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## Non-alcoholic fatty liver disease: a Sri Lankan perspective


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Non-alcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis detected by abdominal imaging (commonly) or histology (rarely), in the absence of secondary causes, especially unsafe alcohol use [1]. It is a term covering a spectrum of diseases ranging from simple non-alcoholic fatty liver (NAFL) (i.e. fat deposition with no or mild inflammation and no fibrosis) through non-alcoholic steatohepatitis (NASH) (i.e. fat deposition with inflammation and hepatocellular injury, with or without fibrosis) to established cirrhosis [1]. Most NAFLD subjects are likely to have one or more features of metabolic syndrome (MetS) associated with insulin resistance, such as, obesity, type 2 diabetes mellitus (T2DM), hypertension and dyslipidaemia [2]. Parallel to the rapid increase in obesity and T2DM, NAFLD has become the leading cause of chronic liver disease worldwide with the global prevalence estimated to be 24% [2].

Sri Lanka has a high burden of NAFLD. The prevalence and annual incidence of NAFLD in an urban adult population near Colombo was reported to be 33% and 6.2% respectively, and prevalence in an adult rural population in a plantation area was 18% [3,4,5]. More worryingly, 8.4% of adolescents living in an urban setting were reported to have NAFLD [6]. Both prevalent and incident NAFLD were associated with components of the MetS and the PNPLA3 gene polymorphism, a polymorphism that has been reported in many other Asian and Caucasian populations [4,7]. The criteria used for ultrasound diagnosis of fatty liver in these studies were stringent: increased hepatic echogenicity with vascular blunting and/or signal attenuation [8], detecting moderate to severe disease. Less severe forms of fatty liver, diagnosed solely on the presence of increased hepatic echogenicity, do not predict incident adverse metabolic outcomes as accurately as the more severe forms of fatty liver. However, even the milder form is associated with prevalent adverse anthropometric indices and metabolic characteristics, thereby being a valuable surrogate for identifying individuals needing medical intervention [9]. Based on the less stringent ultrasound definition, the incidence and prevalence of NAFLD in Sri Lanka are likely to be much higher than previously reported.

NAFLD, which is considered the hepatic component of MetS, is a risk factor for T2DM [10], and Sri Lankan NAFLD patients have a nearly two-fold increased risk of developing new-onset T2DM compared to those without NAFLD [11]. Other new-onset metabolic traits and cardiovascular events are also more common in patients with NAFLD than those without the condition

[12]. Similar findings have been reported from Sri Lanka [4], and interestingly, Sri Lankans with lean NAFLD (BMI<23 kg/m$^2$) have a similar risk to non-lean NAFLD for the development of incident metabolic comorbidities [13]. Although most patients with NAFLD are overweight or obese (non-lean NAFLD), some are lean, and there has been an increasing clinical interest in the group [2]. The prevalence of lean-NAFLD in an urban Sri Lankan community was 4%, with an annual incidence of 4.1% [13]. Lean-NAFLD was commoner among males and had a lower prevalence of hypertension and central obesity than non-lean NAFLD. A high index of suspicion is needed to detect individuals with lean-NAFLD, and these patients also warrant careful evaluation and follow-up.

Most NAFLD patients have a benign hepatic course, but about 10% develop progressive fibrosis leading to cirrhosis and hepatocellular carcinoma (HCC) [14], the disease remaining clinically silent till hepatic decompensation occurs. NAFLD associated morbidity and mortality are strongly related to the degree of hepatic fibrosis and the presence of metabolic abnormalities [15]. In a community-based study in Sri Lanka that had a relatively short follow-up period of 10 years, and in which hepatic fibrosis was not evaluated, MetS but not NAFLD was found to be an independent risk factor for all-cause mortality and cardiovascular mortality [16]. Among those with NAFLD, only those who were metabolically abnormal were at a higher risk of death [16]. There is, therefore, increasing emphasis on aggressively screening patients with NAFLD for metabolic abnormalities and hepatic fibrosis [17]. Furthermore, because of the strong association between NAFLD and T2DM, screening of all T2DM patients for NAFLD and hepatic fibrosis has been recommended [18,19]. All NAFLD patients at high risk of advanced fibrosis/cirrhosis should be referred to specialized liver centres.

