Non-Alcoholic Fatty Liver Disease: The Silent Epidemic

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Non-alcoholic fatty liver disease (NAFLD) was once a negligible concern, but is now rapidly escalating to epidemic proportions. It poses a significant threat to affected individuals and to health systems already strained by a growing burden of chronic non communicable diseases.

NAFLD is a disease spectrum ranging from benign non-alcoholic fatty liver (NAFL) or simple steatosis to the more severe form of non-alcoholic steatohepatitis (NASH). It is characterized by hepatic steatosis or fat deposition of > 5%, without an identifiable secondary cause (1).

In NAFLD, hepatic steatosis is present without evidence of inflammation. A majority of patients with NAFLD remain stable and non-progressive. However, a small proportion of patients progress to NASH, which is hepatic steatosis associated with lobular inflammation and apoptosis. These patients have a higher risk to convert to cirrhosis, liver failure and even hepatocellular carcinoma with time.

Presently, the estimated global incidence of NAFLD is 47 cases per 1,000 population and with a 2.5:1 male preponderance (2). The worldwide prevalence of NAFLD is estimated to be approximately 30 to 32% (2,3). Over the past few decades global prevalence has increased, from about 25% in 1990-2005 to 38% in 2016-2019. Further, NAFLD is one of the leading causes of liver disease globally and the most rapidly rising cause of hepatocellular carcinoma (2).

These alarming developments are in keeping with the exploding, interconnected epidemics of obesity, dyslipidaemia, diabetes mellitus, insulin resistance and metabolic syndromes (4,5). Interestingly, in these populations, incidence, and prevalence of NAFLD is significantly higher. Seventy percent (70%) of obese individuals, 56% of patients with diabetes, 43% of patients with polycystic ovarian disease are estimated to suffer from NAFLD (6,7).

Most patients with NAFLD remain asymptomatic, while some may suffer from unexplained fatigue and right hypochondrial pain. Hepatomegaly, acanthosis, and splenomegaly may be seen in a small proportion of patients (6).

As insights into the pathological and clinical processes of NAFLD grew, the prominent extra-hepatic manifestations of the disease were identified. A majority of patients with NAFLD have associated disorders of the cardiovascular, endocrine, renal systems and malignancies. In fact, cardiovascular disorders are the primary cause of death in patients with NAFLD, followed by extra hepatic malignancies and hepatic complications (6).

In 2020, an international expert consensus statement was issued to introduce the term metabolic dysfunction associated fatty liver disease (MAFLD) in place of NAFLD. It was hoped that MAFLD would better represent the disease process than the term NAFLD. Further, the new

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proposed MAFLD definition places greater importance on the screening and management of the associated metabolic diseases (7).

However, NAFLD/MAFLD still remains largely under diagnosed and under treated, primarily because the onset and progression of the disease is insidious and the early symptoms, vague.

NAFLD is usually an incidental diagnosis during a routine ultrasound scan or while investigating elevated transaminases. The gold standard for diagnosis is liver biopsy. Magnetic resonance spectroscopy (MRS) can identify hepatic steatosis with inflammation and fibrosis but is not routinely available. Elastography or Fibro Scan is used to identify the presence of advanced fibrosis of the liver. Routine ultra-sound, CT and MRI can identify hepatic steatosis but are unable to differentiate inflammation from fibrosis to discriminate between NAFLD and NASH (6).

Increasingly, the Fibrosis-4 Index (FIB-4) is used as a noninvasive alternative to liver biopsy to predict liver fibrosis. FIB-4 can be calculated easily using routinely performed investigations (8).

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FIB-4 = \frac{\text{Age (years)} \times \text{AST (U/L)}}{[\text{PLT (10^9/L)} \times \text{ALT}^{1/2} (\text{U/L})]}
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This index has the added advantage of predicting major adverse cardiac events. According to Chew et al. a FIB-4 score of ≥2.67 is associated with major adverse cardiac events and is associated with a 40% increased risk in cardiovascular mortality (9).

