], where one third of the population is affected^[3]. In Asia, recent reports showed similar prevalence of NAFLD^[4,5], whereas in the Indian continent

it is similar in urban populations, although much lower, less than 10%, in rural populations^[6-8]. The prevalence in Africa is not known^[1], though a Nigerian study showed a prevalence of less than 10%^[9].

Among patients with NAFLD, one to two in each ten patients will have NASH^[3]. A recent survey showed that NAFLD-associated cirrhosis is the third indication for liver transplantation in the United States, and it is expected to be the number one indication in 2020^[10].

NAFLD is strongly associated with obesity, insulin resistance (IR)/type 2 diabetes mellitus (T2DM) and the metabolic syndrome. Obesity, particularly central obesity, is highly predictive of hepatic steatosis and disease progression^[11,12]. In overweight subjects, the prevalence of steatosis is at least two times more frequent than in lean subjects^[13], being directly proportional to the increase of body mass index (BMI)^[14]. In morbid obesity, almost all patients present steatosis and more than one third have NASH^[15]. The association with T2DM is also very strong, being 5-9 times more frequent in patients with NAFLD as compared to the general population^[16]. On the other hand, more than two third of patients with T2DM have NAFLD^[17]. T2DM also associates with disease severity, namely NASH, fibrosis, liver cirrhosis and HCC^[16]. Lastly, the metabolic syndrome is a cluster of cardiovascular risk factors that associates with IR, namely central obesity, hypertension, dyslipidemia and glucose intolerance^[18]. At least one third of patients with NAFLD have the metabolic syndrome and 80% at least one of its components^[19,20]. Noteworthy, the prevalence of NAFLD increases with the number of components of the metabolic syndrome^[20].

There are racial differences in the susceptibility for NAFLD, being more frequent in East Asian Indians, followed by Hispanics, Asians, Caucasians and less frequent in African Americans^[1,19,21,22]. Also, among patients with NAFLD, African Americans have less frequently NASH as opposed to Hispanics^[23]. The racial disparities are not fully understood. A possible explanation may ensue from a higher BMI and adiposity in Hispanics^[24,25] and a lower visceral adiposity in African Americans^[26]. Genetic differences in metabolism and wound healing response may also have an influence. For instance, African Americans have lower fructose absorption rates than Hispanics, and fructose is considered an important driver of liver steatogenesis^[27].

In this review we will summarize the latest evidence in the pathogenesis, diagnosis and management of NAFLD, with a clinical-oriented focus.

PATHOGENESIS

How do we get liver steatosis?

The hallmark of NAFLD is the presence of ectopic fat in the hepatocytes. The underlying mechanisms of this pathological fat deposition in the liver are reasonably known. The main store of lipids in the hepatocyte is in the form of triglycerides, though other lipids can be increased, such as, different free fatty acids (FFA), diac-

ylglycerol, free cholesterol, cholesterol esters, ceramides, and phospholipids^[28]. Triglycerides are synthesized from FFA. The accumulation of triglycerides depends on the presence of FFA in the liver and its disposal. There are three major sources of FFA in the liver, with the following order of relevance: 60% from plasmatic nonesterified fatty acids (NEFAs), 25% from *de novo* lipogenesis and 15% from dietary fatty acids (FA) in the form of chylomicrons lipoproteins^[29]. Starting with the former, the hepatic uptake of FFA is unregulated; as such, it is directly proportional to the plasmatic concentrations of NEFAs^[30]. Of relevance, plasmatic NEFAs come mainly from lipolysis in the adipose tissue, which represents the source of 80% of FA in the fasting state. Postprandial, dietary FA also plays a relevant contribution, but even then, 60% of FFA derives from adipocytes^[29]. Adipose tissue lipolysis is induced, during fasting, through the stimulation of beta-adrenergic receptors by catecholamines^[31]. When adipose tissue storage capacity is overcome, either by energy surplus as occur in obesity, or by primary defect in adipocytes as occurs in lipodystrophies, the efflux of FFA increases. Also, with IR, there is a decreased ability of insulin to suppress adipose tissue lipolysis^[32]. *De novo* lipogenesis, during fasting, is increased by 3 fold in patients with NAFLD as compared to those with lean liver^[33]. Also, it has no diurnal variation^[29]. This probably represents hyperinsulinism, which induces sterol response element-binding protein (SREBP)-1c and peroxisome proliferator-activated receptor (PPAR)- γ that in turn promote the expression of several lipogenic genes^[33]. *De novo* lipogenesis is also important, since when activated, a key intermediate, malonyl-CoA, inhibits the oxidation of FA from any source^[34]. Lastly, the contribution of dietary FA increases with high fat diet (by definition, more than 30% of total energy requirements)^[29]. FFA in the liver may follow 3 different destinations: (1) oxidation, mainly in mitochondria, but also in extra-mitochondrial organelles; (2) assembly and export as very low-density lipoproteins (VLDL); and (3) production of triglycerides and storage as lipid droplets. Regarding the latter, when production of triglycerides is inhibited, it decreases steatosis, but increases liver damage by accumulation of active FA intermediates^[35]. An excessive increase in FFA influx in the liver may over saturate the ability for FA oxidation. Although patients may have mitochondrial abnormalities and dysfunction, there is no evidence of decreased FA oxidation in most of the patients^[36]. On the contrary, when this pathway is overactive it may promote the production of oxygen reactive species and oxidative stress^[37,38]. Hyperinsulinism may decrease VLDL assembly, since insulin decreases the synthesis and stability of apolipoprotein B, one component of VLDL^[39,40]. Also, NAFLD/NASH can occur in familial hypolipoproteinemia, in which there is a defect in VLDL assembly, independently of obesity and IR^[41] (Figure 1).

As described, IR has a major role in the development of steatosis. But steatosis itself also promotes IR, endorsing a self-perpetuating vicious cycle. The most

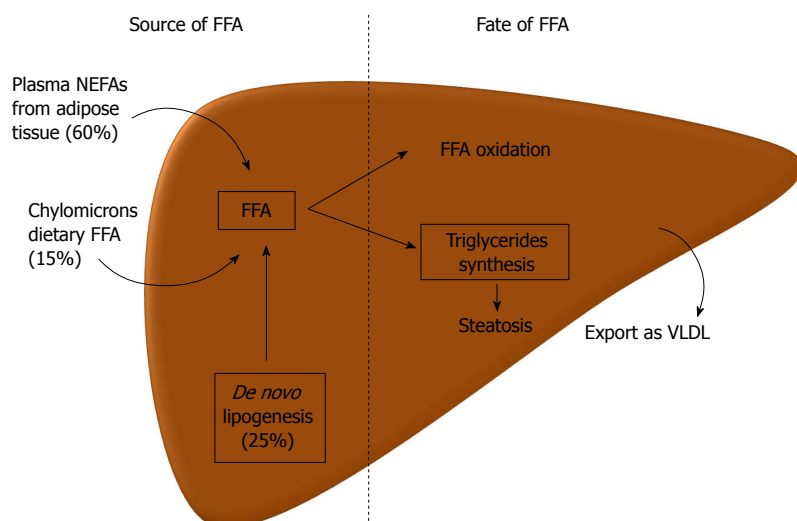


Figure 1 Pathogenesis of liver steatosis. Hepatic steatosis can result from an increased influx of lipids, free fatty acids (FFA), to the liver or a decreased lipid disposal. Three main sources of FFA in the liver are the plasmatic nonesterified fatty acids (NEFAs), which originate predominantly from lipolysis in the adipose tissue, from *de novo* lipogenesis, mainly from glucose or other carbohydrates, and from FFA that come in chylomicrons from the gut (dietary FFA). In the liver, FFA can either be oxidized, mainly in the mitochondria, beta-oxidation, or can be used to produce triglycerides. The latter can be exported as very low density lipoproteins (VLDL) to the circulation or can accumulate in lipid droplets in the hepatocyte leading to steatosis.

