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The study of NAFLD has intensified significantly, with more than 1400 publications since 2018, when the last American Association for the Study of Liver Diseases (AASLD) Guidance document was published.[1] This new AASLD Guidance document reflects many advances in the field pertinent to any practitioner caring for patients with NAFLD and emphasizes advances in noninvasive risk stratification and therapeutics. A separate guideline focused on the management of patients with NAFLD in the context of diabetes has been written jointly by the American Association of Clinical Endocrinology and AASLD.[2] Given the significant growth in pediatric NAFLD, it will not be covered here to allow for a more robust discussion of the diagnosis and management of pediatric NAFLD in the upcoming AASLD Pediatric NAFLD Guidance. A “Guidance” differs from a “Guideline” in that it is not bound by the Grading of Recommendations, Assessment Development and Evaluation system. Thus, actionable statements rather than formal recommendations are provided herein. The highest available level of evidence was used to develop these statements, and, where high-level evidence was not available, expert opinion was used to develop guidance statements to inform clinical practice. Key points highlight important concepts relevant to understanding the disease and its management. The most profound advances in NAFLD relevant to clinical practice are in biomarkers and therapeutics. Biomarkers and noninvasive tests (NITs) can be used clinically to either exclude advanced diseases or identify those with a high probability of cirrhosis.[3,4] NIT “cut points” vary with the populations studied, underlying disease severity, and clinical setting. Those proposed in this guidance are meant to aid decision-making in the clinic and are not meant to be interpreted in isolation. Identifying patients with “at-risk” NASH (biopsy-proven NASH with stage 2 or higher fibrosis) is a more recent area of interest. Although the definitive diagnosis and staging of NASH remain linked to histology, noninvasive tools can now be used to assess the likelihood of significant fibrosis, predict risk of disease progression and decompensation, make management decisions, and, to some degree, assess response to treatment. There is an ongoing debate over the nomenclature of fatty liver disease, which had not been finalized at the time this guidance was published. At the culmination of a rigorous consensus process, it is intended that any formal change in nomenclature will advance the field without a negative impact on disease awareness, clinical trial endpoints, or the drug development/approval process. Furthermore, it should allow for the emergence of newly recognized disease subtypes to address the impact of disease heterogeneity, including the role of alcohol, on disease progression and response to therapy. Input from patients has been central to all stages of the consensus process to ensure the minimization of nomenclature-related stigma. NAFLD is an overarching term that includes all disease grades and stages and refers to a population in which ≥ 5% of hepatocytes display macrovesicular steatosis in the absence of a readily identified alternative cause of steatosis (eg, medications, starvation, monogenic disorders) in individuals who drink little or no alcohol (defined as < 20 g/d for women and 2-fold. This is supported by the projected rise in NAFLD prevalence by 2030, when patients with advanced hepatic fibrosis, defined as bridging fibrosis (F3) or compensated cirrhosis (F4), will increase disproportionately, mirroring the projected doubling of NASH.[5,19] As such, the incidence of hepatic decompensation, HCC, and death related to NASH cirrhosis are likewise expected to increase 2- to 3-fold by 2030.[5] Although expected to increase further, NASH-related cirrhosis is already the leading indication for liver transplantation in women and those > 65 years of age and is on par with alcohol as the leading indication overall.[20–22] Data from meta-analyses and pooled studies demonstrate that fibrosis and the presence of steatohepatitis are the primary predictors of disease progression.[23–25] The collinearity between NASH and the fibrosis it induces makes it challenging to demonstrate the independent contribution of NASH to fibrosis and adverse outcomes in multivariable analyses.[26,27] Although fibrosis is the primary determinant of adverse outcomes, increased liver-related morbidity and mortality and nonhepatic malignancy are observed in patients with NAFLD even in the absence of fibrosis on initial biopsy.[25] Nevertheless, patients with NASH and at least stage 2 fibrosis (F2), referred to as “at-risk” NASH, have a demonstrably higher risk of liver-related morbidity and mortality.