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Nonalcoholic Fatty Liver Disease – A Growing Public Health Problem

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Twenty five years ago, researchers were skeptical of whether nonalcoholic fatty liver disease (NAFLD) was actually a clinical condition. Along with tremendous progress in antiviral agents and treatment strategies, a vigorous national vaccination program for hepatitis B has resulted in a gradually decreasing prevalence of endstage liver disease caused by chronic viral hepatitis. Despite this, with the increasing prevalence of obesity, type II diabetes mellitus (T2DM), insulin resistance and hypertension, NAFLD has become the most common cause of chronic liver disease (CLD) and increasing socioeconomic cost for managing CLD in many developed countries worldwide. NAFLD also has reached epidemic proportions among populations typically considered at low risk, with a prevalence of 15% in China and 14% in Japan. NAFLD is strongly associated with all components of metabolic syndrome (MS) and has been considered as the liver manifestation of the MS. This entity encompasses simple liver steatosis, necroinflammation with varying stages of fibrosis known as nonalcoholic steatohepatitis (NASH), and cirrhosis. Compared with the general population NAFLD increases the risk of endstage liver disease, hepatocellular carcinoma (HCC), as well as liver-related and all-cause mortality.[1-8] A subset of patients with NAFLD have the progressive form of liver disease i.e. NASH which can lead to the development of cirrhosis and its complications, including HCC, especially if metabolic risk factors deteriorate.[5, 6, 9,10] According to the recent review published in JAMA, 66% of patients older than 50 years with T2DM or obesity are thought to have NASH with advanced fibrosis.[2] The incidence of NAFLD–related HCC is increasing and up to 50% of cases may occur in the absence of cirrhosis.[2, 3]

Moreover, recent findings imply that, contrary to current dogma, simple steatosis can progress to NASH and clinically significant fibrosis therefore the majority of NAFLD patients are at risk of progressive liver disease in the longer term.[11]

Based on data from the USA adult liver transplantation (LTs) databases, since 2004 the number of adults with NASH awaiting LTs has almost tripled and today NASH is the second leading etiology of CLD among adults awaiting LTs in the USA.[7] Because of the epidemic of NAFLD, NASH related cirrhosis is anticipated to become the leading indication for LTs within the next one or two decades.[8]

During the last decade, it has been shown that the global health burden of NAFLD is confined not only to potentially progressive liver disease, but there is now growing evidence that NAFLD is a multisystem disease, affecting several extra-hepatic organs. For example, NAFLD increases risk of T2DM, cardiovascular and cardiac diseases, and chronic kidney disease. NAFLD is associated

with an increased risk of developing ischemic heart disease, abnormalities of myocardial function and structure, and cardiac arrhythmias (e.g., atrial fibrillation). Also, there is emerging evidence that NAFLD is linked to other chronic diseases, such as sleep apnea, adenomatous polyps of the colon and colorectal cancer, osteoporosis, polycystic ovary syndrome, psoriasis, and various endocrinopathies. Thus, NAFLD has become a growing public health problem.[3, 9]

Regarding the fact that most of MS components may be either preventable or improved through lifestyle changes or drug treatments, a question arises: "can NAFLD, and consequently NAFLD-related complications be prevented in some way?"[3, 6, 9] Nowadays there is no effective therapy for all NAFLD patients in general population. Most of the studies are directed towards finding the optimal therapy for NAFLD and NASH but still there is no universal protocol to treat this growing problem. Cardiovascular risk factors are highly prevalent among NASH patients and general lifestyle interventions including dietary changes and increased physical activity remain the backbone of treatment regimens for the NASH patients.[10] In the absence of approved treatment modalities for NAFLD/NASH, care should be taken on the detection of advanced fibrosis. NASH is the major predictor of advanced fibrosis. Liver biopsy is still considered the gold standard to distinguish NASH from simple steatosis. However, because of its invasive nature, non-invasive diagnostic modalities are rapidly evolving for identifying highrisk patients who should undergo liver biopsy. Another complicating factor is that liver enzyme levels (mainly serum alanine aminotransferase and γ-glutamyltransferase) are within normal limits in more than half of patients with NAFLD.[6, 11] Gastroenterologists and hepatologists are thus left with more questions than answers when it comes to deciding which patients with NAFLD need a liver biopsy.[6] Accordingly to the current guidelines from the American Association for the Study of Liver Diseases, liver biopsy should be considered in all patients with NAFLD, who are at an increased risk of NASH and advanced fibrosis.[12] Patients with NAFLD who have coexisting MS or T2DM are at higher risk of developing NASH and advanced fibrosis as well as at an increased risk of liver-related morbidity and mortality.[6, 12] Therefore, development of some non-invasive method that will help us to identify high-risk NAFLD patients that have a truly need for liver biopsy is of great importance. Recently, a novel physical parameter based on the properties of ultrasonic signals acquired by the transient elastography (TE; FibroScan®) has been developed. This novel parameter, named Controlled Attenuation Parameter (CAP), can be used for steatosis detection and quantification. Also, CAP can be performed simultaneously with liver stiffness measurement (LSM) on the same measured liver volume, making possible for the simultaneous evaluation of both fibrosis and steatosis, consequently enhancing the spectrum of non-invasive methods for the detection and follow-up of patients with NAFLD. With the development of the new XL probe the obese patients can now be assessed accurately for liver steatosis and fibrosis using the FibroScan®.[13, 14] In our Center we have started to use CAP and LSM in patients with suspected NAFLD three years ago. TE with CAP is non-invasive, accurate, reproducible, convenient, and useful for serial measurement in patients with various CLD. Despite the increasing popularity and reliability of LSM and CAP measurements using TE to assess the degree of liver fibrosis and steatosis in subjects with various CLD, there are still little data regarding the association of CAP and LSM measurements in population of Western patients with one or more components of the MS.

However, according to recent investigations and to our unpublished data, CAP is closely related to MS components and has a good correlation with liver biopsy findings.[14, 15] In the study performed by Kwok *et al* [15] in which diabetic patients were screened for NAFLD using TE-CAP the prevalence of increased CAP and LSM were 72.8% and 17.7%, respectively. Ninety-four of their patients (80% had increased LSM) underwent liver biopsy: 56% had steatohepatitis and 50% had fibrosis grade 3-4 disease.

Regarding the preliminary observations that CAP and LSM have a good correlation with MS components and liver biopsy findings, the presence of MS with high CAP values, and especially with elevated LSM may be used for identifying patients who are at risk for developing NASH and advanced fibrosis and consequently that have a need for a liver biopsy.

Because CAP and LSM are quantitative methods, it can be hypothesized that we will be able to follow patients with NAFLD. TE with CAP could be a reasonable initial assessment for patients with suspected NAFLD, especially in those with one or more components of MS. Further studies for this implications are urgently needed.

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