

Analogy between non-alcoholic steatohepatitis (NASH) and hypertension: a stepwise patient-tailored approach for NASH treatment

Yaron Ilan

Hadassah Hebrew University Medical Center, Jerusalem, Israel

Abstract

Non-alcoholic steatohepatitis (NASH) is a common liver disorder worldwide. Although there has been improvement in our understanding of the natural history and pathogenesis of the disease, there is still no approved therapy for NASH. NASH shares many similarities with primary hypertension, in that both are extremely common disorders that can easily lead to serious complications if left untreated. Both conditions are viewed as “silent killers”, because the disease can progress over a period of time prior to the occurrence of potentially deadly outcomes. While attempts to find the “miracle pill” for NASH are unrealistic, we can make an analogy with the “stepwise combination” approach developed over the last few decades for the treatment of hypertension. In the present review, we summarize some of the similarities in the concepts that underlie NASH and hypertension. The development of a stepwise patient-tailored method for the treatment of NASH is presented.

Keywords Non-alcoholic steatohepatitis, hypertension, treatment, non-alcoholic fatty liver disease

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of a significant amount of lipid accumulation in the liver without significant alcohol consumption [1]. NAFLD represents two distinct entities with two different prognoses: the first is simple fat accumulation in the liver; and the second is non-alcoholic steatohepatitis (NASH), which comprises necro-inflammation and may lead to fibrosis, cirrhosis and hepatocellular carcinoma (HCC) [1,2]. NAFLD is the most common cause of chronic liver disease worldwide [3]. Despite progress in the understanding of the pathophysiology of the disease and diagnostic methods, there is still no approved therapy [4,5].

Gastroenterology and Liver Units, Department of Medicine, Hadassah Hebrew University Medical Center, Jerusalem, Israel

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Correspondence to: Yaron Ilan, MD, Gastroenterology and Liver Units, Department of Medicine, Hebrew University-Hadassah Medical Center, Ein-Karem, POB 1200 Jerusalem, Israel, e-mail: ilan@hadassah.org.il

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Hypertension (HTN) has been recognized for much longer than NASH and the two conditions share many similarities. We describe some of the common features of both diseases in an effort to determine what hepatologists can learn from HTN experts with regard to treatment strategy.

NAFLD and HTN are two global epidemics

NAFLD and HTN are highly common disorders. Approximately 90% of HTN cases are classified as essential HTN, where the precise cause is unknown [6]. Both secondary liver steatosis due to non-NAFLD causes (e.g., HCV genotype 3, Wilson's, etc.) and secondary HTN are less common. NAFLD is one of the main causes of chronic liver disease globally [7]. A recent study determined that the prevalence of NAFLD was 24% and that the global prevalence positively correlated with the gross national income per capita: Europe observed a higher prevalence (28%) than the Middle East (12%) and East Asia (19%) [8]. Like NAFLD, HTN is a major contributor to the global burden of disease and mortality [9]. A national survey estimates the prevalence to be 16-36% [10]. A recent review found that the prevalence of treatment-resistant HTN (RH) is between 13% and 16% [11]. NAFLD and HTN are strongly associated with obesity and insulin resistance states including diabetes. HTN is one of the criteria for metabolic syndrome [12]. NAFLD is associated with components of

metabolic syndrome. Sixty-six percent of patients older than 50 years with diabetes or obesity are thought to have NASH with advanced fibrosis [2]. However, arterial HTN, which is among the various components of metabolic syndrome, was found to be the least closely associated with NAFLD [13]. More advanced stages of NAFLD are associated with HTN [14,15]. Angiotensinogen gene haplotype is associated with the prevalence of Japanese NASH [16]. In the absence of major risk factors for liver disease, NAFLD is a frequent finding in primary aldosteronism. These patients are more insulin resistant and have a higher prevalence of NAFLD [17].

