Digestive and Liver Disease 49 (2017) 471–483

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Position Paper

# AISF position paper on nonalcoholic fatty liver disease (NAFLD): Updates and future directions☆

The Italian Association for the Study of the Liver (AISF)

ARTICLE INFO

*Article history:*
Received 29 December 2016
Received in revised form 8 January 2017
Accepted 10 January 2017
Available online 23 January 2017

*Keywords:*
Diagnosis
Epidemiology
Genetics
Management
Natural history
Physiopathology

ABSTRACT

This review summarizes our current understanding of nonalcoholic fatty liver disease (NAFLD), a multifactorial systemic disease resulting from a complex interaction between a specific genetic background and multiple environmental/metabolic "hits".

The role of gut microbiota, lipotoxicity, inflammation and their molecular pathways is reviewed in-depth. We also discuss the epidemiology and natural history of NAFLD by pinpointing the remarkably high prevalence of NAFLD worldwide and its inherent systemic complications: hepatic (steatohepatitis, advanced fibrosis and cirrhosis), cardio-metabolic (cardiovascular disease, cardiomyopathy, arrhythmias and type 2 diabetes) and neoplastic (primary liver cancers and extra-hepatic cancers).

Moreover, we critically report on the diagnostic role of non-invasive biomarkers, imaging techniques and liver biopsy, which remains the reference standard for diagnosing the disease, but cannot be proposed to all patients with suspected NAFLD.

Finally, the management of NAFLD is also reviewed, by highlighting the lifestyle changes and the pharmacological options, with a focus on the innovative drugs.

We conclude that the results of ongoing studies are eagerly expected to lead to introduce into the clinical arena new diagnostic and prognostic biomarkers, prevention and surveillance strategies as well as to new drugs for a tailored approach to the management of NAFLD in the individual patient.

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## 1. Introduction

Nonalcoholic fatty liver disease (NAFLD) has prompted a growing clinical and research interest over the last 25 years. Paramount information has progressively accumulated on the genetics and behavioral risk factors for disease development and progression [1,2], on hepatic and extra-hepatic complications [3,4] and on putative treatment strategies [5,6]. Nevertheless, the burden of disease is still increasing, mainly due to the rising tide of obesity and type 2 diabetes mellitus (T2DM) epidemics ("*diabesity*") and the lack of effective treatment options. NAFLD which, in a closed loop fuels the "*diabesity*" epidemics [7], may start very early – even in utero [8,9] – and the longer the exposure, the higher the risk to develop an advanced disease and its complications [10].

So, what can be done to halt the development or reduce this burden of disease? European clinical guidelines on the management of NAFLD have been recently published by the three sister societies of Liver Disease, Diabetes and Obesity [11]. At the time of publication of such guidelines, the participating Experts raised considerable concern about the difficulties expected in conducting universal screening and appropriate surveillance strategies and follow-up in such a potentially huge population of individuals. Indeed, the number of individuals at risk seems too large to be affordable by the National healthcare systems, but selection criteria do not guarantee satisfactory sensitivity and specificity to identify disease progression [12]. Surrogate, non-invasive markers of NAFLD can be used for their negative predictive value to spare patients from undergoing liver biopsy; however, their results may assist physicians in dictating the prognosis, not in guiding treatment strategies, given that validated pharmacological interventions are lacking [13].

Disease control may, therefore, only be achieved by appropriate societal interventions aimed at keeping at bay the behavioral risk factors also involved in the pathogenesis of "*diabesity*". Nonalcoholic steatohepatitis-cirrhosis (NASH-cirrhosis)

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☆ Report of 2015 AISF Monothematic Conference on NAFLD.

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http://dx.doi.org/10.1016/j.dld.2017.01.147
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and NASH-hepatocellular carcinoma (NASH-HCC) are only the "*tip of the iceberg*" of the unhealthy consequences of non-communicable diseases [14].

Against this background, this updated position paper aims to summarizing the chief topics discussed during the Associazione Italiana per lo Studio del Fegato (AISF) Single Topic Conference on NAFLD held in Modena (October 8–10, 2015) in memory of late Professor Paola Loria, who was the Coordinator of the first AISF clinical practice guidelines for management of NAFLD [15].

## 2. Pathophysiology of NAFLD

### 2.1. Pathogenesis

NAFLD is a multi-factorial disease resulting from a complex interaction of environmental "hits" and a genetic background (Fig. 1). A high-calorie diet, often coupled with a sedentary behavior, contribute to the development of NAFLD, both directly and via weight gain. Dietary excess of saturated fats and refined carbohydrates has been associated with NAFLD and a high fructose intake may increase the risk of NASH [16,17]. Development and progression of NAFLD are strongly associated with insulin resistance (IR) and metabolic syndrome (MetS) components, particularly abdominal obesity and T2DM [18]. The most common cause of NAFLD is an altered whole-body energetic homeostasis, due to caloric intake exceeding caloric expenditure, with consequent spillover of extra-energy in the form of non-esterified fatty acids (NEFA) from visceral adipose tissue into ectopic fat depots, such as the liver, skeletal muscles and pancreas [19]. NAFLD will invariably develop when the rate of hepatic triglyceride flowing to the liver via the bloodstream or synthesized within the liver exceeds the rate of hepatic triglyceride oxidation and VLDL secretion into the bloodstream [19]. Approximately 60% of hepatic lipids derives from increased peripheral lipolysis of triglycerides (due to adipose tissue IR and failure to adequately suppress peripheral triglyceride lipolysis), while dietary fats and sugars contribute approximately 35–40% [20]. The liver itself may also contribute to steatogenesis by synthesizing triglycerides from dietary carbohydrates through de novo lipogenesis. The contribution of de novo lipogenesis to liver fat content is less than 5% in healthy subjects and may increase to approximately 25% in NAFLD patients [20]. Intra-hepatocytic accumulation of diacylglycerol intermediates impairs hepatic insulin signaling and fuels gluconeogenesis, so promoting hyperglycemia and predisposing to the development of T2DM [21]. Increased amounts of circulating and intracellular NEFAs are also associated with an increase in nuclear factor kappa-B (NF-κB), eventually leading to the expanded and dysfunctional adipose tissue overproducing multiple pro-inflammatory cytokines and under-producing anti-inflammatory adipokines, such as adiponectin which, collectively, may further dictate NAFLD progression [22,23].

