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Editorial

NAFLD: The Enemy Within?

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Editorial

With the discovery of the Directly Acting Antiviral (DAA), hepatitis C related complications may no longer be a seen as a major health hazard in the foreseeable future, at least in the developed countries. However, the world is now facing a new epidemic which has and is affecting all populations and all age groups; Non-Alcoholic Fatty Liver Disease (NAFLD). It may be defined as the presence of fat in the liver after excluding secondary causes of fat deposition (like alcohol or drugs). In fact, NAFLD is not one disease but comprises a clinical spectrum that includes simple Steatosis (nonalcoholic fatty liver; NAFL), Steatosis with necroinflammatory changes (non-alcoholic steatohepatitis; NASH), advanced fibrosis, cirrhosis and even Hepatocellular Carcinoma (HCC) [1].

The clinical burden of NAFLD is immense, and this burden is further going to intensify with the passage of time as NAFLD is closely related to obesity and other risk factors for metabolic syndrome, both of which are on the rise [2]. Its association with hepatitis C genotype 3 (which is the predominant genotype in our part of the world) is also well known. The financial implications in terms of health-care costs and resource utilization is also tremendous, as this disease is increasingly recognized as the most common cause of liver cirrhosis across the globe [3]. Experts have predicted NASH-related chronic liver disease to be the leading cause of liver transplantation in the near future [4]. Although the current prevalence of NAFLD is higher in the West as compared to the Asian population (20-30% Vs. 5-18%), this difference may narrow down in the years to come [5]. Again, this is largely due to the epidemic surge in obesity and the associated metabolic syndrome in Asian countries. Additionally, BMI cut-offs for obesity is lower for Asians as compared non-Asians. There are a large number of patients with NASH who remain undiagnosed. This is because of the fact the only way to confidently diagnose steatohepatitis is by liver biopsy, and because of its invasiveness, it is done in a minority of individuals.

Patients with NAFLD have a significantly higher risk of mortality as compared to age and gender-matched healthy controls, with causes of death including ischemic heart disease, malignancy and liver disease [6]. This holds true more for patients with NASH rather than with simple Steatosis [7]. Additionally, fibrosis is known to be the most important and significant predictor of long-term outcomes in patients with NAFLD.

NAFL, unlike previously thought, is a progressive disease [8]. This was elucidated in a longitudinal Asian cohort study of 52 biopsy-proven NAFLD patients, in which repeat biopsies after 3 years found that 39% and 23% of patients with simple Steatosis had progressed to borderline and definite NASH, respectively [9]. NAFLD related HCC is on the rise in developed countries like Europe and USA, which were supposed to be areas of low HCC prevalence [10]. A recent database study by Younossi et al. demonstrated a 10% annual increase in the incidence of HCC in patients with NAFLD [11]. Interestingly, HCC has also been reported in non-cirrhotic NAFLD patients, highlighting the fact that there may be other complex mechanisms responsible for the development of HCC beyond liver cirrhosis [12]. It is therefore important to undergo regular HCC screening for both cirrhotic and non-cirrhotic NASH.

Our understanding of the underlying pathophysiology of NAFLD and its natural history has expanded to quite an extent. Yet, until now, there is no approved drug for the treatment of NAFLD. Additionally, there have been several misconceptions regarding this disease. In the initial days, NAFLD was considered a benign manifestation of obesity. Later on, it was thought as one of the complications of diabetes. Finally, there were believes that in order to conduct clinical trials regarding NAFLD therapies, histological documentation of NASH would be required, which as we know, is not the case anymore [13]. Because of these myths, the development of drugs for NAFLD and NASH has slowed down considerably. A real hurdle in drug development in NAFLD is the fact that there are certain pharmacological therapies which only work well in rodent models of NASH as opposed to humans. These include PDE4 inhibitors, selective caspase inhibitors, resveratrol, omega 3 fatty acid preparations, anti-TNF alpha and probiotics [14]. This is because there are major differences between humans and rodent NASH models regarding the replication of Insulin Resistance (IR), associated metabolic conditions, genetic variation and progression to advanced fibrosis.

Diet and life-style changes remain the corner-stone for the treatment of NAFLD. This is particularly important as most of these individuals are obese and have significant underlying metabolic risk factors which need to be controlled. Absence of physical activity and unhealthy life-style play an important part in worsening of the overall disease process. NAFLD patients tend to consume more fructose, soft drinks, meat, saturated fat, and less of fiber, fish omega-3 fatty acids and vitamins [13]. Weight loss and dietary modifications should be encouraged in such patients as relatively small amounts of weight loss can result in significant reductions in liver fat with improvement in hepatic IR [15]. Slimming also has histological benefits, as weight loss results in ALT improvement and normalization [16]. Additionally, a minimum of 15 minutes of daily exercise reduce all-cause mortality and cancer mortality.

Randomized Controlled Trials (RCTs) of dietary and life-style interventions in NASH have been published in literature. However, they are very few in number, with smaller sample size, and generally

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involving an intervention team comprising dietitians, psychologists and physical coaches [17]. Furthermore, it is virtually impractical to follow such strict dietary schedules with a complex intervention team. As a result, in real life scenario, patients tend to fail in maintaining these non-pharmacologic interventions. In our opinion, the best way to achieve long-term success with these interventions is to combine exercise with caloric restriction, and to set realistic goals for patients so that they remain compliant to these life-style changes in their everyday life.

Regarding pharmacological therapy for NAFLD and NASH, a number of medications have been tried but with inconsistent results. To date, we are still far from an ideal drug for NASH which could reduce hepatocellular inflammation, correct the underlying insulin resistance if present, and have anti-fibrotic effects at the same time. The best studied agents are pioglitazone (an insulin sensitizer) and vitamin E [18]. However, major guidelines only recommend biopsy-proven NASH to receive medical treatment [1]. Bariatric surgery also has a role in morbidly obese patients with NAFLD, including NASH resolution and fibrosis reduction [19].

Finally, discovery of biomarkers in order to aid diagnosis and monitor disease progression in NAFLD/ NASH is the need of the hour. It is also essential that continuous research be aimed at identifying newer therapy targets in order to control this menace which is fast turning into a global threat as one of the leading causes of liver failure.

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