NAFLD and HTN are associated with a high risk of cardiovascular and kidney diseases

NAFLD and HTN are associated with similar target organ damage. The clinical burden of NAFLD is the result of liver-related morbidity or mortality, although the majority of deaths in NAFLD patients are related to cardiovascular disease (CVD) and cancer [18]. NAFLD is a risk factor for extrahepatic diseases such as CVD, chronic kidney disease (CKD), colorectal cancer, and endocrinopathies, which include type 2 diabetes mellitus (T2DM), thyroid dysfunction, colorectal neoplasms, and osteoporosis [18,19]. The prevalence of NAFLD is three times higher in patients with T2DM [20]. Patients with NAFLD are also at a higher risk for atherosclerosis [21]. It has been suggested that patients with NAFLD should undergo periodic CVD risk assessment [22]. Similarly, the association between systolic and diastolic HTN and the risk of CVD and renal disease is well known. HTN is associated with a higher risk of acute kidney injury [23]. The prevalence of HTN is higher and its control is more difficult with poor kidney function. The presence and severity of CKD increases treatment resistance [24]. Obese individuals are more likely to be at increased risk for developing NAFLD, HTN, CVD, and CKD [25].

A recent Consensus analyzed the effect of treatment using statins alone, or in combination with pioglitazone and other drugs, on CVD as a main cause of death in patients with NAFLD, and on liver-related complications of NAFLD or NASH, including cirrhosis and hepatocellular carcinoma [26]. This Consensus suggested a tailored “HTN-like” therapy.

Prevalent NAFLD may be seen early in the development of HTN, even in the absence of other metabolic risk factors. Controlling blood pressure among non-obese hypertensive patients may be beneficial in preventing or limiting NAFLD [27]. The prevalence of NAFLD among persons with normal blood pressure, prehypertension (PHT), and HTN was 16.5, 37.5, and 59.3%, respectively. In multivariate analyses, PHT and HTN were associated with elevated odds of NAFLD.

Data support the paradigm of NAFLD as a strong determinant for the development of the metabolic syndrome, which has potentially relevant clinical implications for diagnosing, preventing and treating metabolic syndrome. Longitudinal studies support the association of NAFLD with either T2DM or metabolic syndrome, and suggest that NAFLD precedes the development of both conditions [28].

Based on data from 118 consecutive biopsy-proven NAFLD patients, the metabolic syndrome, the homeostatic model assessment of insulin resistance, serum total cholesterol, and serum uric acid were identified as independent predictors of NASH and its individual histological lesions, including fibrosis. These factors were suggested as pathogenic drivers of NASH and as potential targets for treatment [29].

NAFLD and HTN are multifactorial diseases

The pathogenesis of NAFLD and NASH and the mechanisms that lead to liver injury, fibrosis, and HCC are the result of a complex interplay between host and environmental factors. Genetic, biochemical, immunological, and molecular events are associated with disease progression [30]. The pathogenesis of HTN, similar to that of NAFLD, involves genetic, endocrine, metabolic, immune and nervous system parameters.

In NAFLD, environmental factors play a major role in genetically susceptible populations. Diet plays a role in this process, as fructose exacerbates NAFLD, while the Mediterranean diet exerts a protective effect [31]. A diet rich in simple carbohydrates, saturated fat, and highly processed food on a background of several genetic variants presents a risk for NAFLD [32]. De novo lipogenesis, i.e., hepatic triglyceride synthesis, accounts for only 25% of hepatic triglycerides, while the role of lipolysis as a factor contributing to hepatic triglyceride storage remains unconsidered [33]. Increased liver fat induces mitochondrial metabolism and glyceroneogenesis and its conversion from lactate to glycerol is used as a substrate for gluconeogenesis. Hepatic fat removal, i.e., increased mitochondrial β -oxidation and autophagy, contribute to liver damage [34-38]. NAFLD typically results from fatty changes observed in the absence of competing steatogenic factors in dysmetabolic individuals [39]. Reduced metabolic adaptability has been described, in which liver fat accumulation increases the demands on the liver to control metabolic responses [40].

For HTN, a defect in sodium excretion by the kidney is central to the pathogenesis. A congenital reduction in nephron number, obesity, hyperleptinemia, a diet rich in salt and fructose, increased sympathetic nervous system tone, hyperuricemia, renal arteriolar vasoconstriction, and intra-renal activation of the renin-angiotensin system are significant in the pathogenesis.

