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Perspective

Non Alcoholic Fatty Liver Disease (NAFLD) A Perspective from Diabetologist

*Suhas Erande**

Department of Medicine, Akshay Hospital, India

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In1980s, an entity named as Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH), resembled histopathologically with Alcoholic Liver Disease (ALD) [1,2]. Even then, the biochemical & clinical features of NAFLD & ALD were noted as distinct from each other. Association of NAFLD with T2DM & obesity was described in 1970 [3]. When Ludwig first used the term NASH, this association was noted, however, this was largely ignored over years allowing NAFLD to be the established nomenclature. But researchers were struggling to pinpoint evolution of inflammation in NASH until Day & James proposed their 2 hits model [4], suggesting oxidative stress as driver of inflammation. Insulin resistance came into picture when Marchesini showed NAFLD association with it even in lean individuals [5]. This paved way to link NAFLD as a part of metabolic syndrome subsequently [6]. Last 2 decades have clearly shown that NAFLD is a progressive, metabolic disease the prevalence parallel to T2DM & obesity & liver manifestations as a part of multisystem entity. In this background lies the recent nomenclature Metabolic Associated Fatty Liver Disease (MAFLD) [7,8]. The change is more than semantic- catalyzing process to better conceptualize the disease for health promotion, patient orientation, case identification, ongoing clinical trials & healthcare delivery. The definition needs hepatic steatosis to be accompanied by obesity/overweight, T2DM or metabolic dysregulation. At least 2 components should be present in metabolic dysregulation i) waist circumference >90/80 cm in men/women, ii) prediabetes, iii) raised hsCRP, iv) Elevated BP or on treatment, v) decreased HDLc vi) increased TG vii) HOMA IR score >2.5. MAFLD & not NAFLD also deemphasize alcohol from the picture.

NAFLD is historically defined as excess accumulation of triglyceride droplets in hepatocytes ->5% on histopathology or >5% proton density fat fraction on MRI, in people who consume little or no alcohol. (It is to be noted that other liver diseases or other etiologies of steatosis need to be ruled out). Some experts also say that these features should be accompanied by lack of hepatocellular injury (ballooning of hepatocytes, lobular inflammation) to be defined as steatosis. Liver biopsy is the gold standard for diagnosis & staging of whole spectrum of NAFL-NASH-fibrosis-cirrhosis & hepatocellular carcinoma HCC. A number of noninvasive tests (biochemical & imaging) are used obviously to avoid biopsy. A battery of tests are summarized in the following table, most of these being research tools [9,10]. All scores available on Smartphone or Google.

No markers of fibrosis approved in USA. Alpha test or enhanced liver fibrosis test approved in Europe. NAFLD Fibrosis Score (NFS) is computed using platelet count, albumin, AST/ALT & 3 clinical parameters-age, BMI & glucose intolerance. It performs well to assess likelihood of advanced fibrosis or cirrhosis (AUROC 0 .85, sensitivity 90%, specificity 60%, NPV 88%, PPV 82%). Lesser specific but implementable are FIB-4 (platelet count, ALT, AST & age based computation) or APRI (platelets, ALT). A new best fitting multivariable logistic regression model based on liver stiffness FibroScan & AST-called as FAST can better identify at risk NASH & progression to cirrhosis [11]. FIB-4 value <1.3 implies low risk & >1.3 suggests need of transient elastography or MR studies. MR Elastography reading >3.3 kpa & FIB-4 value >1.6 has positive predictive value (NASH & fibrosis) >90%.

A simple risk score of conversion of NAFLD → NASH is based on hypertension, T2DM, OSA, ALT>27, AST>27 (each scoring 1) & black race scoring 2. Total 0-2 carries less risk & total more than 6 or 7, higher risk of conversion.

NAFL is slowly progressive disease, but in ~20% people it can progress to NASH faster (conversion rate ~14%). NASH → fibrosis → cirrhosis → HCC is even slower; however, T2DM obese people convert/deteriorate faster.

An evolving area of studies looks at nonobese or lean people with NAFLD, having some different features than obese NAFLD & emphasizing need to approach NAFLD independent of BMI [12]. NAFLD prevalence in T1DM is also on the rise given the increasing lifespan of these patients [13].

Epidemiology of NAFLD –Global Asian Indian

NAFLD is the umbrella term for liver diseases characterized primarily by excess fat accumulation in hepatocytes because of perturbations of homeostatic mechanisms regulating synthesis *vs.* utilization of fat in liver [14]. NAFLD has become the leading cause of liver disease across the Western World-pooled global prevalence 25.24% with high geographical variations e.g., 30% in Middle East & South America by USG & 13% in Africa, 24% to 25% in North America & Europe. In developing Asian countries, smaller studies reveal NAFLD prevalence as 10% to >50%, depending on rural/

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***Corresponding author:** Suhas Erande, Department of Medicine, Akshay Hospital, Pune, India, E-mail: drsse@rediffmail.com

urban locations or by methods (USG or biomarkers). A study from Hongkong using MR spectroscopy revealed incidence of NAFLD over 3 to 5 years as 13.5%. Rising global prevalence of obesity, T2DM, sedentary lifestyles & excess calorie consumption (calorie dense fatty foods, sugar sweetened beverages, high corn fructose syrup) underlie rise in NAFLD. Even childhood/adolescent obesity/overweight culminates in NAFLD. Effects of such foods on gut microbiota-both by pregnant mothers or by children may result in NAFLD which could be independent of BMI.