accepted model is the initiation of IR peripherally in the adipose tissue^[42,43]. Obesity translates an expansion in adipose tissue. That expansion may occur in inert subcutaneous tissue, being more an esthetical condition, but it may also occur in visceral, metabolically active adipose tissue. The excessive accumulation of fat in adipocytes promotes an increase in oxidative stress, which deregulates adipocytokines production^[44] and promotes low grade inflammatory state in the adipose tissue, through release of interleukin (IL)-6 and monocyte chemotactic protein (MCP)-1 among others^[44]. Subsequently, there is activation of macrophages, M1, and lymphocytes, Th1, promoting further release of proinflammatory cytokines, tumor necrosis factor (TNF)- α and interferon- γ . The latter also promotes IR^[45] directly or through the deregulation of adipocytokines secretion, namely through inhibition of adiponectin. In fact, with obesity, adiponectin, an anti-inflammatory, insulin sensitizer adipokine, decreases, whereas leptin, a pro-inflammatory, pro-fibrogenic and satiety inducer adipokine increases. Of note, central resistance to leptin also develops, decreasing its anorexigenic effects^[46]. The spillover of FFA from the adipose tissue leads to ectopic accumulation of fat in muscle and liver. In those tissues, ectopic fat induces IR by generation of lipid-derived second messengers such as diacylglycerol (DAG) and ceramides that directly interfere with the insulin receptor pathway^[47]. Noteworthy, in the liver, not all insulin actions are impaired; it preserves its lipogenic actions further inducing steatosis, and its pro-mitogenic actions, which may enhance hepatocarcinogenesis^[48].

Injury and inflammation leads to NASH and fibrogenesis

Lipid accumulation in the liver is linked with endoplasmic reticulum (ER) stress, oxidative stress/mitochondria stress, and impaired autophagy, resulting in the condition known as lipotoxicity^[31]. In some patients, lipotoxicity leads to cell damage and cell death, which induces an inflammatory and wound healing response that can drive fibrogenesis. Why in some people lipid accumulation in the liver is inert and in others is toxic to cells is still not fully understood. It may be related to the type of fat it-

self, since triglycerides *per se* do not seem toxic^[35], whereas FA, mainly saturated FA^[49,50] as well as cholesterol^[51] and its metabolites do seem highly toxic. The higher toxicity of saturated FA as compared to polyunsaturated FA may be in part due to a limited capacity of hepatocytes to use them to produce triglycerides^[52]. Also, individual differences in lipid metabolism (*e.g.*, in the enzymes that desaturate FA^[50]) and susceptibility for cell damage, may promote NASH development (Figure 2).

Cell death

Apoptosis is a form of programmed cell death that plays an important role in NAFLD^[53,54]. Considerable amounts of evidence show an increase in hepatocyte apoptosis in animal models^[55-58] and in human NASH^[59-62]. FFA can increase the susceptibility of hepatocytes to cell death through induction of expression of cell death receptors that promote the extrinsic pathway of apoptosis, Fas and DR5, TRAIL (TNF related apoptosis inducing ligand) receptor 5^[56,59,63]. FFA and free cholesterol can also promote apoptosis through dose-dependent mitochondrial toxicity, which leads not only to increased production of oxygen reactive species^[64], but also through activation of pro-apoptotic proteins Bim and Bax that trigger intrinsic apoptotic pathway^[36,65]. Ceramide, a sphingolipid that can also accumulate in NAFLD, can be synthesized *de novo* from long chain saturated FA^[28]. It has been associated with apoptosis induction and inhibition of insulin pathway leading to IR^[66].

FFA-promoted oxidative stress has several deleterious effects, through direct injury of DNA, proteins and lipids^[52], but also by promoting cell death with the activation of stress-sensitive pathways such as NF- κ B, p38 MAPK and c-Jun N terminal kinase^[67] as well as promoting ER stress^[68]. Lipotoxicity is, in fact, associated with an ER stress response and unfolded protein response, mainly by saturated and not polyunsaturated FA^[69].

Sterile inflammation

Lobular chronic inflammatory infiltrate, in the absence of pathogens, is a hallmark of NASH. Injured cells and

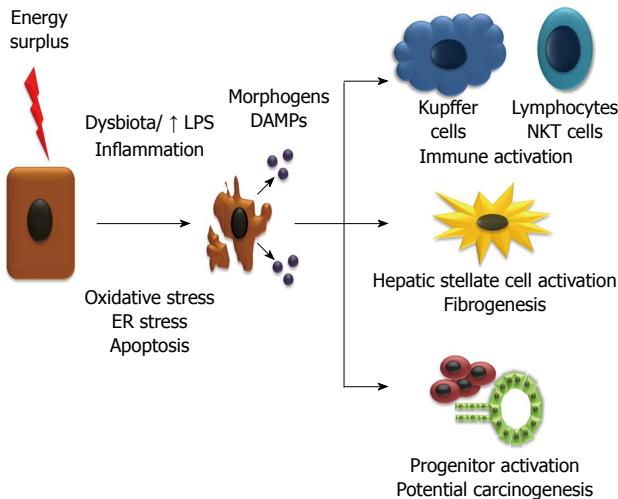


Figure 2 Injury and inflammation leads to non-alcoholic steatohepatitis and fibrogenesis. Energy surplus leads to fat accumulation in the hepatocytes which promote oxidative stress, endoplasmic reticulum (ER) stress and apoptosis. The injury of hepatocytes is promoted by an inflammatory state, among other factors, favored by a deregulated gut microbiota and increase in lipopolysaccharide (LPS). Injured and dying hepatocytes release damage associated molecular patterns (DAMPs) and morphogens (e.g. hedgehog and Wnt), that act on the immune system increasing inflammation, in stellate cells and progenitors cells activating them and inducing fibrogenesis and pathways of hepatocarcinogenesis. FFA: Free fatty acids; NEFA: Nonesterified fatty acids.