Screening for and detecting metabolic abnormalities in patients with NAFLD may be relatively straightforward. Screening for hepatic fibrosis is more complicated. Because liver biopsy, the gold-standard test to assess the degree of hepatic fibrosis, is impractical for all patients with fatty liver disease, several non-invasive tests have been proposed to screen for significant hepatic fibrosis. Serological tests such as the FIB-4 score (which uses the patient's age, platelet count, AST and ALT levels for calculation), and the NAFLD Fibrosis Score (which uses the patient's age, BMI, presence of T2DM, platelet count, AST and ALT levels and serum albumin level), are both used in clinical practice to screen patients with NAFLD for advanced hepatic fibrosis – screening is recommended 2-3 yearly for NAFLD patients and annually for NAFLD patients with T2DM [17]. Like the serology tests, Vibration Controlled Transient Elastography (VCTE), which has now been included in the diagnostic work-up of selected NAFLD patients, can detect advanced hepatic fibrosis and exclude the presence hepatic fibrosis [17]. However, neither these serological tests nor VCTE can accurately detect moderate degrees of fibrosis.

One of the common clinical dilemmas that physicians face is that metabolic dysfunction is also commonly seen in patients with fatty liver disease who misuse alcohol, but are excluded by the NAFLD definition [20]. There is debate whether a recently proposed disease acronym, metabolic (dysfunction)-associated fatty liver disease (MAFLD), is more suited to describe the metabolic entity of fatty liver disease than NAFLD. MAFLD, which is defined as the presence of fatty liver and a body mass index (BMI) ≥23 kg/m$^2$ or T2DM or at least two other features of metabolic dysregulation, with no other exclusion criteria appears to be more descriptive and better encompass the metabolic dysfunction associated with hepatic steatosis [21]. As there is considerable overlap between the definitions, redefining NAFLD as MAFLD leads to only a small increase in the index population [22,23,24]. NAFLD and MAFLD also seem to have similar metabolic traits and outcomes [23]. However, a study from Sri Lanka, has found that those excluded by the NAFLD definition but captured by the MAFLD definition have a higher risk of adverse outcomes than those excluded by the MAFLD definition but are captured by the NAFLD definition [24]. Thus, redefining NAFLD as MAFLD may improve clinical utility, but the debate is far from over.

With the high incidence and prevalence of NAFLD and increasing rates of obesity and T2DM, even among our very young, Sri Lanka should expect a high burden of NAFLD related chronic liver disease and cirrhosis in the time to come. There are already signs of this: in a specialized liver centre receiving referrals from all over Sri Lanka, 63% of patients referred for liver transplantation had NASH-cirrhosis [25]; 59% of hepatocellular carcinomas were secondary to NASH-cirrhosis [26]; nearly half of all potential liver donors had to be rejected because of NAFLD [27].

Lifestyle modification – a low calory diet and regular aerobic exercise leading to weight loss, is still the mainstay of treating NAFLD [2]. Fast food and added fructose (abundant in soft drinks and colas) should be avoided. Few pharmacological therapies have proven efficacy in NAFLD. The disease tends to persist in the absence of aggressive lifestyle modification. Passive improvements in anthropometric indices, such as weight and waist circumference over time, seem inadequate [28]. More intense, sustained lifestyle interventions are necessary to achieve the degree of improvement in anthropometric measurements for the resolution of NAFLD.

Sri Lanka is faced with a highly prevalent chronic liver disease that can have severe adverse outcomes – both metabolic and hepatic, for which there are limited treatment options other than lifestyle modification. The preventive health response to NAFLD is, therefore, crucial. Together with community-based strategies directed at reducing the incidence of risk factors for NAFLD, such as

obesity and T2DM, the unmet need for educational programs to increase awareness of the disease for both the medical community and the general population should be addressed [29,30]. Education programmes, starting in schools, should emphasize healthy eating and regular physical exercise. Such measures may help to dampen the adverse effects of NAFLD.

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