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Introductory Chapter: Nonalcoholic Fatty Liver Disease - What Should We Know?

Emad Hamdy Gad and Yasmin Kamel

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is considered a major challenge because of its prevalence, difficulties in diagnosis, complex pathogenesis, and lack of approved therapies. It will become the main cause of chronic liver disease in adults and children and the leading indication for liver transplantation (LT) in the next decades replacing hepatitis C virus (HCV) infection [1]. It is characterized by excessive hepatic fat accumulation, associated with insulin resistance (IR), where liver pathology shows steatosis in >5% of hepatocytes or a proton density fat fraction >5.6% assessed by proton magnetic resonance spectroscopy (1HMRS) or quantitative fat/water selective magnetic resonance imaging (MRI) [2]. It represents a group of conditions ranging from simple asymptomatic liver steatosis (nonalcoholic fatty liver (NAFL)) (known by imaging or histology) to cirrhosis (nonalcoholic steatohepatitis (NASH) or cryptogenic), end stage liver disease (ESLD), and hepatocellular carcinoma (HCC), passing through nonalcoholic steatohepatitis (NASH), which is characterized by the presence of apoptosis, ballooning, inflammation, and fibrosis with the absence of secondary causes of hepatic fat accumulation such as significant alcohol consumption or viral infection [3]. In the majority of patients, NAFLD is commonly associated with metabolic comorbidities such as obesity, type 2 DM (T2DM), and dyslipidemia. So it became common after increased prevalence of these comorbidities [4].

Our book discusses some new topics related to NAFLD, where we divided it into four sectors: the first sector includes introductory chapter about NAFLD; the second sector contains experimental work related to the disease, while the third sector discusses diseases related to NAFLD; and finally the fourth sector includes a new noninvasive tool to diagnose NAFLD. The book gives hints regarding NAFLD prevalence, etiology, pathogenesis, pathology, diagnosis, and treatment.

This introductory chapter discusses the recent updated data on the prevalence, natural history, pathophysiology, pathology, diagnosis, and treatment of the disease.

2. Natural history and disease progression

NAFLD prevalence in general population ranges between 13.48 and 31.79% differing according to diagnostic method, age, sex, and ethnicity [5, 6], while NASH prevalence in the general population ranges between 1.5 and 6.45% [5]. It is a slowly progressive disease [7]. Patients with histological NASH, especially those with some

degree of fibrosis, are at higher risk for disease progression and adverse outcomes such as decompensated cirrhosis, HCC, LT, or liver-related mortality [5, 8].

3. Pathogenesis

NAFLD is tightly associated with IR not only in the liver but also in muscle and adipose tissues and also with metabolic syndrome (MetS), defined as the cluster of any three of the following five features associated with IR: impaired fasting glucose (IFG) or T2DM, hypertriglyceridemia, low high-density lipoprotein (HDL), increased waist circumference (WC), and high blood pressure. So, the presence of MetS in any given patient should lead to an evaluation of the risk of NAFLD and vice versa [9].

A high-calorie diet, saturated fats, and a high fructose intake have been associated with obesity and NAFLD [10]. It is documented that visceral obesity is one of NASH predictors; it is associated with insulin resistance, oxidative stress, inflammatory cascade, and overflow of portal triglycerides [11, 12]. So, follow-up of the disease and its progression is mandatory in obese persons.

T2DM is associated with NAFLD severity, NASH development, advanced fibrosis, and HCC [13]. It is also related to IR, obesity, dyslipidemia, and elevated liver enzymes [14].

Recently, multiple parallel hits are responsible for NAFLD pathogenesis and progression (i.e., impaired mitochondrial adenosine triphosphate (ATP) activity [15], depletion of mitochondrial glutathione [16, 17], hypoxia associated with impaired blood flow or obesity-related obstructive sleep apnea [18], dysregulated adipokine production [19], the effects of a high fructose diet [20], and rapid weight loss [21]).

However, hepatic iron is a source of oxidative stress and hepatocyte dysfunction; its role in NAFLD and NASH remains controversial [22].

Both animal and human studies support the concept that the hepatocellular injury in NAFL persons that lead to NASH is caused by overload of primary metabolic substrates (glucose, fructose, and fatty acids) in the liver, resulting in diversion of fatty acids into pathways that promote cellular injury and dysfunctional response to that injury [23, 24].