necrotic cells (to a lesser extent also apoptotic cells) can release molecules, termed “damage-associated molecular patterns” (DAMPs), which trigger inflammation, through the binding of several receptors^[70]. Those receptors can be specific or shared with pathogen-associated molecular patterns (PAMPs) that recognize molecular patterns associated with microbial pathogens or cellular stress, such as some toll-like receptors (TLR). An important mechanism to initiate inflammation is through the inflammasomes, cytosolic multiprotein complexes, present in the liver in parenchymal and non-parenchymal cells, which respond to DAMPs and PAMPs. It requires two signals: the first, through the NF- κ B pathway having upstream TNF receptor or TLRs, increases the transcription of components of the inflammasome; and the second in response to DAMPs and PAMPs with assembly of the inflammasome. The inflammasome is formed by a complex of a receptor from the family of NOD-like receptors, with pro-caspase-1 and an adaptor: apoptosis-associated speck like CARD-domain containing protein (ASC). The assembly of the complex leads to autocatalytic cleavage and activation of caspase-1 which then cleaves pro-IL-1 β , pro-IL-18 activating them and IL-33 neutralizing it^[71]. The first 2 cytokines are pro-inflammatory and IL-33 drives Th2 responses^[72]. Kupffer cells, resident macrophages in the liver, seem to be a crucial element in detecting DAMPs, and reacting with an inflammasome response^[73,74], though that can also occur in endothelial cells, stellate cells and hepatocytes^[71].

This pathway seems to be important in the pathogenesis of NASH. In fact, several animal models of NASH showed an increase of IL-1 β ^[73-77]. Also, mice deficient in

Table 1 Summary of the management of non-alcoholic fatty liver disease

Lifestyle interventions - diet and physical exercise
Weight loss: 3%-5% if simple steatosis, 7%-10% if NASH
Accompanied by cognitive-behavior therapy program
Diet - hypocaloric, adjusted to the patients needs and body weight
Fat - prefer PUFAs, mainly ω 3 - advise 2-3 oily fish meals/wk
$\leq 25\%$ as MUFA's, avoid SAF (less than 7% total energy)
Cholesterol ≤ 200 mg/d
Carbohydrates - $\geq 50\%$ as whole grains, avoid high fructose corn syrup
No need to restrict coffee
Mild alcohol intake - do not prohibit, do not advise; recommend against in patients with cirrhosis
Exercise - aerobic and restrictive, $\geq 3-4$ times/wk, ≥ 400 calories per session
Treat risk factors when present
Insulin sensitizers - no clear evidence to prefer thiazolidinediones or biguanides
Lipid-lowering drugs - statins are safe; protect from cardiovascular risk (more than in non-NAFLD)
Anti-hypertensive drugs - prefer ARAII if no contraindication, mainly telmisartan
Specific treatment for NAFLD
Consider vitamin E in patients with NASH, non-diabetic and without hypertension or at risk for prostate cancer
Pentoxifylin - promising agent that needs more evidence from large randomized clinical trials
Probiotics - promising agents that need more evidence from large randomized clinical trials
Screening for cancer
Screening for hepatocellular carcinoma every 6 mo in cirrhotic patients
Screening program (colorectal, breast, prostate and cervical cancer) as general population

NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; PUFA: Polyunsaturated fatty acids; MUFA: Monounsaturated fatty acids; SAF: Saturated fatty acids; ARA II: Angiotensin II receptor antagonists.

IL-1 β ^[76] or components of the inflammasome^[77] were protected from NASH and fibrosis. Moreover, increased expression of inflammasome components has been shown in liver biopsies from patients with NASH^[75].

The role of Kupffer cells in the inflammatory and fibrogenic response in NAFLD is starting to be highlighted by hepatologists. Studies with human biopsies showed an increase in CD68, a pan-macrophage marker in patients with NASH, as compared with simple steatosis^[78,79]. Also, *in vitro* studies with co-cultures with Kupffer cells and hepatic stellate cells, showed increased proliferation and activation of the latter, with increased production of collagen 1a, which was inhibited by catalase^[80]. Regarding studies with animal models, methionine-choline deficient diet fed mice, in which Kupffer cells were depleted by administration of clodronate-containing liposomes, developed less features of NASH^[81]. In the early phases of NAFLD, the classic activation of macrophages, M1, in the liver, may promote more inflammation and IR, as well as steatosis. However, an alternative activation of macrophages, M2, which is anti-inflammatory and insulin-sensitizer, but also profibrogenic seems to play a major role. In fact, in several mouse models, ob/ob, high fat-diet and

lipoatrophic diabetic A-ZIP transgenic mice with fatty liver, an M2 response, in the adipose tissue and in the liver, protects from glucose intolerance and IR, as well as hepatic steatosis^[82-84]. The effect of M2 polarization in liver fibrogenesis is still not characterized with conflicting results in the literature^[85]. However, there are concerns that M2 polarization may promote carcinogenesis^[86].

Other inflammatory cells in the innate immune system, such as NKT cells and NK cells play a crucial role in the development of NAFLD and NASH. Also, adaptive immune system seems to have a role, having been described a Th1-polarization in the liver and peripheral blood of patients with NASH^[87,88]. A more profound review is out of the scope of this article^[89,90].

Microbiota

Obesity and the metabolic syndrome have been associated with disturbances in the gut microbiota. Microbiota can induce a higher extraction of energy from diet and change whole-body lipid metabolism shifting it from oxidation to *de novo* production^[91]. Also, the diet itself can modulate the microbiota, with high-fat diets favoring a metabolically less favorable microbiome^[91]. Dysbiota also seems important in the development of NAFLD and NASH. Recently, a mouse model with dysbiota, induced by defects of inflammasome in the gut, promoted NASH development. Noteworthy, when the gut microbiota from affected mice was transferred to regular mice lead to the induction of NASH *per se*^[92]. Furthermore, NAFLD has been associated with small intestinal bacterial overgrowth^[93-95] and increased intestinal permeability^[96]. That can result in an increase in endotoxin, lipopolysaccharide (LPS)^[97-99]. TLR-4 is a receptor for the LPS from Gram-negative bacteria, being one of the most potent activators of Kupffer cells. Rivera *et al.*^[100] found that mice under methionine-choline deficient-diet expressed higher TLR-4, which was blunted after Kupffer cells depletion with clodronate liposomes. Additionally, mice with a mutant TLR-4 were protected from steatohepatitis development^[100]. Gut dysbiosis can promote NASH by other mechanisms, such as ethanol production and disturbing choline metabolism^[91].

Morphogens inducing fibrogenic and progenitors response

Injured cells, such as ballooned hepatocytes and dying cells that will undergo apoptosis and necrosis, release cues to hepatic stellate cells, inflammatory cells and progenitors^[101]. It is adaptive because it promotes a wound-healing response, with repair and regeneration, which could not be accomplished by the senescent hepatocytes. However, if those cues are sustained, it leads to excessive activation of stellate cells driving fibrogenesis. Sustained activation of progenitor cells may also promote hepatocarcinogenesis. Some of those cues have been proved to be morphogens such as hedgehog and Wnt ligands. In fact, ballooned hepatocytes produce sonic hedgehog^[102]. Hedgehog is known to activate hepatic stellate cells^[103,104] as well as progenitor cells^[105]. The role of hedgehog path-

way has been extensively demonstrated in NASH development and fibrogenesis in animal models^[106-108] and corroborated by association studies in human NAFLD^[109]. Recently, administration of a hedgehog antagonist protected from liver injury in a mouse model of diet-induced NASH^[110].