Gene expression profiling and genome-wide association studies have identified disease pathways and polymorphisms in genes that determine NAFLD progression [41,42]. The polygenic background with multiple independent modifiers determines disease prognosis. The risk allele frequencies of NAFLD-associated single nucleotide polymorphisms were analyzed in distinct populations that have high risk scores [43]. Patatin-like phospholipase domain-containing 3 (PNPLA3) has both anabolic and catabolic activities in lipid metabolism and has been reported to be linked with liver fat content [44]. A link from the 148 isoleucine to a methionine protein variant of PNPLA3, NAFLD and fibrosis has been described. Genes involved in lipolysis, adipokine, and cytokine production

are being explored [45-47]. Target genes for peroxisome proliferator-activated receptor (PPAR) α , a ligand-activated transcription factor, are involved in fatty acid metabolism [48]. During PPAR α activation, the combination with PPAR β/δ agonism improves steatosis, inflammation and fibrosis in NAFLD [49].

Genetic congenital (fetal programming) and acquired mechanisms for defects in natriuresis increase the risk for development of HTN. Genetic polymorphisms regulate sodium excretion. It is estimated that 30% of the variance in blood pressure relates to genetic factors [9]. Genome-wide studies identified more than 65 loci affecting blood pressure [50].

Chronic low-level inflammation is associated with the metabolic syndrome [51]. While the liver provides a “tolerogenic” environment, abnormal activation of innate immune cells triggers inflammation that contributes to hepatic injury, fibrosis, and carcinogenesis [52,53]. Innate immune cells, the adaptive system, liver macrophage Kupffer cells, stellate cells, and dendritic cells contribute to the development of fibrosis. Adiponectin, leptin and ghrelin, resistin, visfatin and retinol-binding protein 4, along with tumor necrosis factor (TNF)- α , interleukin (IL)-6, IL-1, and IL-18 are some of the major factors involved [53].

Like NAFLD, HTN is linked with inflammation. Hence, both the innate and adaptive immune responses participate in this process [54]. Oxidative stress and endothelial dysfunction are contributing factors for the development of HTN [6]. Increased sympathetic and/or decreased parasympathetic outflow or low-grade infections generate neoantigens and damage-activated or pathogen-activated molecular patterns, which trigger Toll-like receptors on innate cells [54]. Innate responses, mediated by monocytes, macrophages, dendritic cells, and natural killer cells, contribute to inflammation by activating a T-cell-mediated adaptive immune response [54]. Activation of the sympathetic nervous system, aging and elevated aldosterone are potentially proinflammatory. Intrarenal T cells are associated with persistence of HTN, suggesting induction of a local autoimmune response to neoantigens, such as heat shock protein 70 and protein aggregates resulting from lipid peroxidation [55].

NAFLD has also been linked with alterations in the nervous system. Altered neuroendocrine and autonomic signals controlled by the suprachiasmatic nucleus contribute to steatosis, obesity and glucose intolerance. Excess free fatty acids in hepatocyte storage lead to lipotoxicity, hepatocyte damage, and apoptosis. Glucagon-like peptide (GLP)-1 analogues stimulate pancreatic β -cell insulin output and affect the liver's free fatty acid metabolism [56].

Likewise, for HTN, the renal sensory afferent nerves and efferent sympathetic nerves control the extracellular fluid volume and hence the level at which blood pressure is set. Afferent and efferent renal innervation contribute to neural dysregulation of the kidney in RH [57]. Sympathetic neural regulation of renin release and fluid reabsorption in the kidney affect HTN. RH is attributed to aldosterone excess in over 20% of patients. The function of amiloride-sensitive sodium channels and mineralocorticoid receptors in the systemic vasculature supports aldosterone-mediated RH [58].

The gut microbiome plays a role in the pathogenesis of both NAFLD and HTN [59]. Altered intestinal permeability supports a link between gut lumen antigenic/toxic substances and systemic and liver inflammation in NAFLD [59]. Patients with NASH have increased Gram-negative microbiome and endotoxemia. Microbial metabolites aid in the development of hepatic steatosis and inflammation, NASH and fibrosis [60]. Short-chain fatty acids, the products of microbial fermentation, enhance intestinal absorption by activating GLP-2 signaling [60]. However, many NASH patients show normal serum endotoxin levels, indicating that endotoxemia may not necessarily be required for the development of NASH [60].