[24,28] Fibrosis progression is influenced by many factors such as the presence and severity of comorbid disease, genomic profile, and environmental factors. A meta-analysis of placebo-treated patients in 35 NASH trials found minimal progression, suggesting that nonpharmacologic factors (frequent visits/monitoring, dietary or lifestyle counseling, or changes) may reduce progression.[29] An earlier meta-analysis of cohorts with longitudinal paired biopsies[30] demonstrated a NAFLD fibrosis progression rate of one stage per 7 years in those with NASH versus 14 years for those with NAFL.[30] The diagnosis of cirrhosis, determined by biopsy or noninvasively, is important because it changes clinical management. Those with cirrhosis require biannual screening for HCC as well as screening for varices and monitoring for signs or symptoms of decompensation.[31,32] Among patients with cirrhosis, progression to clinical decompensation ranges from 3% to 20% per year.[12,33–35] The most common causes of death in patients with NAFLD overall are cardiovascular disease (CVD) and nonhepatic malignancy, followed by liver disease. The amount of liver fibrosis identified histologically in patients with NAFLD has been strongly linked to the development of liver-related outcomes and death.[24,26,36,37] Bridging fibrosis and cirrhosis are associated with an exponentially greater risk of liver-related morbidity and mortality than earlier stages of fibrosis.[23,24,35] In a prospective study of 1773 patients, all-cause mortality in those with fibrosis stages 0–2 was 0.32 per 100 person-years, compared with 0.89 per 100 person-years in those with bridging fibrosis and 1.76 per 100 person-years in those with cirrhosis. After correcting for multiple factors, hepatic decompensation was associated with all-cause mortality (HR, 6.8; 95% CI, 2.2–21.3).[35] Cirrhosis regression has been associated with a 6-fold reduction in liver-related events in clinical trials.[38] The presence and severity of NAFL and NASH are substantially determined by factors that govern the supply and disposition of fatty acids, diacylglycerols, ceramides, cholesterol, phospholipids, and other intrahepatic lipids. Energy oversupply and limited adipose tissue expansion contribute to insulin resistance and metabolic disease.[39] When energy intake exceeds metabolic needs and disposal capacity, carbohydrates, in the form of dietary sugars (eg, fructose, sucrose, and glucose), drive the formation and accumulation of intrahepatic fat from de novo lipogenesis (DNL).[40,41] There is substantial interindividual heterogeneity in the role of DNL among patients with NAFLD.[42,43] In addition, the type of fat consumed plays a role in the development of NASH, with a higher risk associated with saturated versus unsaturated fat consumption (Figure 1).[44–46] Pathogenic drivers of NAFLD as therapeutic targets. Overview of the major mechanisms that lead to the phenotype of NASH and its consequences, many of which can be leveraged therapeutically. Not shown are the many areas where genetic polymorphisms may play a role and where important modifying factors such as cholesterol, types of dietary fats consumed [saturated vs. polyunsaturated fatty acid (PUFA)], the gut microbiome, uric acid, and periodic hypoxia (sleep apnea) may also influence these pathways. A primary disease driver may be an oversupply of fat to adipocytes such that their ability to store triglyceride without inducing cell stress is exceeded, which activates inflammatory pathways and causes insulin resistance. Understanding the major drivers of NASH facilitates the rational development of therapies for patients with NASH. Specific sites of intervention that might prevent or resolve NASH include interventions that modulate food intake (eg, portion sizes, bariatric surgery, satiety regulators), increase energy disposal (eg, exercise, thermogenesis), improve adipocyte insulin sensitivity [eg, peroxisome proliferator-activated receptor (PPAR)γ ligands], impair de novo lipogenesis (eg, acetyl-coenzyme A carboxylase and fatty acid synthase inhibitors), increase hepatic oxidative metabolism (PPARα ligands and thyroid hormone receptor beta agonists), and attenuate inflammation, cell death, and fibrogenesis. Therapeutic agents affecting multiple metabolic pathways throughout the body with potential beneficial effects on the liver include peptide hormone analogs (eg, analogs of fibroblast growth factor-19, fibroblast growth factor-21, glucagon-like peptide-1, gastric inhibitory peptide, glucagon) and nuclear receptor ligands such as drugs that target PPARα, PPARδ, PPARγ, thyroid hormone receptor β, and farnesoid X receptor. Abbreviations: ER, endoplasmic reticulum; CVD, cardiovascular disease.Insulin resistance is nearly universal in patients with NAFLD and is present in the liver, adipose tissue, and muscle.