Lastly, the mechanisms that promote steatosis are intricate with the pro-fibrogenic process. For instance, hyperinsulinism may be profibrogenic by itself, since insulin promotes stellate cell proliferation and activation increasing the production of collagen 1a and alpha-smooth muscle actin^[111,112].

GENETICS

NAFLD development is highly dependent on the environment, with tremendous influence by the dietary patterns and a sedentary lifestyle. However, it surely requires an interaction with a genetic susceptibility. In fact, independent studies showed a strong familial aggregation^[113-116]. The racial differences in the prevalence of NAFLD and NASH also highlight a genetic background. Furthermore, a study on 157 patients with familial combined hyperlipidemia and 20 spouses, showed higher NAFLD prevalence in the patients and its direct family members as compared to their spouses, which differentiates an inherited transmission rather than shared lifestyles^[117]. In fact, a recent large population study suggested that the heredity of NAFLD is 26%-27%^[118].

Genetic associations with NAFLD have been widely studied. The first studies looked for candidate genes with case-control designs. Recently, in the era of omics, a non-biased approach has been applied, with several genome wide associations studies (GWAS) already published in this topic^[118-125].

The most consistent genetic association is with patatin-like phospholipase domain containing 3 (PNPLA3) or adiponutrin. That association was described in the first GWAS study performed in NAFLD patients^[119]. Romeo *et al.*^[119] studied a multiethnic population from the Dallas Heart Study comprising 2111 subjects, including African Americans, European-Americans and Hispanics. Hepatic steatosis was assessed by proton-magnetic resonance spectroscopy (¹H-MRS). They found a specific non-synonymous single nucleotide polymorphism (SNP), rs738409, with a substitution of cytosine by guanine (C>G) translating in a substitution of an isoleucine for a methionine in residue 148 (I148M), that strongly associated with hepatic fat content and serum levels of aminotransferases. It did not associate, however, with metabolic factors such as BMI, presence of diabetes, indices of insulin sensitivity or plasma lipid profile. Noteworthy, that SNP was more frequent in Hispanics, followed by European-Americans and less frequent in African Americans, resembling the racial differences in the prevalence of NAFLD. They also described another SNP, with a non-synonymous substitution of an isoleucine for methionine at residue 48 (I48M) that associated with lower hepatic fat content and was more frequent in African Ameri-

cans. The association of *PNPLA3* rs738409 was reproduced in different genetic backgrounds, by several other GWAS^[121,122,125] and candidate gene studies^[126-137]. This SNP has also been associated with severity of histological NAFLD, namely with severity of steatosis^[126,129], presence of NASH^[121,126,133], NAFLD Activity Score (NAS)^[129] and fibrosis^[131,133,136,138,139], irrespective of degree of obesity or metabolic co-morbidities. The function of adiponutrin is not clearly understood. In humans it is predominantly expressed in the liver but in mice in the adipose tissue. Its expression is positively regulated by carbohydrate-responsive element-binding protein (ChREBP), in response to glucose and SREBP-1c in response to insulin^[140]. It is located in the ER and lipid droplets membrane^[141]. *In vitro* studies have shown lipolysis properties, triglyceride hydrolase and diacylglycerol transacylase activities^[142], but also possible function in lipid synthesis with lysophosphatidic acid acyltransferase activity, converting lysophosphatidic acid in phosphatidic acid^[143].

Other genetic associations suggested by GWAS and confirmed by case-control candidate gene studies are: neurocan (NCAN), an adhesion molecule, with steatosis^[118,136,137,144], lobular inflammation^[136] and perivenular fibrosis^[136]; glucokinase regulatory gene (GCKR) also not only with NAFLD^[118,144-146], but also with NASH^[137,146] and fibrosis^[146]; lysophospholipase-like 1 (LYPLAL1), an enzyme in triglycerides breakdown, and protein phosphatase-1 regulatory subunit 3b (PPP1R3B), an enzyme in glycogen breakdown, with steatosis^[118,125,137,144].

A vast amount of genetic polymorphisms have been evaluated in case-control studies on NAFLD. Most of them either were not reproduced by different groups or presented conflicting results among studies, needing more extensive validation. Four genes are, however, worthy mention. Manganese superoxide dismutase, encoded by the gene *SOD2*, is a mitochondrial enzyme relevant in detoxification of reactive oxygen species. It is synthesized in the cytosol and, after posttranslational changes, transported to the mitochondria. Patients with NAFLD have been shown to present lower hepatic levels of manganese superoxide dismutase^[147]. A non-synonymous polymorphism in *SOD2*, C1183T, with substitution of cysteine for threonine at residue 47 (C47T), associates with less efficient transport of the protein to the mitochondria^[148]. Four independent cohorts, from different ethnic backgrounds, Japanese^[149], European^[150,151], African^[152], showed an association with NASH and hepatic fibrosis. Kruppel-like factor 6 (KLF6) is a transcriptional factor expressed in activated stellate cells that regulates the expression of several fibrogenic genes such as collagen 1 α , transforming growth factor (TGF)- β and its receptors^[153]. KLF6-IVS1-27G>A is a functional polymorphism that induces a site of alternative splicing, inactivating it^[154]. A study with 415 patients^[155], from 3 different cohorts, one from United Kingdom, other from Italy and a trio with 2 parents with an affected child showed an association between that SNP and steatosis, inflammation and hepatic fibrosis severity. More recently, a pediatric study also showed an association with NASH^[151]. Furthermore, the

renin-angiotensin system is believed to promote hepatic fibrogenesis. Variants in the angiotensin II receptor-1 (ATGR-1) were associated with NAFLD and hepatic fibrosis, in two independent cohorts^[156,157]. Lastly, TNF- α is a crucial pro-inflammatory cytokine in NAFLD that also promotes IR. Two polymorphisms in the promoter of *TNF* gene, -308A/G and -238A/G, known to associate with increased expression of TNF- α and IR, have been evaluated in several studies as potential modifiers of disease risk, with conflicting results^[158-163]. Recently, a meta-analysis on 8 studies and more than 1500 NAFLD patients and healthy controls, showed that the polymorphism -238G/A in homozygosity conferred a two-fold increased risk for NAFLD, whereas the polymorphism -308A/G was not associated with an increased risk^[164].