Dysbiosis in the gut microbiota has also been described in association with HTN in both animal models and humans [61]. An abundance of the *Firmicutes* and *Bacteroidetes* gut microbes has been found in HTN. Decreases in gut microbiota caused by antibiotics can increase or decrease blood pressure depending on the patient's genotype. Products of the fermentation of nutrients by gut microbiota change the blood pressure by altering the expenditure of energy, intestinal metabolism of catecholamines, gastrointestinal and renal ion transports, and finally, salt sensitivity [61].

NAFLD and HTN are “silent killers” with marked interpatient variability in disease progression

In NAFLD and HTN, there is considerable interpatient variability in both severity and rate of progression [62]. NAFLD and HTN can be present with different phenotypes as a result of the multiple factors associated with disease progression. Patients with NAFLD can present with simple steatosis, different stages of fibrosis and pre-cirrhotic NASH, compensated cirrhosis, or advanced NASH cirrhosis. The rate of disease progression differs among patients [63]. Likewise, hypertensive patients may have diverse degrees of disease progression and different complications.

For NAFLD and HTN, a substantial proportion of the population is at risk of progressive disease, while the minority experience associated morbidity. In both disorders, the term “silent killer” is used, because in both conditions a relatively long-term “silent disease” may lead to serious complications and increased mortality. NAFLD is associated with a high rate of mortality from CVD, late-stage liver disease and HCC [64]. About one third of patients with early-stage NASH progress to cirrhosis over a period of 5-10 years. Among those who progress to NASH cirrhosis, approximately 25% develop the major complication of portal HTN within 3 years. HCC is described in the setting of NASH as well as of obesity and diabetes [65]. It has also been suggested that HCC may develop in “silent NAFLD” patients without cirrhosis [66]. The majority of deaths in NAFLD patients are related to CVD and cancer [67]. However, it remains unproven whether NASH carries excess CVD risk compared with simple steatosis [68]. NAFLD is associated with subclinical manifestations of atherosclerosis, including increased intima-media thickness,

endothelial dysfunction, arterial stiffness, impaired left ventricular function and coronary calcification [69]. HTN is responsible for 7.6 million deaths per year worldwide, 13.5% of the total, more than any other risk factor [70]. HTN is also responsible for approximately 41% of CVD-related deaths [61]. HTN is associated with over 50% of the cases of stroke and coronary heart disease. An association between CVD deaths and relatively low blood pressure was described, which further supports “the silent killer” paradigm of HTN [70].

Difficulties in developing treatments for NAFLD and HTN: from lifestyle modification to a combination drug strategy

There are challenges to optimizing the treatment strategies for both NAFLD and HTN to improve outcomes and prevent long-term complications. For NASH and HTN, an intervention targeting key environmental factors is required, and both require collaborative efforts from specialists in various medical fields as well as from primary care physicians.

There is no approved therapy for NASH at present [71]. The lack of a valid biomarker for both NAFLD and NASH makes it complex to monitor the effect of therapy on the disease. Hepatologists treating NASH can adopt some of the strategies developed over the last decades for HTN. These treatments are based on three major principles: (i) non-pharmacological management; (ii) a multi-drug combination regimen targeting different disease-relevant pathways; and (iii) a patient-tailored approach to therapy.

- i. Guidelines for non-pharmacological management are fundamental in the treatment of HTN. Weight reduction, reduced salt intake, increased dietary intake of fresh fruits and vegetables, increased low-fat dairy intake, physical activity and a reduction in saturated fat and cholesterol intake, along with regular fish intake are recommended for a healthy lifestyle change [7]. Most studies and recommendations suggest an association between salt intake and HTN, in which decreased salt intake has been proven to be effective in decreasing HTN over the years. However, the new “salt controversy” suggests that even “simple” lifestyle modifications are not always straightforward [9,72,73]. An important finding was the J-shaped relationship between salt intake, mortality and CVD events. Likewise, lifestyle modifications should be an important part of any therapeutic program in NASH, irrespective of the disease stage [64]. Weight loss can improve the histological changes of NAFLD and can also alleviate NASH [74]. Dietary counseling and regular exercise must be a necessary treatment strategy in all patients.
- ii. For HTN, effective implementation of a combination drug regimen, such as triple drug-based therapies, can control blood pressure in about 90% of patients [9]. HTN patients on multiple drugs have better blood pressure control than patients on monotherapy [75] and also have better protection against CVD. While the recommended combinations of therapies differ, they are all based on