Lifestyle changes, the rise of obesity, diabetes, and metabolic syndrome worldwide, have created a perfect niche for NAFLD to thrive. Rapid urbanization, excessive consumption of refined carbohydrates, carbonated sugary beverages and ultra-processed foods together with a sedentary lifestyle lead to the vicious cycle of hepatic steatosis, insulin resistance and metabolic syndrome.

Prevention of NAFLD and NASH or risk reduction depends on the ability to introduce sustainable life-style changes. Health promotion lies at the heart of an effective strategy to combat any disease by empowering people to make more informed choices regarding how they navigate through health and disease.

Lifestyle modifications such as weight loss, healthy diet, and regular exercise still remain the foundation of NAFLD/MAFLD management. Diet and exercise should be aimed at maintaining a calorie deficit and consistent weight loss. Weight loss of >10% of bodyweight will even reverse liver involvement. (6) Promoting a Mediterranean influenced diet, rich in whole grain, pulses, fruits, vegetables, and lean meat together with regular exercise will reduce the risk of NAFLD. Coffee aficionados would be happy to note that regular consumption of coffee is thought to be liver protective, due to its ability to reduce oxidative stress and hepatic inflammation. Kositarongkol et al reports that it improves fibrosis of NAFLD, however coffee consumption doesn’t seem to prevent NAFLD in the normal population (10). It is also noted that vitamin E, a potent antioxidant, in high doses (dosage exceeding 600 IU/day or with a treatment duration of > 12 months) improves liver transaminases, steatosis and fibrosis in NAFLD (11,12). Finally, most importantly, all lifestyle changes should be achievable and sustainable.

As of now, there is no approved medication for the specific treatment of NAFLD or NASH. Certain drugs are prescribed off label for the reversal and prevention of NAFLD.

However, a few medications are under clinical trial to identify their efficacy against NAFLD. Hypoglycaemic medications such as glucagon-like peptide (GLP-1) receptor agonists, sodium-glucose co-transporter-2 (SGLT-2) inhibitors and pan-peroxisome proliferator-activated receptor-γ (PPAR) agonists have shown to improve hepatic fibrosis and induce remission of NASH (13).

In Sri Lanka, the estimated prevalence of NAFLD is about 25% (2,3). Though the value is lower than the global prevalence and less than in other South Asian and East Asian countries, ultimately, the personal and financial cost would be detrimental to the country (14). Furthermore, unlike in the rest of the world, South Asians have a higher prevalence of lean NAFLD (BMI <23 kg/m2) and non-obese NAFLD (BMI <25 kg/m2). Without clinical suspicion, the diagnosis is often delayed or made only when complications arise. NAFLD in the absence of obesity, is thought to be due to higher visceral fat deposition (as opposed to subcutaneous deposition) in South Asians. Unfortunately, lean and non-obese NAFLD is
associated with higher incidence of insulin resistance and diabetes and its ensuing complications (3).

The global prevalence of NAFLD is forecasted to reach 55.4% by 2040 (15) leading to a public health crisis. In 2022, Larzarus et al noted that the majority of the world’s nations, individually and collectively are significantly underprepared to handle the impending epidemic of NAFLD and its complications. Further, as the life expectancy of the global population rises and the age at diagnosis of NAFLD falls, the burden of the disease and its complications will escalate significantly (16).

While interventions at the individual level can be delivered through the health system, policy makers and health advocacy groups must act to address the social factors causing the rise of fatty liver disease. Regulating the marketing of unhealthy food products to vulnerable populations, particularly children and adolescents, and promoting physical activity would play a major role. Routine active screening programs to identify individuals at risk, regular monitoring, early intervention, and treatment is the cornerstone in combating the disease. Pharmacological and bariatric treatment options should be personalized to the individual patient according to the co-morbidities, disease severity and risk stratification. All governments and health care providers must ensure equitable access to prevention and treatment for all. Most importantly, continued research into novel therapeutic targets and pharmacotherapeutic agents is essential for improving outcomes and reducing the burden of NAFLD on the individual and the collective healthcare system of the world.

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