In the recent years, there has been a change in how we think in genetics. Not only the genes are important, but also epigenetic that regulates how the genes are expressed has been shown highly relevant in the pathogenesis of NAFLD. In fact, several independent studies showed that the male offsprings of female mice fed high fat diet during pregnancy, presented a higher risk for developing advanced NASH^[165-170]. Also, they presented increased genetic expression of genes in lipid metabolism, inflammation and oxidative stress^[165,170], which was associated with a correspondent different pattern of DNA methylation^[170]. An animal study with male Wistar rats fed with NAFLD-inducing high fat diet, showed increased expression of genes in lipid metabolism, with correspondent decrease in the methylation status of their promoters^[171]. In human NAFLD, two important studies were done with epigenetics. Ahrens *et al*^[171] studied NAFLD associated with morbid obesity; comparing with healthy controls, patients had different methylation status in lipid metabolism and insulin signaling, that was partially reversed by bariatric surgery. Murphy *et al*^[172] studied patients with NAFLD with mild or advanced fibrosis and found differences in the methylation status of fibrogenic genes, enzymes of one-carbon metabolism and components of inflammasome, which correlated with gene expression.

DIAGNOSIS

For better understanding the diagnosis, there is need to clarify some definitions. Fatty liver or steatosis, is considered when more than 5% of the hepatocytes present ectopic lipid droplets in a liver biopsy^[173,174]. Though this is an arbitrary definition, it is corroborated by quantitative data using H¹-MRS in a large healthy population, showing that 95% of subjects will have less than 5% steatosis^[175]. However, it should be noticed that H¹-MRS does not measure the same as a liver biopsy. In fact, it measures the amount of triglycerides in the parenchyma and not the number of positive hepatocytes. Steatohepatitis requires the presence of lobular inflammation and hepatocyte lesion, usually in the form of hepatocellular ballooning with or without Mallory-Denk bodies, besides steatosis^[176]. When cirrhosis is fully developed, features

of NASH may be lost, such as ballooning and even steatosis, which is called burned-out NASH. To be considered non-alcoholic, the patient must drink less than the amounts of alcohol that have been linked to increased risk for liver disease. Large prospective cohort studies done in the nineties, showed that alcohol intake of more than 2-3 drinks per day in men and 1-2 drinks per day in women increased the risk for liver-associated mortality^[177-179]. Taking that into consideration, European^[173] and American^[174] guidelines consider the threshold to be non-alcoholic intakes lower than 210 and 140 g per week (roughly equivalent to 3 and 2 drinks per day) in men and women, respectively. The Asian guidelines are a little more restrictive, considering intakes lower than 140 and 70 g per week (two and one drink per day) in men and women, respectively^[180].

The gold standard for the diagnosis is the liver biopsy, mainly for diagnosing NASH and staging fibrosis. However, for the diagnosis and quantification of steatosis, H¹-MRS may be the new reference since it assesses larger volumes of liver and it detects amounts of triglycerides that may not be enough to form macrovesicles amenable of histological visualization^[181]. Liver biopsy cannot be used routinely, since it is an invasive and expensive procedure, in which the low rate of complications would be significant if massively applied to all patients with NAFLD. Also, it has some limitations that should not be forgotten: it is prone to sample error, since it only assesses an insignificant volume of the liver, and this is a disease in which lesions are unevenly distributed throughout the liver, which results in wrong exclusion of NASH in one forth of cases and misclassification of fibrosis severity in one third^[182]. On the other hand, it is highly dependent on the pathologist, mainly for the diagnosis of NASH. Kleiner *et al.*^[183] proposed a histological score, NAS, that combines different degrees of steatosis, hepatocellular ballooning and lobular inflammation. It was not intended to diagnose NASH, though several studies have used it with that purpose. It was designed to help monitoring the effect of interventional and therapeutic strategies. The utility of the NAS score as a prognostic marker and even as a guidance to evaluate treatment-efficacy has been questioned^[184-186]. In fact, it has several limitations, including the fact that the degree of steatosis confers a huge impact on the score, although the severity of steatosis does not have proven prognostic value. On the other hand, it does not take into account the stage of fibrosis. More recently, Bedossa *et al.*^[187] proposed a different score, steatosis activity fibrosis (SAF) score that sequentially adds steatosis, ballooning and lobular inflammation for the diagnosis of NASH. It needs external validation.

Most of NAFLD patients will have an incidental diagnosis, mainly because the majority of patients are asymptomatic and symptoms, when present, are unspecific such as fatigue and abdominal discomfort. Aminotransferases are generally in normal-range values, and when altered, the increase is usually mild and fluctuant^[188]. Adding to that, it is not recommended to screen the population, even in high risk groups, since a cost-effective analysis

has not been done and there is no effective specific treatment for NAFLD^[174]. Having said that, the first method to be used in the clinical setting for diagnosing NAFLD is abdominal ultrasound. It is non-invasive, inexpensive, widely available, and presents reasonable accuracy for the diagnosis of hepatic steatosis, with 60%-94% sensitivity and 66%-97% specificity^[189]. However, its sensitivity decreases extremely for mild steatosis, being only reliable for steatosis higher than 30%^[190]. Also, its specificity is compromised by the presence of fibrosis, edema, necrosis and extra-hepatic adipose tissue. Computed tomography does not add accuracy to the ultrasound, and because it is more expensive and exposes patients to radiation, should not be used with the sole purpose of diagnosing hepatic steatosis. Magnetic resonance is more sensitive than ultrasound, mainly for the diagnosis of mild steatosis^[191], but it is time-consuming and expensive, so it is seldom used in clinical practice. The most accurate radiological method is H¹-MRS^[175], but it is costly and lacks broader availability, which limits its use to research sets. More recently, a method that uses the equipment of transient elastography, controlled attenuation parameter (CAP), is promising, with great accuracy, not being influenced by fibrosis^[192]. Though the added benefit in accuracy with ultrasound has not been properly assessed, it seems more sensitive for lower levels of steatosis^[193]. There are several combined panels with clinical and laboratorial data that were designed to predict steatosis^[194-197]. They are particularly relevant to large-scale epidemiological studies without availability of ultrasound and for a quick clinical suspicion of the presence of NAFLD in high-risk populations such as patients with T2DM. For large-scale epidemiological studies, fatty liver index (FLI), which incorporates BMI, waist circumference, serum levels of triglycerides and γ -glutamyltranspeptidase, can be very useful, and has been extensively validated^[195]. For high-risk populations, NAFLD Liver Fat score, is a very simple score that incorporates the presence of metabolic syndrome or T2DM, fasting serum insulin levels, aspartate aminotransferases (AST) and AST/alanine aminotransferases (ALT) ratio^[196]. It showed good performance in predicting NAFLD in the original publication and when reproduced by independent authors.

As important as diagnosing NAFLD, is the stratification of patients as having NASH and/or fibrosis. Again, clinical clues such as symptoms and physical examination do not help, though the presence of metabolic syndrome should raise the clinical suspicion of NASH. Aminotransferases are also not reliable, though if increased associate with a higher risk^[198]. Several complex models incorporating different clinical and chemical variables have been proposed, most of them with suboptimal accuracy or lacking external validation^[199-206]. The fragments of keratin 18 (CK18) is for now, the best surrogate marker for NASH, showing AUROC 0.82 in a meta-analysis of 10 studies and more than 1000 patients with NAFLD^[207]. However, it is not a perfect tool, and more recent studies including a second meta-analysis showed lower accuracy with sensitivity about 60%^[208,209].