[47] Adipose tissue insulin resistance is characterized by increased release of free fatty acids from adipocytes (lipolysis) in the fasting state[48] and worsens with the progression of NAFLD to NASH.[39,47,49] Important factors that govern energy disposal include the frequency and intensity of exercise, the activation of brown adipose tissue to an energy-consuming thermogenic phenotype, and counterregulatory mechanisms that diminish energy disposal in response to reductions in calorie intake.[39,50] The ability and desire to engage in regular exercise can be strongly influenced by personal, community, corporate, societal, and legislative decisions, all of which thus have roles in the development of NASH. The heterogeneity of factors contributing to the pathophysiology of NASH among patients has impeded the development of diagnostic tests and therapeutics.[51] Although in some patients, the development and progression of NASH are driven by substrate overload and insulin resistance, in other patients, disease progression is heavily influenced by genetic factors impacting hepatocyte lipid handling.[43] Genetic polymorphisms have been associated with more advanced liver disease and the development of HCC in NASH. The I148M polymorphism of PNPLA3 impairs lipolysis of triglyceride in lipid droplets,[52] and polymorphisms in other proteins that play a role in hepatocyte fat metabolism have also been linked to the prevalence and severity of NAFLD, including transmembrane 6 superfamily member 2 (TM6SF2), which may play a role in cholesterol metabolism,[53] and MBOAT7, which influences phospholipid metabolism.[54] Recently, lossof-function variants in HSD17B13, a gene that encodes an enzyme that also localizes to lipid droplets in hepatocytes, have been linked to protection against NASH, progressive fibrosis, and HCC.[55] Rare loss-of-function mutations in CIDEB, a protein needed for activation of DNL,[56] have also been shown to be protective.[57] A host of additional factors, the review of which is beyond the scope of this guidance, contribute to heterogeneity in disease activity and progression.[49,58–63] Additional factors such as hepatocyte uric acid production, exposure to products derived from the gut microbiome, and perhaps low hepatic magnesium levels, may also contribute to the NASH phenotype.[64–69] Transcriptomic profiling of large cohorts of patients is further contributing to our understanding of this disease heterogeneity and its progression.[70,71] The response of the liver to lipotoxic injury includes activation and recruitment of resident macrophages, which further contributes to hepatocellular injury and stellate cell activation as part of a complex interplay among hepatic cell types.[60,72,73] Although markers of oxidative stress have been a consistent finding in NASH, its role in the pathogenesis of NASH in humans remains uncertain.[74] NAFLD is closely linked to and often precedes the development of metabolic abnormalities (insulin resistance, dyslipidemia, central obesity, and hypertension).[47,61,75–77] Having several metabolic abnormalities confers an even greater risk of histological progression of NASH and all-cause mortality.[8,47,78–81] The association between NAFLD and metabolic comorbidities may also reflect bidirectional interactions between the liver and other endocrine organs (eg, pancreas, adipose tissue, muscle) through the secretion of hepatokines that regulate fatty acid metabolism, insulin action, and glucose metabolism,[82–88] adipokines, and myokines.[39,89,90] The presence and severity of obesity are associated with NAFLD and disease progression.[91–93] Body fat distribution is an important determinant of the contributory role of obesity in NAFLD (Table 1). Android body fat distribution, characterized by increased truncal subcutaneous fat and visceral fat confers a higher risk of insulin resistance, CVD, and hepatic fibrosis, irrespective of body mass index (BMI).[94–99] In contrast, gynoid body fat distribution, characterized by increased subcutaneous body fat predominantly in the hips or buttocks, appears to be protective against NAFLD.[39,100] Visceral fat, which is more metabolically active and inflammatory than subcutaneous fat, mediates the majority of this risk.[101–105] As adipose tissue becomes more metabolically stressed, dysfunctional, and inflamed, insulin signaling is progressively impaired, promoting the inappropriate release of fatty acids leading to intrahepatic lipid accumulation and inflammation.