variations of any two renin-angiotensin system blockers, calcium-channel blockers, and diuretics. The use of β -blockers as a major agent is still recommended in Europe. A step-by-step guide on how to manage the increased RH has been developed [7]. These guidelines are based on a large meta-analysis, which determined the effect of therapy on morbidity and mortality. The inferiority of low-dose thiazides was shown when compared with other drug classes and also compared with other diuretics [76]. An additional important factor in drug selection that may also be relevant for patients with NASH is the potential side effects; for example, higher-dose thiazides have fallen out of use because of their detrimental effects on potassium levels. The guidelines of the European Society of Hypertension, the American and International Society of Hypertension, and the Eighth Joint National Committee (JNC8) proposed the use of two drugs in combination to initiate therapy for a large proportion of patients [77]. The use of single-pill combinations of two antihypertensive agents is associated with considerably better adherence [78]. A recent study summarizing 68 randomized controlled HTN trials showed that lowering blood pressure significantly reduced major CVD outcomes independently of the agents used [79]. A significant risk reduction was observed in all stages of HTN.

- iii. Optimizing drug therapy for HTN needs to be done in a patient-tailored way. The effect of genetic loci and phenotypic features, including ethnicity, on a patient’s response to therapy should be considered. The patterns of response to treatment and the rate of complications in patients with HTN differ between White, Hispanic and African American patients [24]. All guidelines make an effort to differentiate the recommendations on the basis of age and ethnic group when they propose the use of combination therapies. Drug selection, however, varies among the different guidelines [80]. Patients with RH are a subgroup at high risk and a treatment regimen for these patients is being developed [81]. Both drug selection and treatment targets need to be patient-tailored in HTN. Previous guidelines suggested a target of 130/80 mmHg or lower for all patients with diabetes or chronic renal failure. Because of insufficient data, the targets were increased to 140/85 mmHg and 140/90 mmHg, respectively [82]. For patients over 60 years of age, the treatment threshold increases to 150/90 mmHg.

Like HTN, the treatment goals in patients with NAFLD should vary depending on the stage of the disease, the potential risk of progression and any comorbid diseases [64]. Patients with NASH should be targeted for treatment, especially if they have concomitant fibrosis, because they are more likely to develop cirrhosis and HCC than those without fibrosis [64].

Several of the drugs used for the treatment of HTN were shown to exert some beneficial effect in pre-clinical and small proof-of-concept clinical trials. These include losartan [83], pioglitazone in combination with candesartan [84], combined ursodeoxycholic acid and angiotensin-II type 1 receptor blocker [85], angiotensin-receptor blockers [86],

telmisartan [87], angiotensin II type 1 receptor blocker, and irbesartan [88].

The therapeutic methods being developed for NASH were recently reviewed [89]. Hepatic fat accumulation and metabolic stress are major targets for therapy using peroxisome proliferator-activator receptor agonists (e.g., pioglitazone, elafibranor, saroglitazar). Other drugs target the gut microbiome or the gut immune system [90]. Drugs targeting the bile acid-farnesoid X receptor axis (obeticholic acid), inhibitors of *de novo* lipogenesis (aramchol), incretins (liraglutide) and fibroblast growth factor (FGF)-21 and FGF-19 analogs are in various stages of development [89]. Another approach is targeting the inflammation underlying the disease using antioxidants (vitamin E), medications with a target in the TNF- α pathway (emricasan, pentoxifylline) and immune modulators (amlexanox, cenicriviroc, anti-CD3, anti-TNF [90,91]). Antifibrotics (simtuzumab and GR-MD-02) are also being tested with the aim of reversing the fibrosis process. Metformin revealed no biochemical or histological improvement and is not recommended [92]. Bariatric surgery is recommended for morbidly obese patients and leads to a significant improvement in liver histology and metabolic syndrome [3,93].

Several controlled trials have shown some benefits in patients with NASH. The PIVENS trial showed that vitamin E was superior to placebo for the treatment of NASH in adults without diabetes [94]; in the Flint trial, obeticholic acid improved the histological features of NASH [95]; the LEAN trial showed liraglutide to be safe and associated with histological resolution of several parameters of NASH [96]; in the Golden trial, GFT505, a dual agonist of the PPAR α and PPAR δ isoforms, showed some benefits in subsets of patients [97].