Regarding estimation of liver fibrosis, several biomarkers^[210-212] and composite scores have also been proposed^[185,213-219]. Of those, the most robust, with more extensive evaluation by different groups and good performance is the NAFLD Fibrosis score^[216]. It incorporates, in an equation, age, glycemia, BMI, platelet count, albumin and AST/ALT ratio. Values lower or equal to -1.455 and higher than 0.676, presented high accuracy in excluding and identifying advanced fibrosis, respectively. A meta-analysis of 13 studies, comprising more than 3000 patients, confirmed those results^[207]. One limitation of this score is that nearly one fourth of the patients will not be classified, because will fall in between those cut-offs - intermediate risk. More recently, NAFLD Fibrosis Score (among other non-invasive scores) has been shown to be useful in predicting overall and liver-related mortality, in 3 studies with follow up ranging from 8 to 14 years^[220-222]. Transient elastography (Fibroscan[®]), already widely used in chronic hepatitis C, also has good accuracy to predict advanced fibrosis and exclude it in NAFLD, with cutoffs higher and lower than 9.6 and 7.9, respectively^[207,209,223-227], although probably not as sensitive as in hepatitis C^[228]. A concern is that elastography is more prone to failure in obesity, which is not completely overcome by the XL probes, and also in the presence of ascites and narrow intercostals spaces. Also, elastography is influenced by meals, acute hepatitis, cholestasis and liver congestion. Other methods to evaluate elastography, such as real-time elastography that takes advantage of a B mode conventional mechanism, and magnetic resonance elastography that allows estimation of elasticity in whole liver, are promising. More recently, acoustic radiation force impulse (ARFI) that is integrated in conventional ultrasound systems shows very good results that need further validation^[229-233].

In conclusion, most of the times, the diagnosis of NAFLD is incidental. When a patient presents in the clinic with ultrasound-diagnosed NAFLD, there is no clinical or laboratorial accurate way to stratify the patient in terms of presence of NASH and fibrosis. However, several risk factors should increase the suspicion, such as, older age and postmenopausal women, being Hispanic, obese, with IR, T2DM, hypertension or the metabolic syndrome, and increased aminotransferases levels^[234]. NAFLD Fibrosis Score is a simple test with good prediction ability for fibrosis and even prognostic implications. If the score is lower than -1.4555, the risk of having fibrosis is very low. If none of the other risk factors are identified, it can be discharged for primary care follow up. If the above risk factors are present, and there is availability for performing CK18 fragments determination, it could be done, and if predictive of NASH, confirmed by liver biopsy. On the other extreme, NAFLD Fibrosis Score higher than 0.676, a liver biopsy should be performed to confirm advanced fibrosis, unless there is clinical evidence of liver cirrhosis. Lastly, patients with intermediate NAFLD Fibrosis Score values should be offered another non-invasive tool for assessing fibrosis, such as transient elastography, and if high level of suspicion of fibrosis, should be considered

for liver biopsy.

NATURAL HISTORY AND PROGNOSIS

Patients with NAFLD have a decreased survival as compared to the general population^[235]. The number one cause of death in patients with NAFLD is cardiovascular disease, followed by malignancies and only then liver disease^[235-237]. In fact, patients with NAFLD die two fold more frequently due to cardiovascular disease than to liver disease itself^[207]. Even in patients with liver cirrhosis, cardiovascular disease is still the second cause of death^[207]. Importantly, patients with NAFLD have a two-fold increase in cardiovascular mortality as compared to the general population^[235,237,238]. However, liver death takes the third position in the ranking of mortality in patients with NAFLD, whereas it is only the thirteenth cause of death in the general population^[235]. As such, NAFLD patients die 9 times more often from liver disease than the general population^[236]. Despite the fact that NASH is considered the progressive form of NAFLD^[239,240], there is no difference on overall or cardiovascular mortality between patients with simple steatosis and NASH, though the latter group does have a more than 10 fold increase in liver mortality^[237].

The high cardiovascular mortality may be explained by the fact that NAFLD is a surrogate marker of metabolic derangement. Moreover, NAFLD itself may contribute to the pathogenesis and development of T2DM and the metabolic syndrome. In fact, in longitudinal studies, NAFLD either diagnosed by altered liver enzymes^[241], abdominal ultrasound^[242-247] or non-invasive scores markers of NAFLD^[248,249], showed an increased risk for developing T2DM and metabolic syndrome. That increase in T2DM risk was even higher in patients with NASH *vs* simple steatosis^[240].

Regarding liver prognosis, NAFLD is a slowly progressive disease. Simple steatosis is believed to be a non-progressive condition, whereas NASH can develop progressive fibrosis in more than one fourth of the patients in 4 years and nearly half of the patients in 6 years^[207]. Fibrosis may evolve in liver cirrhosis. Over 14 years of follow up, 13% of patients with F2 grade fibrosis and 25% with F3 grade are expected to develop liver cirrhosis^[240]. Grossly, one fifth of patients with NASH will develop liver cirrhosis in the long term^[1].

The main risk factors for having advanced fibrosis are older age^[250,251], presence of obesity and central obesity^[12], as well as T2DM^[252] and hypertension^[199]. A systematic review^[253] of 10 studies comprising 221 patients submitted to paired biopsies apart on average from 5 years, showed that fibrosis progression, of at least one stage, occurred in a little more than one third of the patients. Overall, the mean rate of fibrosis progression was 0.03 stages per year; however, analyzing only the patients in whom fibrosis progressed, the rate was 0.41 stages per year. The stronger predictor of fibrosis progression was necroinflammation. Having any lobular inflammation increased by 2.5 fold the likelihood of developing advanced

fibrosis. Steatosis severity did not correlate with fibrosis progression. Of note, ballooning was not possible to assess. In fact, ballooning correlates with severity of fibrosis^[184].

Patients with NAFLD can also progress to HCC, even without cirrhosis^[254]. Some cases of HCC were reported in patients with simple steatosis, without NASH or fibrosis^[255,256]. A recent systematic review on 17 studies showed that in non-cirrhotics, the cumulative HCC mortality rate was 3% over a 20 year follow up. In patients with cirrhosis, that rate was 2.4-12.8 after 3 to 12 years of follow up^[257]. In fact, NAFLD-associated cirrhosis accounts for 15%-30% of cases of HCC^[258].