[47,106,107] Initial evaluation of a patient with NAFLD History Weight history; medical comorbidities; recent and current medications; family history of T2DM, NAFLD, or cirrhosis; screening for OSA; alcohol use, including amount, pattern of use, and duration Physical examination Body fat distribution (eg, android vs. gynoid, lipodystrophic), features of insulin resistance (eg, dorsal-cervical fat pad, acanthosis nigricans), features of advanced liver disease (eg, firm liver, splenomegaly, prominent abdominal veins, ascites, gynecomastia, spider angiomata, palmar erythema) Laboratory tests Hepatic panel, CBC with platelets, fasting plasma glucose and glycated hemoglobin (A1c), fasting lipid profile, creatinine and urine microalbumin or protein to creatinine ratio, hepatitis C if not previously screened. Consider as appropriate other causes of steatosis/steatohepatitis (Table 2). Additional evaluation if elevated liver chemistries present: autoimmune serologies, transferrin saturation, ceruloplasmin, alpha-1 antitrypsin genotype, or phenotype T2DM is the most impactful risk factor for the development of NAFLD, fibrosis progression, and HCC.[108–111] Given the central pathogenic role that insulin resistance plays in the pathogenesis of both T2DM and NAFLD, it is not surprising that patients with T2DM have a higher prevalence of NAFLD (ranging from 30% to 75%) [10,112,113] and a higher risk of developing NASH with fibrosis.[93,114–117] Furthermore, the probability of advanced fibrosis increases with the duration of T2DM. Although there is potential for lead time and length time biases, these studies underscore the strong relationship between T2DM and NAFLD. The relationship between NAFLD and T2DM is bidirectional in epidemiological studies. Early in its course, NAFLD is associated with a reduction in insulin sensitivity,[47] even in the absence of overt diabetes. The presence of NAFLD is associated with a 2- to 5-fold risk of incident diabetes,[75,118–121] and therefore, patients with NAFLD should be screened for the presence of T2DM (Table 1). Furthermore, as liver disease progresses, so does insulin resistance and beta cell failure, making diabetes more challenging to manage.[107] The role of glycemic control in the progression of NAFLD/NASH remains controversial, with 2 small studies showing an association between poor glycemic control and hepatocellular injury and liver fibrosis,[68,122] whereas other studies have not corroborated this finding.[116,117,123] Although NAFLD has also been described in patients with type 1 diabetes, its prevalence is much lower than in T2DM, and it is closely related to coexistent metabolic risk factors (eg, higher BMI).[124,125] Hypertension is commonly associated with NAFLD. There is a higher incidence of hypertension in those with NAFLD across the disease spectrum, with incidence rates of 6.5 per 100 person-years in early disease to 14.5 per 100 person-years in those with cirrhosis.[35] The presence of hypertension is clearly additive to other metabolic comorbidities with respect to the epidemiological risk of NASH[126,127] and has been associated with fibrosis progression.[30] Whether hypertension mechanistically promotes the development of NAFLD/NASH or the inverse, or both are manifestations of underlying metabolic disease drivers, has not been established.[128,129] Patients with NAFLD are twice as likely to exhibit plasma lipid abnormalities as those without NAFLD,[120] and the serum lipid subfractions are more atherogenic in patients with NAFLD.[130,131] NASH resolution can lead to improved plasma HDL cholesterol and triglyceride levels and favorably impact lipoprotein subfractions, although it is unclear to what extent this is driven by the mechanism of the therapeutic intervention.[132–134] As patients progress to cirrhosis, they continue to remain at high risk for coronary artery disease[135] despite the normalization of serum lipids and lipoproteins due to hepatic synthetic failure.[130,136] Management of dyslipidemia in NAFLD should include the use of moderate-intensity to high-intensity statins as first-line therapy based on lipid risk levels and atherosclerotic CVD risk scores. Combination therapies of statins with other hypolipemic agents, such as ezetimibe, PCSK-9 inhibitors, inclisiran, bempedoic acid, fibrates, omega 3 fatty acids, or icosapent ethyl, should be considered when monotherapy with a statin does not achieve therapeutic goals. Statins are safe in patients with NAFLD across the disease spectrum, including advanced liver disease, and lead to a demonstrable reduction in cardiovascular morbidity and mortality.[137–140] However, in clinical practice, they are often underused despite extensive data demonstrating safety, even among patients with cirrhosis.[141–144] Statins are also considered safe in the context of compensated cirrhosis and may have beneficial effects on future decompensation and HCC risk, although additional confirmatory data are needed.