### 2.2. Lipotoxicity and inflammation

As shown in Fig. 1, NASH progression results from numerous events originating within the liver and in distal organs, including the visceral adipose tissue and the gastrointestinal tract [24]. Fat-induced damage to the hepatocytes (lipotoxicity), is more linked to the abundance of specific toxic compounds, such as NEFAs and ceramides, than to the total amount of stored fat [25]. Evidence from genetic studies, on the other hand, suggests that the amount of fat accumulation is important [26]. Toxic lipids can determine cell injury through a variety of mechanisms, including increased oxidative stress and mitochondrial dysfunction. Saturated fatty acids are increased in NASH [24,25] and induce inflammation and hepatocyte apoptosis by activating Jun N-terminal kinase (JNK) and mitochondrial pathways [27]. Free cholesterol is a prominent mechanism for NASH development and progression. Interestingly, necroptosis has been recently described as a cell death mechanism potentially involved in lipotoxicity, which is morphologically comparable to necrosis, though characterized by definite biochemical pathways [28].

Endoplasmic reticulum (ER) stress also takes part in NASH pathogenesis, as the result of the induction of the unfolded protein response, which is an adaptive mechanism potentially triggering apoptosis. JNK, an activator of inflammation and apoptosis implicated in NAFLD progression, is one of the major mediators of ER stress [29]. Hypoxia perturbs lipid homeostasis and insulin signaling pathways. Moreover, reduced oxygen availability induces secretion of pro-inflammatory cytokines [30]. These adverse effects are mediated by two hypoxia-inducible transcription factors (HIF-1α and HIF-2α), which regulate cellular response to oxygen deficiency and can be activated by additional stimuli involved in NASH, including oxidative stress or inflammatory signals [30].

Chronic inflammation is a key factor in NASH pathogenesis. Kupffer cell activation occurs at an early stage, and precedes the recruitment of other cells. Attention has been paid to the different phenotypes of Kupffer cells, i.e., M1 and M2, considered primarily immuno-regulatory [31]. Hepatocyte death is a strong trigger of inflammation and fibrosis, through signaling pathways that include tumor necrosis factor (TNF)-related apoptosis-inducing ligand receptor, Fas and TNF receptor, and promote the expression of several cytokines and chemokines. Differentiation toward a pro-inflammatory 'M1 phenotype' is driven by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) interacting with toll-like receptors (TLR), and induces expression of pro-inflammatory factors, such as interleukin (IL)-1β, IL-12, TNF-α, and chemokines CCL2 and CCL5 [32]. Remarkably, chemokines such as CCL2 and CCL5 may induce hepatic stellate cell activation, triggering fibrogenesis. Besides resident and infiltrating macrophages, the role of other inflammatory cells, such as neutrophils, lymphocytes, NK cells and dendritic cells is actively being evaluated [24].

TLRs recognize endogenous danger signals, such as DAMPs or PAMPs [32]. TLR-induced pathways play a central role in the activation of hepatic cells, primarily Kupffer cells, but also hepatocytes and stellate cells. TLR2 interacts with multiple PAMPs, which are increased in NAFLD, and its inhibition prevents hepatic/systemic IR in high-fat diet–fed mice [32]. TLR9 is activated by unmethylated DNA, typically expressed in viruses and bacteria but rare in mammalian cells. TLR9 downstream signaling involves IL-1, and is associated with NASH severity and fibrosis. The pivotal role of TLR4 in the pathogenesis of NASH has been shown in TLR4-deficient mice that display lower levels of inflammation and fibrosis. TLR4 is primarily activated by bacterial lipopolysaccharide, triggering expression of cytokines and chemokines (e.g., TNF-α, IL-1β, IL-6 and IL-12) [33]. Reactive oxygen species are also induced in TLR4-activated Kupffer cells. TLR4 is expressed by other hepatic cells, including stellate cells and hepatocytes, where TLR-4 exerts actions relevant for the pathogenesis and progression of NAFLD toward fibrosis [33]. TLR4-mediated inflammatory responses can also be elicited by DAMPs released by necrotic cells, such as high mobility group box-1 [34].

The NOD-like receptors (NLR), which participate in the assembly of inflammasomes (multi-protein complexes required for initiation of inflammatory signals) play a major role in NASH pathogenesis. Activation of the inflammasome is induced by TLRs together with signals linked to cellular damage, e.g., uric acid, reactive oxygen species or adenosine triphosphate, and results in the secretion of mature IL-1 and IL-18. A role for NLRP3 inflammasome in NAFLD development and progression

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