

## Non-Alcoholic Fatty Liver Disease – An Emerging Silent Killer

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Non-alcoholic fatty liver disease (NAFLD) refers to a group of conditions where there is accumulation of excess fat in the liver of people who drink little or no alcohol<sup>1</sup>. Presence of  $\geq 5\%$  hepatic steatosis must be present to define NAFLD<sup>2</sup>. There are two types: Non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH)<sup>3,4</sup>. NAFL is more common and non-serious condition, usually asymptomatic and does not damage the liver. NASH includes both fatty liver (steatosis) and liver inflammation or steatohepatitis. It is potentially serious condition that may lead to hepatic fibrosis, cirrhosis, liver cancer, liver failure and cardiovascular diseases (CVD)<sup>5</sup>. It has been shown that clinical burden of NAFLD is not only confined to liver related morbidity and mortality, but there is now growing evidence that NAFLD is a multisystem disease affecting extra-hepatic organs and regulatory pathways. For example, NAFLD increase risk of type 2 Diabetes Mellitus, CVD including stroke and IHD, and also CKD. NAFLD and CVD are both manifestation of end organ damage of the metabolic syndrome<sup>6</sup>. Hepatocyte death via apoptosis and necroptosis is increased in NASH compared with simple steatosis, and inflammation is one of the NASH hallmarks<sup>7</sup>. One debated mechanism proposes a second hit or further injury enough to cause changes that leads from hepatic steatosis to hepatic inflammation<sup>8</sup>. By multiple pathophysiological mechanisms, NAFLD and CVD, are associated with each other. Systemic inflammation, endothelial dysfunction, hepatic insulin resistance, oxidative stress (imbalance between pro-oxidant and antioxidant chemicals), hormonal imbalance, mitochondrial abnormalities and altered lipid metabolism are some of the mechanisms by which NAFLD increases the risk of CVD. Patient with NAFLD develop increased atherosclerosis, cardiomyopathy and arrhythmia including atrial fibrillation which clinically result in cardiovascular morbidity and mortality. Defining these mechanisms and linking these two diseases offers opportunity to further develop targeted therapy<sup>9</sup>. Risk factors include obesity, diabetes, high fructose diet and omega 6 fatty acid, choline deficiency and older age. Gut microbiota may play a role in liver inflammation. NAFLD is considered as hepatic manifestation of metabolic syndrome (MS). This includes obesity, insulin resistance (pre-diabetes), diabetes, dyslipidemia, hypertension etc. It is also linked to hypoxia caused by obstructive sleep apnea, polycystic ovarian syndrome (PCOS), endocrinopathy like panhypopituitarism and primary hypothyroidism<sup>10</sup>.

NAFLD is prevalent twice in men compared to women which can be explained by estrogen deficiency in men. Genetic mutations for NAFLD has been identified<sup>11</sup>.

NAFLD is the commonest liver problem worldwide and it is estimated that 24% of world's population was affected in 2017. NAFLD is the most common liver disorder in developed countries affecting 75-100 million Americans in 2017. About 12-25% of the people in USA have NAFLD. Annual economic burden<sup>12</sup> was estimated at US \$103 billion in US in 2016. Its prevalence varies between 15-46% in Western countries and 8-40% in Asian countries<sup>13</sup>. Up to 80% of the obese and up to 20% of the normal weight people might develop it. NAFLD is the most common cause of chronic liver disease (CLD) worldwide and the number is gradually increasing, and it is thought that by now, up to 1/3rd of the general population affected by it. It is predicted to become the most frequent indication of liver transplantation<sup>14</sup> by 2030. The growth of NAFLD has been epidemic, is related to increasing prevalence of obesity, diabetes and metabolic syndrome in general population. In parallel with industrialization, urbanization, change of lifestyle towards sedentary works and western type dietary habits, prevalence of NAFLD is increasing rapidly in Asian countries. Furthermore, recently NASH/NAFL is noticed in non-obese Asians, which is called Asian paradox. Bangladesh is a rapidly developing country and experiencing detection of NAFLD in increasing numbers. A few studies in Bangladesh showed prevalence of NAFLD is 18.4-35.4%<sup>15</sup>.