[138] Although statins have been safely used in patients with decompensated cirrhosis, the risk of statin-induced adverse events might be higher in this population,[144] and thus more caution is warranted. In patients with decompensated cirrhosis and high CVD risk undergoing evaluation for liver transplantation, statin use can be considered with careful monitoring.[136] In patients with NAFLD and severely elevated triglycerides levels (eg, > 500 mg/dL), fibrates, or a combination of fibrates with prescription grade omega-3 fatty acids or icosapent ethyl, should be used to reduce the risk of pancreatitis. Fibrates may also improve atherosclerotic CVD outcomes when triglyceride concentrations are ≥ 200 mg/dL and HDL-C concentrations are 20 g/d) was associated with less improvement in steatosis and aspartate aminotransferase (AST) and lower odds of NASH resolution, compared with patients who did not consume alcohol.[217] In addition, daily alcohol may increase the risk for extrahepatic malignancies[218] and HCC.[219,220] Importantly, there is substantial variability in individual susceptibility to alcohol-induced liver injury, with an attendant lack of clarity on the dose required to impact disease course at an individual patient level. The impact of alcohol use (type, pattern, frequency, duration, and quantity) on the natural history of NAFLD/NASH requires further investigation. In addition to its strong association with obesity and other metabolic risk factors, higher rates of NAFLD have been reported in patients with hypothyroidism, hypogonadism, growth hormone (GH) deficiency, and polycystic ovarian syndrome (PCOS). Despite the known role of thyroid hormone in the regulation of hepatic lipid metabolism,[221,222] the association between NAFLD and systemic hypothyroidism in humans remains controversial.[223–225] No significant association between NAFLD and hypothyroidism (subclinical or overt) was observed in a large meta-analysis[226]; however, a cohort study of nearly 9500 patients followed for a mean of 10 years found hypothyroidism was associated with a 24% higher chance of NAFLD.[222–228] GH and the primary mediator of its metabolic effects, insulin-like growth factor-1, are important regulators of glucose and lipid metabolism, growth, body composition, and cellular regeneration.[229–232] GH deficiency is associated with body fat redistribution and increased visceral adipose tissue mass and can result in insulin resistance, hyperglycemia, hyperlipidemia, and NAFLD.[233] In a meta-analysis, insulin-like growth factor-1 levels were lower in patients with NAFLD and strongly associated with obesity and insulin resistance.[234] One cause of GH deficiency, panhypopituitarism, is associated with weight gain, insulin resistance, impaired glucose tolerance, and dyslipidemia, with a small case series demonstrating an increased risk for NASH and fibrosis.[235–237] Studies evaluating effects of GH replacement in subjects with GH deficiency and NAFLD have been small and uncontrolled. In a study of adults with hypopituitarism (n = 69), GH replacement reduced AST (n = 11 with NAFLD) and improved liver histology in NASH (n = 5 with paired biopsies).[235,238] In another study, GH replacement (n = 12 subjects) reduced visceral fat and hepatic steatosis by magnetic resonance spectroscopy.[239] In patients with HIV, lipodystrophy, and NAFLD, tesamorelin, a GH-releasing hormone analog, which augments pulsatile GH secretion and increases insulin-like growth factor-1 without adversely affecting insulin sensitivity,[240] reduced liver fat.[241] Overall, the association between a disturbance in the GH axis and NAFLD is strongly linked to changes in visceral fat and insulin resistance, but screening is not recommended for all patients. A number of studies report associations among hypogonadism, impaired glucose and lipid metabolism,[242] and NAFLD.[242–245] A meta-analysis found that NAFLD was associated with lower serum testosterone levels in men but higher levels in women,[246] a finding confirmed by others.[247] The association between hypogonadism and NAFLD is often confounded by the presence of obesity and insulin resistance, both of which are known to be associated with hypogonadotropic hypogonadism. In contrast, low testosterone levels can also negatively affect body composition, worsen insulin resistance, and thus contribute to the development of hepatic steatosis.[248] One study in men suggested that a low serum total testosterone level was independently associated with NAFLD, and the association was unchanged even after controlling for visceral adipose tissue volume and insulin resistance.[249] In contrast, in another study including 175 men with T2DM evaluated by 1H-magnetic resonance spectroscopy (MRS) and liver histology, the relationship between lower total testosterone and steatosis disappeared when adjusted for insulin resistance and obesity, with no relationship to the severity of liver necroinflammation or fibrosis.