The potential risks of using some of these drugs may prohibit their long-term use in large populations of patients with NAFLD: pioglitazone is associated with weight gain [98]; obeticholic acid may lead to hyperlipidemia in a significant proportion of patients; and vitamin E is associated with potential long-term risks [4].

Development of a multi-step, patient-tailored drug combination treatment strategy for NASH

The best treatment for NASH is based on the three principles described above, combining a non-pharmacological approach with patient-tailored multi-drug combination therapy (Fig. 1). The drug combination needs to target inflammatory as well as fibrosis pathways. While resolution of inflammation may also contribute to the inhibition of fibrogenesis, direct antifibrotic drugs are required for reversal of existing liver damage.

Developing the personalized treatment protocols needed in a patient-tailored way is based on genomic, proteomic, metabolomic, lipidomic, and microbiome studies (Fig. 2). Identifying those patients left in the stage of simple steatosis, a benign condition, compared to those at risk for developing liver inflammation, fibrosis, cirrhosis and HCC, is essential [45].

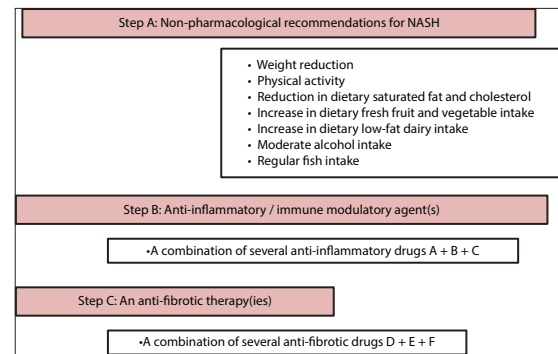


Figure 1 A schematic stepwise approach for the treatment of nonalcoholic steatohepatitis (NASH)

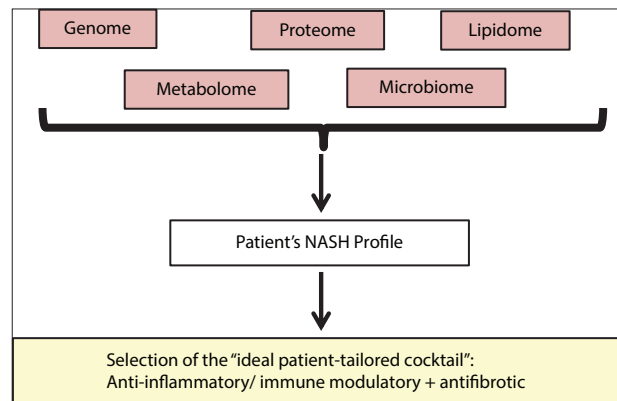


Figure 2 Selection of the ideal anti-inflammatory/immune modulatory and antifibrotic drug combination for patients with nonalcoholic steatohepatitis (NASH) based on a patient-tailored regimen

Analyzing the proteome of the liver mitochondria revealed a platform that distinguished NASH [99,100]. Over 550 proteins were identified in the NAFLD proteome, and several were found to be significantly up- and downregulated in NASH [99]. These include apolipoprotein E, insulin-like growth factor-binding protein 3, vitamin D-binding protein and lymphocyte cytosolic protein. These proteins are involved in fatty acid β -oxidation processes, lipid metabolic processes, cell-cycle arrest, cell polarity maintenance, and adenosine triphosphate/sex hormone metabolic processes [100]. Liver samples obtained from diabetic and non-diabetic morbidly obese subjects showed a decreased abundance of mitochondrial enzymes, proteins involved in methionine metabolism and a reduction in the oxidative stress response. Patients with T2DM exhibited decreased levels of glutathione, the antioxidant byproduct of methionine metabolism, via the transsulfuration pathway and a higher level of protein and lipid oxidative damage, along with alterations in detoxifying enzymes, carbohydrate metabolism, proteasome subunits and retinoic acid synthesis.