In this issue of JAFMC, an article on 'Clinical Profile of Patients with Incidentally Detected Non-Alcoholic Fatty Liver Disease' has been published. The authors have found that out of 470 participants, 333 (81.81%) had visceral obesity. Obesity, diabetes mellitus, hypertension and metabolic syndrome were present in 68.5%, 48.2%, 36.4% and 87.5% cases respectively. Hyperlipidemia was found in large number of cases. Authors of another article published in this issue, namely, 'Fatty Liver in Primary Hypothyroidism' found significant correlation between primary hypothyroidism and NAFLD.

The majority of NAFLD are asymptomatic, but patients may complain of fatigue, malaise, right upper quadrant abdominal pain and discomfort. Clinically mild jaundice and hepatomegaly may be found<sup>16</sup>.

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The diagnosis of NAFLD is usually first suspected in an overweight or obese, diabetic person who is found to have mild elevations in their liver tests during a routine blood testing or incidentally detected on radiologic investigations such as abdominal ultrasound or CT scan. Other imaging modalities include MRI, Fibroscan of liver, MR Elastography, Proton Density Fat Fraction estimation by MRI (MRI-PDFF). Liver biopsy is the widely accepted gold standard test for distinguishing NAFLD from other forms of liver disease and can be used to assess the severity of the inflammation and resultant fibrosis. In case of NAFLD, there is increased liver enzyme when there is significant damage to hepatocytes. Other investigations may be done such as blood sugar, renal function, serum albumin, coagulation profile, lipid profile etc<sup>3,17,18</sup>.

Management guidelines are available from the American Association for the Study of Liver Diseases (AASLD), National Institute for Health and Care Excellence (NICE) and the European Association for the Study of the Liver (EASL)<sup>3,19,20</sup>. These include lifestyle modification, dietary modification such as moderate to low-carbohydrate diet and low-fat diet, energy restriction to 500-1000kcal/week, physical activity, medications and surgery<sup>21</sup>. Medications include metformin, thiazolidinediones such as pioglitazones, Vitamin E, Obeticholic acid, Cenicriviroc, Selonsertib and Elafibranor. Surgical measures include Bariatric Surgery. In addition to treating NAFLD, other associated diseases such as DM, hypertension, hyperlipidemia and hypothyroidism should also be treated<sup>22</sup>.

NAFL and NASH increase the risk of cirrhosis and liver cancer. Liver cancer develops in NASH in the absence of cirrhosis in 45% cases and people with NASH cirrhosis have more chance of liver cancer<sup>23</sup>. Although NAFLD patients can die from cirrhosis, liver cancer and liver failure, the majority of deaths among NAFLD patient is attributable to cardiovascular failure. Indeed, according to a meta-analysis of 34,000 patients with NAFLD over 7 years, they have 65% increased risk of developing fatal or nonfatal cardiovascular events<sup>24</sup>.

Trends of modernization such as sedentary lifestyle and fatty food intake must be limited to reduce the incidence of NAFLD. Lifestyle changes with weight loss and exercise along with control of underlying risk factors remains the cornerstone of the therapy. High risk population should be screened using easily available imaging techniques and liver enzyme levels to detect fatty changes at an early stage<sup>14</sup>. NICE advises regular screening of NAFLD for advanced liver fibrosis every three years to adults and every two years for children using the enhanced liver fibrosis (ELF) blood test. Since NAFLD is a complex disease that involves several organs and tissues, combination therapies (combining compounds)

and conjugate therapies—combining drugs and non-pharmacological therapies, which includes lifestyle modification and behavioral therapies, may be used for better management of patients.

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