NAFLD & T2DM an Intricate Bidirectional Association

SPRINT study [15] from Indian T2DM patients revealed NAFLD prevalence to be 56.5% against general population prevalence of 9% to 32%. Remission of T2DM over 2 years was less common in those with NAFLD at baseline (USG based), compared to those without (8.7% *vs.* 13.1%) [16]. Hepatic steatosis & fibrosis are associated with significant LV dysfunction in T2DM patients due to impaired myocardial glucose uptake [17]. Prof. V. Mohan in his CURES study subgroup of 541 patients noted overall prevalence of NAFLD 32% but it was 54.5% in T2DM patients. He showed increasing prevalence of NAFLD with increasing degree of glucose intolerance [18]. Drivers of NAFLD (obesity, dyslipidemia, sedentary habits, excess calorie intake, systemic inflammation & insulin resistance, metabolic syndrome) also are drivers of T2DM & CVD. Angiopoietin like protein 8 (ANGPTL 8) is increased in NAFLD & is associated with hepatic lipid content independent of obesity, IR & liver injury. It could prove as biomarker to assess severity of NAFLD in T2DM. Over years, the old two hit theory (excess fat accumulation in liver steatosis+one more trigger like drugs or lipid peroxidation) has understandably evolved into multiple hits theory (impaired mitochondrial ATP activity, depletion of mitochondrial glutathione, hypoxia associated with impaired blood flow or obesity related OSA, dysregulated adipokine production, effects of high fructose diet & rapid weight loss). Role of gut microbiota & genetic markers (PNPLA3) is being researched in.

NAFLD & CVD

Insulin resistance, dyslipidemia, obesity, excess visceral fat, systemic low grade chronic inflammation (metabolic syndrome) is common soil for both NAFLD & CVD. NF kappa beta & JNK pathway activation in NAFLD drives IR, dyslipidemia, procoagulant states, pro inflammatory(IL 1 alpha, beta- IL 18, IL 33, TNF alpha) condition & hence, CVD. Numerous studies have shown liver fibrosis scores incrementally linked with increased CVD risk. The Framingham Risk Score is validated to calculate CVD risk in NAFLD.

Whom to Screen for NAFLD? How to Follow?

Since NAFLD does not have FDA approved drug treatment as yet, is it necessary to give importance to it? (NAFLD worsening to NASH, fibrosis, cirrhosis or HCC & end stage liver disease, accompanying MetSyn T2DM CVD). Different associations recommend against universal screening, but, active surveillance is advised in obese T2DM people (EASL, NICE, Asia-Pacific AASLD). USG, liver enzymes & transient elastography modalities are advised for the same [19]. AASLD feels that mass screening is not cost effective & the benefits in long term are unclear.

Though gold standard, liver biopsy is advised only if advanced fibrosis is suspected-(the Asian guidelines differing from American & European). Scores based on biomarkers/USG/elastography can be followed & if worsening, biopsy is recommended.

Life Style Modification in NAFLD Treatment

Dietary restrictions/modifications, physical exercise aimed at weight loss are recommended by all guidelines to treat NAFLD. Low cal(~1200-1500/d),VLCD (450 or 800 cal/d), low carb (<20% to 45%), low fat (20% to 27%), DASH diet or Mediterranean Diet, Intermittent Fasting have favorable effects on weight loss, liver enzyme reduction, USG improvement, hepatic TG reduction on MRS & even biopsy proved NAFLD/NASH improvement [20].

Drug Treatment for NAFLD

A variety of drugs are under investigations to treat NAFLD. Those which improve fibrosis & histopathology are more important than those (*viz* statins), which improve only liver enzymes. Amongst antidiabetic drugs, pioglitazone, saroglitazar can be used (the latter DCGI approved label)-so also liraglutide injection. SGLT 2 inhibitors hold some promise in small studies. Vitamin E 800 mg/d can be used for nondiabetic/noncirrhotic NAFLD. Farnensoid Receptor Agonist (obeticholic acid, cilofexor, tropifexor, EDP-305) inhibitors of de novo lipogenesis (Armachol, Firsocostat, PF-05221304) are also being studied [21]. Bariatric surgery can remarkably improve NAFLD, wherever appropriate.

It needs to be noted by physicians, that NAFLD having global prevalence of 25% & risk to progress/deteriorate to advanced stages like NASH, fibrosis, liver cirrhosis or hepatocellular carcinoma, needs surveillance. Obese, T2DM & metabolic syndrome patients are at higher risk of getting NAFLD. NASH being the 2nd most reason/ indication of liver transplant (after Hepatitis C), it needs serious considerations. Higher index of suspicion for NAFLD/NASH, using routine USG & biochemistry to calculate indices like FIB 4, timely advice on weight loss by lifestyle modification & use of GLP 1 As to lose >10% or even 15% weight (if needed), may go a long way to manage the menace of NAFLD/NASH/Cirrhosis& HCC. The search for drugs to treat NAFLD/NASH may yield success in future.

Readers may refer to illustrious publications by Prof. Anoop Misra & Late Dr. Deepak Amrapurkar for in depth NAFLD research in Indian population.

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