MANAGEMENT

The first difficult decision is who to treat and who to discharge from a specialized assistance to a general physician. Patients who should continue to be followed by hepatologists are the ones at risk for progressive liver disease, that is, patients with NASH, particularly if they have liver fibrosis. However, non-pharmacological measurements should be applied to all patients with NAFLD, even simple steatosis, since NAFLD confers an increased risk for metabolic derangement and cardiovascular disease as well as an increased risk for several malignancies (Table 1). Screening for hepatocellular carcinoma should be offered to all patients with liver cirrhosis. In patients with NASH and even simple steatosis with no fibrosis, though there are several reports on the literature of liver cancer, there is not sufficient evidence to recommend a screening program. Though a cost-efficacy analysis has not been done in patients with NAFLD without fibrosis, the incidence of liver cancer in those patients is so low that would not warrant its application. Also, because patients with NAFLD are at increased risk of malignancies, they should be carefully monitored in the regular screening programs for colorectal, prostate, breast and cervical cancer.

Despite huge investigation on it, we still do not have available an effective treatment for NAFLD. Most of the trials done in patients with NAFLD showed some efficacy in decreasing steatosis, inflammation and even ballooning, though there is no solid evidence for a treatment being able to decrease fibrosis. This apparent failure could be either because we still did not find a good anti-fibrotic agent in NAFLD, or because the design of the trials, that usually have no more than 2 years of intervention, was unable to detect differences in fibrosis progression. Also, the desirable trials would be the ones that could show an effect on survival and major events such as liver decompensation. However, due to the slowing progressive nature of NAFLD, those trials would have needed long follow up, which makes them impractical.

Non-pharmacological approach

It is recommended a personalized approach with lifestyle intervention, focusing on diet and exercise, in order to lose weight, to all patients with NAFLD. Except for the

rare patients with normal weight, it should be promoted weight loss of 3%-5% in patients with simple steatosis and 7%-10% in patients with NASH^[174]. In the long term, normal weight should be the goal. Though several studies have shown a benefit of weight loss in NAFLD^[259-272], the rationale for those weight goals comes mainly from 3 studies, one observational^[273] and two interventional^[274,275]. The first is a longitudinal study, by Zelber-Sagi *et al.*, with 7 years follow up of 147 healthy subjects^[273]. The authors found that weight gain and loss associated, respectively, with *de novo* NAFLD and NAFLD remission. Of notice, if the weight loss was 5% of the body weight or more, the remission rate of NAFLD was 75%. The two interventional studies were both on 31 obese or overweight patients with NASH, managed either for 48 wk^[274] or 36 wk^[275]. What collectively they found was that weight loss of at least 5% of body weight associated with improvements in steatosis and IR, but only when weight loss was at least 7%-9% there were improvements in inflammation, hepatocellular ballooning and NAS. Of notice, compliance in lifestyle intervention programs and weight loss are difficult to accomplish, usually almost half of the patients cannot achieve the proposed goals. To improve the efficacy of those programs, it would be preferable to associate them with cognitive-behavior therapy programs^[276].

The effect of weight loss is independent of the composition of the hypocaloric diet^[277-280]. However, some recommendations should be made. Patients with dyslipidemia may benefit from low fat diets^[277], whereas patients with IR/T2DM from low carbohydrate diets^[278]. Regarding lipids composition, polyunsaturated FA should be preferred, mainly $\omega 3$ from fish oil; up to 25% of fat should be in the form of mono-unsaturated FA, in detriment of saturated FA that should account for less than 7% of total energy^[281]. Cholesterol intake should be lowered to 200 mg per day^[282]. Those recommendations rely on several lines of evidence. Patients with NAFLD, and even more with NASH, eat a lower polyunsaturated *n-6* saturated FA ratio, a lower $\omega 3$ *n-6* ratio, and a higher amount of cholesterol, as compared to the general population^[283-287]. Also, saturated FA associate with IR^[285], oxidative stress^[288], ER stress and apoptosis^[49,50], whereas polyunsaturated FA may decrease hepatic lipid content through inhibition of SREBP-1c^[289]. Furthermore, several studies evaluated the effect of supplementation with $\omega 3$ polyunsaturated FA in patients with NAFLD^[290-292], and a recent meta-analysis^[293] suggested a benefit in decreasing liver fat and aminotransferases, starting at doses as low as 0.83 g per day. The authors could not infer the ideal dose, due to the high heterogeneity among studies. Lastly, two large-scale population-based prospective cohort studies found a positive correlation between cholesterol intake^[287] and a negative correlation between $\omega 3$ polyunsaturated FA-rich fish consumption^[294] and increased risk for liver cirrhosis and HCC.

Concerning carbohydrates consumption, at least half should come from whole grains. Most importantly, high fructose corn syrup, a major source of fructose in oc-

cidental diet^[295], should be avoided. Actually, higher fructose consumption, in the form of soft drinks, has been associated with NAFLD^[296] and fibrosis stage, inflammation as well as hepatocellular ballooning^[297]. In fact, the steatogenic effect of fructose can be explained by its metabolism that bypasses the regulatory points of glycolysis and thus can act as an unregulated source of substrates for lipolysis; it regulates the expression of lipogenic genes through induction of SREBP-1c and ChREBP; it decreases fatty acid oxidation through downregulation of PPAR- α ; and it promotes bacterial overgrowth and hence increases the load of endotoxin that reaches the liver^[298].

Several studies have shown that exercise alone, even when weight loss is not achieved, has beneficial effects on NAFLD^[268,270], and in IR^[299-301]. However, the combination of exercise and diet has synergic value^[302,303]. The type of exercise does not matter^[302,304,305], as long as at least 400 kcal are spent per session^[306]. Patients should be advised to perform moderate exercise, preferentially 3-4 times per week^[307].

Regarding alcohol consumption, it is known, since the nineties, that consumption higher than 2-3 drinks per day not only increases the risk for liver cirrhosis, it also increases the risk for overall death and some malignancies^[177,179,308,309]. However, there is a U relation between alcohol consumption with lower intakes decreasing overall mortality at expense of a decrease in cardiovascular events^[310,311], less risk for diabetes mellitus^[312] and the metabolic syndrome^[313-315]. Some studies also showed a possible beneficial effect in NAFLD for very mild alcohol consumption^[199,316-320]. In our view, we should not actively recommend mild alcohol consumption in patients with NAFLD since the evidence come largely from cross-sectional studies^[321]. Also, the benefit of mild alcohol consumption in obese patients is not known, since obesity and alcohol are synergic in promoting NAFLD and HCC^[322-325]. In patients with NASH-associated cirrhosis, however, it should be strongly recommended against, since any regular alcohol consumption, in this set of patients, increases by more than 3-fold the risk for HCC^[326].

Lastly, coffee should not be recommended against, because an important amount of evidence, either by epidemiological studies either by studies in animal models^[327-331], suggest a protective effect in terms of metabolic control^[332,333] and NAFLD development and progression^[334-339].

Pharmacological therapy to promote weight loss does not seem to confer any benefit over lifestyle intervention alone, as been shown in trials with orlistat^[275,340]. Lastly, bariatric surgery may be an alternative to promote weight loss and improve metabolic profile in morbid obese patients^[341]. Even in moderately obese patients, it showed beneficial effects in promoting metabolic control^[342]. A meta-analysis on bariatric surgery applied to morbid obese patients with NAFLD, but without cirrhosis, and paired liver biopsies, showed improvement in steatosis in 92% of patients, steatohepatitis in 82% and fibrosis in 65%^[343].