For metabolomics, proteins implicated in transportation, metabolic pathways, acute phase reactions, anti-inflammatory effects, the extracellular matrix, and the immune system are explored [45,101]. Profiling of metabolic products

using nuclear magnetic resonance spectroscopy and mass spectrometry combined with statistical modeling and top-down systems biology identified metabolic signatures in NAFLD [102]. A small-molecular screen of human liver tissue showed that hydroquinone and nicotinic acid were inversely correlated with histological NAFLD severity [103]. γ -Glutamyl dipeptides may differentiate between NASH and simple steatosis. A non-targeted metabolomics approach to the plasma from morbidly obese patients undergoing bariatric surgery detected differences between patients with or without NAFLD. Accumulation of lipids in hepatocytes is linked with α -ketoglutarate, decreased β -oxidation energy production, reduced liver function, and altered glucose metabolism [104]. Plasma α -ketoglutarate levels distinguish between those with or without NAFLD. Assessment of the bile acid metabolome indicated a higher total serum bile acid concentration in NASH. Increased taurine- and glycine-conjugated primary and secondary bile acids were identified [105]. The metabolome is also able to identify patients likely to respond to therapy such as vitamin E. At baseline, phenyl-propionic acid and indole-propionic acid levels were directly connected with a subsequent histologic response to vitamin E treatment, while γ -carboxyethylhydroxychroman levels were inversely related to the response. The end-of-treatment levels of γ -glutamyl leucine and γ -glutamyl valine were lower in vitamin E respondents.

Lipidomic studies characterized the potential relationships between lipotoxicity, inflammation, oxidative stress, and cellular function [106]. Lipidomic data from the portal and systemic blood defined a NASH signature [107]. Increased concentrations of several glycerophosphocholines, glycerophosphoethanolamines, glycerophosphoinositols, glycerophosphoglycerols, lyso-glycerophosphocholines and ceramides were detected in the systemic circulation of NASH subjects. Analysis of lipids from the portal system at the time of surgery revealed limited lipid alterations compared with the systemic circulation, but glycerophosphoethanolamines (PE), and, glycerophosphoglycerols (PG) classes were significantly increased in NASH subjects [107]. Lipid species may also serve as markers of advanced liver disease. An increase in diacylglycerols was demonstrated in NAFLD, supporting their role in the progression of NAFLD and liver fibrosis [108]. Lipid-modifying enzymes used in converting saturated fatty acids to monounsaturated fatty acids are relevant for the development of HCC [109-111]. Increased ratios of long-chain n6-polyunsaturated fatty acids over n3-polyunsaturated fatty acids are a risk factor for both NASH and HCC [112,113].

Dysbiosis and the gut-microbiota-liver network determine the phenotype in patients with NAFLD [114]. The transfer of gut microbiota from lean and obese individuals induced the metabolic features of the donor in the recipients. Bidirectional interactions of the gut microbiota, including with food, bile and the intestinal epithelium, are associated with the progression from steatosis to steatohepatitis, fibrosis, and cancer [115]. Caloric extraction from the diet, intestinal epithelial damage and entry of bacterial components into the portal circulation are important contributors to innate activation, liver inflammation and fibrosis [116]. Gut microbiota-linked

compounds, including short-chain fatty acids, bile acids, choline metabolites, indole derivatives, vitamins, polyamines, lipids, neurotransmitters, neuroactive compounds, and hypothalamic-pituitary-adrenal axis hormones, are additional factors [117]. Serum lipid levels of phospholipids, free fatty acids, polyunsaturated fatty acids, especially eicosapentaenoic acid, arachidonic acid, and docosahexaenoic acid, correlate with specific fecal flora. Cytokines, amino acids, vitamins, and fatty acid metabolism also correspond with gut microbiota [117].

The use of a combination of proteome- and/or metabolome- and/or lipidome- and/or microbiome-based data can serve to tailor selected therapies to the appropriate patients in order to increase response rates and avoid exposing patients with low response potential to unnecessary side effects.

Concluding remarks

Although an effort has been made over the last two decades to understand the natural history and pathogenesis of NAFLD and NASH and to develop noninvasive diagnostic measures, there is still no approved therapy for NASH [4]. Moreover, it appears that the therapies developed to date are unlikely to provide a “one-pill” type of treatment for NASH. The development of patient-tailored “HTN-like” therapy protocols is suggested as a way to offer therapy to patients with different risk levels and this should be our goal for the near future.

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