Editorial

Non-alcoholic fatty liver disease: beyond the liver is an emerging multifaceted systemic disease

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Non-alcoholic fatty liver disease (NAFLD) has become the most frequent liver disease in the world and is characterized by an accumulation of intrahepatic triglycerides above 5% of hepatocytes in the absence of significant alcohol use and other causes recognized to induce fatty liver (1). Its prevalence is increasing, reflecting the global epidemic of obesity and type 2 diabetes (T2D). Although NAFLD occurs in all age groups, its peak is observed in individuals over 60 years of age. Men are more likely to develop NAFLD, but this predisposition disappears in diabetic patients (2). In the general population, the prevalence of NAFLD is reported in a wide range from 6.3% to 51%, with an average global prevalence of 25% (3). This wide variability depends on the diagnostic method used and the population and ethnic group studied. Ultrasonography, the most frequently used diagnostic tool, is operator-dependent and less sensitive than MR spectroscopy, which is expensive and not available in all facilities. Furthermore, the occurrence of NAFLD varies in different countries, with the highest prevalence reported in the Middle East and South America and the lowest in Africa (3); in Europe and the United States it is reported in 25–30% of subjects (3). However, the prevalence of NAFLD increases up to 80–90% in cohorts of subjects with dysmetabolic conditions such as overweight/obesity, T2D and metabolic syndrome (MetS) (2), emphasizing the primary role of metabolic factors in its development. It has been shown that NAFLD occurs in 10–15% of normal-weight subjects (4) in whom the disease can remain undiagnosed over a long period of time. Recent studies have shown that even lean subjects with NAFLD have excess visceral adiposity and some features of MetS (4), and such patients are often referred to as "metabolically obese, normal weight".

The data accumulated in recent years have substantially changed the pathogenic concepts of NAFLD that had dominated the scene over the last 30 years (2). The previous "two-hits" pathogenic theory, in which insulin resistance (IR), a feature of NAFLD, acted as a "first hit" inducing the deposition of fatty liver, predisposing to further insults that acted as a "second hit" promoting the progression of liver damage, has proved too simplistic and is now being replaced by a more complex multifactorial model that emphasizes the various pathways involved in the same hepatic injury (2). As a result, NAFLD emerges from a complex multi-factorial interaction between multiple environmental and metabolic "hits" and a genetic background, and therefore a hypothesis of "multiple parallel hits" is more appropriate to summarize the complexity of the pathogenesis of NAFLD (2). This hypothesis brings together the many concomitant events occurring in NAFLD as an unhealthy lifestyle, characterized by a sedentary lifestyle and high-calorie diet, IR, hormones and pro-inflammatory cytokines released by adipose tissue, hepatic over-expression of pro-inflammatory cytokines/chemokines and oxidative stress, changes in the composition of the intestinal microbiota, environmental, epigenetic and genetic factors (2). Among the single

nucleotide genetic polymorphisms, the protein 3 containing patatin-like phospholipase (PNPLA3), the trans-membrane 6 super-family 2 (TM6SF2) and the gene containing 7 domains of O-acyltransferase bound to the membrane (MBOAT7) are considered to play a significant role both in the development of fatty liver and in the progression of liver injury (2).

The diagnostic approach of NAFLD has also changed substantially in recent years. Currently, physical and chemical non-invasive biomarkers are available for the evaluation of NAFLD (2,5) and this allows to reserve liver biopsy for selected cases (6). In the latter case, new histological classifications have been proposed to better evaluate the severity of the disease (2,7).

NAFLD is a major cause of liver-related morbidity and mortality (2) causing a wide spectrum of liver disorders ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (HCC). Simple steatosis can evolve in NASH (8) and both conditions can evolve into cirrhosis, but in the case of simple steatosis it has been estimated that the duration of the disease could be 50–60 years, while the evolution in the case of NASH takes about 20–30 years (8). In patients with NAFLD, the annual incidence of HCC is 0.44 per 1,000 person/year and, of interest, about 50% of cases occur in the absence of cirrhosis (3,9). In addition, NAFLD has become a major cause of liver transplantation for both cirrhosis and HCC. Despite the impressive clinical impact of NAFLD on liver disease, it would be extremely reductive to limit the disease to this organ. Liver damage appears to be only one side of a complex, multifaceted systemic condition. IR not only participates in the progression of liver disease but also promotes the development of T2D. Currently, there are indisputable data on the close relationship between NAFLD, MetS and T2D as well as the concept of their bidirectional cause-effect relationship; in other words, NAFLD is not only a consequence, but also a cause of T2D and MetS (2).