Pharmacological approach

Since there is no clear curative treatment for NAFLD, the management of these patients should rely first on the control of co-morbidities known to promote not only liver disease, but also cardiovascular disease and overall mortality, such as IR/T2DM, dyslipidemia and hypertension. The effect of some of those treatments in the liver has been evaluated. For now, the presence of NAFLD alone should not be an indication to use anti-diabetics, lipid-lowering drugs or anti-hypertensive drugs. However, in patients who also present those metabolic disturbances, some drugs may be preferred in patients with NAFLD.

Agents that target risk factors

Starting with anti-diabetics, there is no clear evidence to prefer a specific class of drugs. Thiazolidinediones have been widely studied on NAFLD, mainly rosiglitazone and pioglitazone. We will focus on the latter, since rosiglitazone has been abolished from the European market and has very restricted use in the United States, due to its association with increased risk of adverse cardiovascular events. Three well designed randomized controlled trials evaluated pioglitazone against placebo treatment, during 6, 12 and 24 mo, including 55, 74 and 247 patients with NASH, respectively^[344-346]. Collectively they found pioglitazone to be better than placebo in improving glucose metabolism, decreasing aminotransferases levels and improving steatosis, ballooning and inflammation, but not in improving liver fibrosis. Though pioglitazone, during the time-course it was administered, did not improve fibrosis, it decreased the rate of fibrosis progression, as described by two meta-analysis^[347,348]. Of notice, only the smaller study included patients with glucose intolerance or T2DM, the other two were in non-diabetics, which might not be the better target for insulin-sensitizers. There are some concerns that preclude us to propose its systematic use in patients with NAFLD with glucose intolerance. First, there are some safety issues, as it associates with considerable weight gain that does not return back to baseline after stopping the drug^[349]. Also, it has been associated with increased risk for congestive heart failure^[350], bone fractures^[351] and bladder cancer after two years of treatment^[352]. Lastly, it showed no additional benefit after one year of treatment, and even more importantly, the relapse is certain after discontinuation of pioglitazone^[349]. Other insulin-sensitizer, the biguanide metformin, though it has obvious benefic metabolic effects, not only in terms of glucose control, but also in increasing high density lipoprotein (HDL)-cholesterol, it promotes weight loss, which can be an advantage when starting treatment in patients with NAFLD and overweight. However, it has no proved benefit in liver histology^[3,348,353].

The effect of lipid lowering agents in NAFLD is still not completely understood, though small studies suggested a mild benefit in steatosis and NAS score, without clear effect on fibrosis, for either statins^[354], fibrates^[355,356], probucol^[357,358] and ezetimibe^[359,360]. However, the ben-

efits of statins in these patients go beyond the liver. In fact, *post-hoc* analysis of two large studies on the effect of statins in cardiovascular outcomes in high risk patients, showed that patients with NAFLD, as assessed by an increase in aminotransferases without other cause for liver disease, had an even greater decrease in cardiovascular events, as compared to patients with normal aminotransferases baseline^[361,362]. We can then conclude that we should not be afraid of treating patients with NAFLD and elevated aminotransferases with statins, and they might even be used with a lower threshold for dyslipidemia.

Lastly, a specific class of anti-hypertensive, angiotensin II receptor antagonists, should be preferred in patients with NAFLD, regarding no contraindication is obvious. In fact, losartan has been shown to decrease liver fibrosis and hepatic stellate cells activation in a very small pilot study^[363,364]. Telmisartan looks even more promising^[365] since it has, unlike other drugs from the same class, anti-steatogenic and insulin-sensitizer actions through agonistic effects on PPAR- γ ^[366].

Agents specific for NAFLD

Vitamin E is the one with more evidence. Two large randomized controlled studies in patients with NASH, without diabetes mellitus, in adult and pediatric population, showed similar results. It had benefit over placebo in decreasing aminotransferases, and in improving liver histology, steatosis, NASH, inflammation and ballooning, but not fibrosis. Also, in patients who did not achieve weight loss, the disease seemed to progress less in the ones taking vitamin E. Again, we do not recommend its systematic use since, though it was better than placebo, more than half of the patients did not show any histological improvement. On the other hand, there is no evidence for treating patients with diabetes, nor patients with simple steatosis or liver cirrhosis, so it should not be prescribed in those cases. Lastly, several safety concerns cannot be under looked: it has been associated with increased mortality, starting at doses as low as 150 IU/d^[367], increased risk for prostate cancer after 3 years of treatment^[368], and increased risk for hemorrhagic stroke, though decreased for ischemic ones^[369].

Ursodeoxycholic acid has been widely studied and it showed no effect in NAFLD^[348,370-373], though it may improve adiponectin levels^[374] and IR^[373]. Pentoxifylin^[375-378] and probiotics^[379-383] look promising in pilot studies, but more robust evidence from large scale randomized controlled-trials is warranted.

Several anti-fibrotic, anti-apoptotic and immune therapies are in the pipeline in pre-clinical and phase II trials, and hopefully in the next decade, we will achieve a more efficient liver-specific treatment.

CONCLUSION

NAFLD is the new pandemic of the twenty first century, walking together with obesity. It can be seen as a consequence of metabolic deregulation associated with

energy surplus and exceeded reservoir ability of adipose tissue to store fat/energy. However, it is becoming clearer that hepatic steatosis also drives that metabolic deregulation, promoting T2DM development and cardiovascular disease. In fact, patients with NAFLD have increased mortality, mainly at expenses of cardiovascular disease, though liver-associated mortality becomes relevant in patients with more severe disease, particularly, with NASH and fibrosis.

Though NAFLD has profound influences by environmental factors, such as obesity, western diet and a sedentary lifestyle, genetic influences play together with environment in orchestrating the pathogenesis of the disease and its spectrum. In the last 5 years, genetic susceptibility has been studied by GWAS unbiased studies, with some important genes popping out that otherwise would have not been linked to NAFLD. More recently, a new layer of complexity has been added, with the understanding that epigenetic modifications also can modulate the susceptibility for this disease.

In patients with NAFLD, the gold standard for diagnosing NASH and fibrosis is liver biopsy, but some non-invasive methods have high accuracy in predicting fibrosis, which can help us selecting patients for histological assessment.

Treatment should be aimed not only to decrease liver disease progression, but also to decrease cardiovascular events and mortality. The basis remains lifestyle education with hypocaloric diet and physical exercise promoting weight loss. Metabolic risk factors, such as IR/T2DM, hypertension and dyslipidemia should be treated aggressively. There is no approved specific treatment for the liver disease itself, although vitamin E could be used, with caution, in non-diabetic patients with NASH and fibrosis, but without cirrhosis and with no expected increased risk for prostate cancer.

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P- Reviewer: Anty R, Inzaugarat E, Ji G, Kobylak NK
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ISSN 1007-9327



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