[250] Testosterone replacement in men improves insulin resistance, serum lipids, and visceral adiposity, indicating a more direct role of testosterone on metabolic risk factors for NAFLD in men,[195] but it should be reserved for carefully selected patients, particularly as it may exacerbate OSA. In women, hypogonadism is associated with increased liver enzymes as well as a higher prevalence of NAFLD and advanced fibrosis.[251–254] The prevalence of NAFLD is higher in postmenopausal compared with premenopausal women.[255] Limited data suggest that higher free testosterone levels in premenopausal women are associated with an increased risk of prevalent NAFLD after menopause. Furthermore, there is a 25% likelihood of NAFLD in higher quintiles of testosterone as well as an association between lower serum estradiol levels and NASH.[244,256] Limited studies demonstrate the benefit of hormone replacement therapy on NAFLD, although adverse hepatic effects were found in one study that were attributed to progesterone.[256] Apart from estrogen deficiency, relative androgen excess and decreased sex hormone-binding protein levels are observed in postmenopausal women. The associated increased abdominal adiposity closely relates to the severity and progression of NAFLD, although direct causality has not been established. In PCOS, hyperinsulinemia promotes hypothalamic luteinizing hormone stimulation of ovarian theca cells resulting in excessive androgen production.[257,258] Large meta-analyses and population studies have demonstrated a 2- to 4-fold increase in the prevalence of NAFLD and an increased risk of T2DM among women with PCOS, suggesting that insulin resistance is the main driver of disease in PCOS.[257,259,260] In a retrospective study of women with biopsy-confirmed NAFLD (n = 102), PCOS was associated with the severity of steatohepatitis and advanced fibrosis after adjusting for age and BMI.[261] However, this study did not account for insulin resistance, which may have influenced the association. Although NAFLD is commonly associated with obesity, it can also occur in nonoverweight (BMI 6 mo) in liver chemistries. Although liver biopsy assessment remains the reference standard for the grading and staging of NASH, it has important limitations related to risk, cost, and resource utilization. Therefore, liver biopsies for grading and staging of NASH are not consistently performed in clinical practice and should be reserved for specific clinical scenarios (Figure 2).[317] Noninvasive biomarkers are emerging as valuable tools for predicting adverse liver-related outcomes (see more below), hitherto an important function of liver biopsies. Validation of noninvasive biomarkers in accordance with the US Food and Drug Administration (FDA)–National Institutes of Health guidance[318] will facilitate the diagnosis of patients with clinically meaningful disease and evaluate their response to treatment without the need for liver biopsies. Although commonly used in clinical practice, conventional B-mode ultrasound lacks sufficient sensitivity for lesser degrees of steatosis, particularly in those with concomitant obesity,[319,320] and provides only a subjective semiquantitative assessment of steatosis severity. The absence of detectable steatosis on ultrasound does not exclude the presence of NASH or the presence of fibrosis, although ultrasound can be helpful when cirrhotic liver morphology is identified or if it identifies evidence of portal hypertension (eg, ascites, splenomegaly, portosystemic collateral vessels). For the assessment of hepatic steatosis, the controlled attenuation parameter (CAP), typically measured in conjunction with VCTE, provides a point-of-care semiquantitative assessment of hepatic steatosis but does not accurately quantify or monitor changes in liver fat[321] (Table 5). Parameters for the noninvasive assessment of NAFLD according to clinical context of use Modality type Cut point Strengths/limitations, references/caveats Likely Unlikely Identification of hepatic steatosis Imaging Ultrasound “Detected” NA Semiquantitative assessment: mild/moderate/severe; low sensitivity with less severe steatosis[322]; steatosis can have similar echo characteristics as advanced fibrosis FibroScan: CAP ≥ 288 dB/min Limited accuracy for quantification[323] MRI-PDFF ≥ 5% < 5% Most sensitive across spectrum of steatosis; accurate to assess dynamic change[324] Identification of “at-risk” NASH FAST ≥ 0.67 < 0.35 ≤0.35 (sensitivity 90%), ≥ 0.67 (specificity 90%); in validation cohorts, the PPV of FAST ranged between 0.33 and 0.81[28,325] MAST ≥ 0.242 ≤ 0.165 0.242 (specificity 90%),[326] 0.165 (sensitivity 90%)[326] MEFIB FIB-4 ≥ 1.6 plus MRE ≥ 3.3 kPa FIB-4