In the recent literature, an extremely high and heterogeneous spectrum of clinical conditions associated with NAFLD has been reported. On this basis, the question arises whether NAFLD is an independent risk factor for all or part of the associated conditions, and therefore should be considered a multisystem disease, or whether NAFLD can be considered a bystander sharing common etiological factors. The question remains to be clarified, at least for a certain number of associations. The review published in a recent issue of *Gut*, by Adams *et al.* (10) provided further information on the relationship of NAFLD and cardiovascular disease (CVD) and other extrahepatic diseases, reinforcing the concept that NAFLD is a multisystem disease (10). The authors have reviewed critically the main and most significant works, in particular on the association NAFLD and CVD, chronic kidney disease (CKD), T2D, adenomas/colorectal cancer and other extrahepatic neoplasms, and osteoporosis, also examining the putative mechanisms involved. The extensive revised literature (10), consisting of case-control studies, population-based cohort studies, retrospective and prospective studies and meta-analyses, showed a compelling association between NAFLD and the conditions above. In particular, a strong association of NAFLD with CVD, CKD and T2D has been demonstrated. In addition, increased frequency of gallstones, psoriasis, hypothyroidism, sleep apnea and polycystic ovary syndrome have been reported in NAFLD (2).

The NAFLD and MetS association means that these patients typically exhibit atherogenic dyslipidemia with an increased cardiometabolic risk. A close association between NAFLD and numerous subclinical atherosclerosis markers has been reported; independently of the classic CVD risk factors, an increased risk of calcification of the coronary arteries, intima-media thickness, arterial stiffness, atrial fibrillation and aortic valve sclerosis, as well as an altered flow-mediated vasodilation was demonstrated (10,11). Furthermore, there is compelling evidence that CVD is a major clinical problem in NAFLD and that patients with NAFLD have a significant increase in CVD-related death compared to that related to liver disease. Based on the extensive data analyzed, there appears little doubt about a close association between NAFLD and an increased prevalence and incidence of CVD (10). This has important clinical implications that could influence the therapeutic prevention strategies, and patients with NAFLD should also be screened for CVD.

CKD appears to be closely associated with NAFLD even after adjustment for hypertension, T2D and other CKD risk factors. The prevalence of CKD among patients with NAFLD is reported with a range between 20% and 55%, while among those without NAFLD it is 5–30% (10).

The prevalence of NAFLD is of 70–80% among patients with T2D, while patients with NAFLD showed a 2- to 5-fold risk of developing T2D after adjustment for metabolic confounding factors (2,10). There are common epidemiological conditions, risk factors and natural history between NAFLD and T2D, such as overweight and

obesity, high calorie diet and sedentary lifestyle, IR and MetS components (2). On this basis, it is not clear whether NAFLD is causally responsible for the development of T2D or is simply a marker of other shared risk factors. However, screening in patients with NAFLD for T2D is recommended.

A robust association between NAFLD and extrahepatic neoplasia has been reported, in particular with colorectal adenoma and cancer. To be underlined is that mortality for malignancies is the second leading cause of death in patients with NAFLD (12).

The recent extensive literature on NALFD emphasizes that it is an emerging multiform systemic disease with a high epidemiological load, which makes screening of the general population impossible. In addition to the risks of liver disease, NAFLD also influences cardiovascular, metabolic, renal, endocrine systems and cancer development with a significant morbidity and hepatic and extrahepatic mortality. It is universally accepted that dietary changes (13) and physical activity (14) are the basis for the treatment of NAFLD, a condition in which no drug is specifically authorized for its treatment. A 3–5% weight loss will improve steatosis; however, 5–7% reductions are needed to reduce the hepatic inflammatory status and 7–10% to achieve NAFLD remission and fibrosis regression (13-15). It has also been shown that an improvement in NAFLD has a positive impact on the incidence of extrahepatic conditions. A selective screening strategy should be performed for high risk subjects for whom early and more aggressive treatment programs should be implemented.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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