In human models and in the setting of established IR and a diet high in saturated fats, hepatic traffic of excess free fatty acids (FFA) induces hepatocyte injury via lipotoxicity, caused by oxidative stress through the generation of lipotoxic metabolites (such as ceramides, diacylglycerols, and lysophosphatidyl choline) and reactive oxygen species (ROS) [25]. However, in animal models, the oxidative stress that occurs in the setting of obesity-related IR and lipotoxicity is central to hepatocyte injury and is critical to the pathogenesis of NASH [26].

It is documented that lipotoxicity leads to hepatic cell injury and death, via apoptosis and/or necrosis, and this is an important driver of inflammation, NASH, and fibrosis [27, 28]. Oxidative stress is a major driver of hepatocyte senescence that represents a cellular stress response and an irreversible cell cycle arrest aimed to limit the proliferation of damaged cells and subsequent tumor development. Furthermore, senescent cells can mediate NAFLD progression via the active secretion of pro-inflammatory factors that affect the microenvironment, and this represents the adoption of a “senescence-associated secretory phenotype” (SASP) [26]. In NASH, the inflammatory response includes both the innate and adaptive immunity; the cascade begins with hepatocyte injury in the setting of IR and lipotoxicity and is propagated by cellular apoptosis, culminating with the activation of hepatic stellate cells (HSCs) and ensuing fibrosis [26].

In short, the pathogenesis of NASH goes as follows: Hepatocytes are affected by lifestyle factors as a high saturated fatty acid (SFA) diet, obesity, IR, and hepatic steatosis; these multiple parallel metabolic hits lead to cellular damage, via a process called “lipotoxicity,” involving excessive oxidative stress principally driven by the lipotoxic metabolites of SFA. Injured hepatocytes release damage-associated metabolic patterns (DAMPs) that initiate an inflammatory response, predominantly via toll-like receptors (TLRs) and activate pro-inflammatory signaling pathways in the setting of increased adipokine levels. Furthermore, injured hepatocytes undergo necrosis, apoptosis, and senescence that have a great role in disease progression. Direct recruitment of Kupffer cells (KC) and other components of the innate immune response occurs with activation of the inflammasome and the coordinated release of pro-inflammatory and pro-fibrogenic cytokines and ligands (e.g., Hh, OPN). Also, KC promotes a pro-inflammatory microenvironment that initiates adaptive immune response. HSC are subsequently activated to produce extracellular matrix leading to progressive fibrosis, cirrhosis, and its complications (e.g., HCC). Engulfment of apoptotic bodies and factors produced by senescent cells (SASP) can also influence HSC activity directly [26].

4. Diagnosis

NAFL encompasses (a) steatosis alone; (b) steatosis with lobular or portal inflammation, without ballooning; or (c) steatosis with ballooning but without inflammation. The diagnosis of NASH requires the joint presence of steatosis, ballooning, and lobular inflammation. So, liver biopsy is essential for its diagnosis [29]. Biopsy should give comment on steatosis severity (mild, moderate, or severe). Specific scoring systems such as NAFLD activity score (NAS) and/or steatosis activity fibrosis (SAF) may be appropriate. Moreover, the presence or absence of fibrosis should be described (stage 1 is zone 3 (perivenular or perisinusoidal fibrosis) or periportal fibrosis, stage 2 is both zone 3 and periportal fibrosis, stage 3 is bridging fibrosis with nodularity, and stage 4 is cirrhosis) [5]. Because of liver biopsy invasive nature, sampling errors, cost, and its related morbidity and mortality and noninvasive tools to detect NAFL and NASH were thoroughly studied and developed. They have the following advantages: (i) identification of the risk of NAFLD in people with high metabolic risk in primary care settings, (ii) identification of those with worse prognosis (i.e., severe NASH) in secondary and tertiary care settings, and (iii) disease progression and therapeutic response monitoring [2]. US, computed tomography (CT), and MRI are noninvasive diagnostic methods of moderate and severe steatosis, and they can provide additional hepatobiliary information; hence, they should be performed as first-line diagnostic tools for steatosis [2]. Moreover, MRI, either by spectroscopy (MRS) or by proton density fat fraction (PDFF), is a good noninvasive tool for quantifying steatosis [5]; furthermore, the best-validated steatosis scores are the fatty liver index (FLI) and the SteatoTest and the NAFLD liver fat score; they variably predict metabolic, hepatic, and cardiovascular outcomes [2]. Regarding NASH, clinical, biochemical, and imaging measures cannot distinguish it from steatosis. However, cytokeratin-18 fragments (CK-18), which are generated during cell death or apoptosis, have modest accuracy for the diagnosis of NASH (66% sensitivity, 82% specificity) [5, 30]. Clinical decision aids (e.g., NAFLD fibrosis score (NFS), FIB-4 index, aspartate aminotransferase [AST] to platelet ratio index [APRI]), serum biomarkers (enhanced liver fibrosis [ELF] panel, fibrometer, FibroTest, and Hepascore), or imaging (e.g., vibration controlled transient elastography (VCTE; FibroScan), MR elastography [MRE], acoustic radiation force impulse imaging, and supersonic shear wave elastography)

