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Editorial

Non-alcoholic fatty liver disease (NAFLD): The burgeoning liver disease at the interface of metabolic syndrome and type 2 diabetes

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Editorial

Over the last four decades, epidemics and pandemics like human immunodeficiency virus (HIV), severe acute respiratory syndrome (SARS), and Coronavirus disease 2019 (COVID-19), have made such an impact that the attention of physicians and scientists is solely, and rightly, on bringing appropriate solutions immediately to save millions of lives globally. Even with this heightened attention to the emerging epidemics and pandemics, there are other diseases emerging during the same period to which many other physicians and scientists are paying attention. Excess body weight and obesity are significant risk factors for the development of type 2 diabetes mellitus (T2D). Globally, one disease that is developing silently, but at an alarming rate in individuals with obesity and T2D, is fatty liver disease without a significant amount of alcohol usage known as non-alcoholic fatty liver disease (NAFLD) [1].

To establish the diagnosis of NAFLD, histological evidence of accumulation of fat in more than 5% of hepatocytes is required [2]. Hepatocytes are the functioning components for metabolism, drug/chemical disposition, and cholesterol biosynthesis. They also provide precursors for the synthesis of steroids and absorption of food from the intestine [3]. According to a meta-analysis, the average global prevalence of NAFLD is estimated to be 32.4%, highest in South America and the Middle East followed by Asia, the USA and Europe; prevalence increased from 25.5% in or before 2005 to 37.8% in 2016 or later [4]. Overall, prevalence of NAFLD was found to be 46.9 cases per 1000 person-years with significantly higher prevalence in men (39.7%; 70.8 cases per 1000 person-years) than in women (25.6%; 29.6 cases per 1000 person-years) [4]. Chronic alcohol intake also results in alcoholic liver disease whose first stage is alcoholic fatty liver disease which resolves itself with the cessation of alcohol intake while NAFLD among obese and T2D patients may not resolve itself [5]. Detecting NAFLD is difficult due to the absence of any set guidelines, while increased levels of enzymes such as transaminases (ALT, AST) indicate liver (hepatocyte) injury which can occur during many stages of liver injury. Liver MRI is a reliable diagnostic tool to determine fat deposition, while high levels of ALT and AST indicate abnormal liver function requiring physicians to evaluate the possibility of fat deposition in the liver [6].

NAFLD occurs due to lipolysis in adipose tissue, dealing of free fatty acids by liver, and *de novo* synthesis of fatty acids in liver. The excessive free fatty acids become the source of NAFLD; additionally, adipose tissues also produce inflammatory cytokines, such as tumor necrosis factor-alpha (TNFα). These lead to an inflammatory condition in liver referred to as Non-alcoholic steatohepatitis (NASH) in approximately 5-10% of NAFLD patients [7]. NAFLD can progress to NASH causing hepatocyte death [8]. Upon death, the hepatocytes are replaced by non-hepatocyte cells such as hepatic stellate cells. Hepatic stellate cells secrete alpha smooth muscle actin protein (αSMA) which causes fibrosis of the liver [9]; fibrosis can also be caused in conjunction with fibroblast growth factor. Fibrosis can

lead to scarring of the liver, referred to as liver cirrhosis. In certain NAFLD cases, liver cancer, such as hepatocellular carcinoma, can also develop whose mechanism is still not understood. Both fibrotic and cirrhotic livers may result in potentially fatal liver failure needing liver transplant [10].

Diet and exercise are the only effective means of reversing the development of NAFLD. They improve nutrition and metabolism and help in controlling obesity [11]. Currently, there is no drug available that can block the development of NAFLD. Peroxisomal proliferator activator receptor gamma (PPARγ) is a member of the nuclear receptor superfamily (NR) that controls lipid metabolism and sensitizes the liver to insulin. Other NR members (e.g., farnesoid X, pregnane X, liver X, and constitutive androstane) are also involved in cholesterol and fat metabolism and transport and thus in NAFLD [12]. PPARγ agonists, such as rosiglitazone and pioglitazone have been used in the management of T2D. The increase in insulin sensitivity by the aforementioned agents occurs by the activation of PPARγ. Clinical trials of agents directed to PPARγ are continuing to ascertain the efficacy of agents for the treatment of NAFLD. PPARγ, in addition to sensitizing liver for insulin and metabolism, also causes differentiation of fat cells in adipose tissue and therefore comes at the cost of increasing the fat depots in the body [13]. Due to many genes controlling obesity, picking a single agent to control NAFLD will be difficult and likely will come at the cost of secondary adverse effects.

On March 14, 2024, U.S. FDA approved a medication, resmetirom (Rezdiffra™, Madrigal Pharmaceuticals, Inc.), for patients who have progressed from NASH to fibrosis, the advanced stage of NAFLD [14]. Resmetirom is a highly selective thyroid hormone receptor-β (TRβ), a nuclear receptor superfamily, agonist. Resmetirom significantly decreases intra-hepatic lipids mainly through increased mitochondrial β oxidation and thus improving hepatocyte mitochondrial function in NASH patients [15]. Several clinical trials are underway (https://clinicaltrials.gov/) and we hope treatments for NAFLD will also become available soon.

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