are acceptable noninvasive procedures for the identification of cases with advanced fibrosis or cirrhosis; furthermore, their combination might confer additional diagnostic accuracy, and monitor disease progression, saving a number of diagnostic liver biopsies [5].

5. Treatment

It is considered that NAFLD treatments are limited; as the pathogenesis of NASH (as discussed above) involves the complex interaction of cellular responses to chronic injury, furthermore, the development of the disease over many years cannot be easily repaired with short-term intervention (most updated studies have involved short-term treatment only); moreover, NAFLD is thought to be a heterogeneous disease [26]. The management of NAFLD should consist of treating liver disease as well as the associated metabolic comorbidities such as obesity, hyperlipidemia, IR, and T2DM [5].

NAFLD can be treated with lifestyle changes (i.e., healthy diet and habitual physical activity) as weight loss results in improvement of liver enzymes and histology (steatosis, hepatocyte ballooning, and necroinflammation) and healthy diet improves IR; moreover, both aerobic exercise and resistance training reduce liver fat with no need for drug therapy if there is no NASH or fibrosis [31, 32]. However, successful treatment of NASH should improve outcomes, i.e., decrease NASH-related mortality, and reduce progression to cirrhosis or HCC [2]; this can be achieved with drug therapy that is indicated for progressive NASH (bridging fibrosis and cirrhosis), for early-stage NASH with increased risk of fibrosis progression (age > 50 years; diabetes, MetS, increased ALT) [33], and for active NASH with high necro-inflammatory activity [34].

The oxidative stress from lipotoxicity has a central role in disease progression, and therefore, the use of antioxidants and other approaches to limit this oxidative stress was considered. In some studies, vitamin E (800 IU/day) as an antioxidant improved steatosis, inflammation, and ballooning and induced resolution of NASH [35]. It may be used in non-cirrhotic nondiabetic NASH patients, but further studies are needed before making firm recommendations.

Ursodeoxycholic acid (UDCA) has been investigated in several RCTs as a treatment for NASH at different doses for up to 2 years with some biochemical improvement without any histological effect [36–38]. Recently, a negative correlation was shown between the degree of coffee intake as antioxidant and fibrosis stage in NASH. However, the role of phlebotomy in management of NASH by decreasing hepatic iron overload and its oxidative stress effect is still controversial. On the other hand and despite being under study, newer approaches for managing NASH were developed (pentoxifylline, infliximab, NK inhibitors, STAT3 blockade, and anti-CD3 therapy); they aimed at affecting the intercellular mechanisms that have a role in the pathogenesis of NASH. Also, the use of specific medical therapies that are effective in patients with metabolic comorbidities (e.g., insulin sensitizing agents (pioglitazone), statins, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers) has also been tried in patients with NASH with promising results [26].

Bariatric surgery decreases liver fat and NASH progression by treating obesity, IR, and diabetes; prospective data showed an improvement in histological NASH lesions, including fibrosis [39–41].

Lastly, LT is an accepted procedure in NASH patients with ESLD, liver failure, or HCC with comparable overall survival to other indications, despite a higher cardiovascular mortality [42, 43].

Finally, I think the book will give readers important knowledge regarding NAFLD.

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