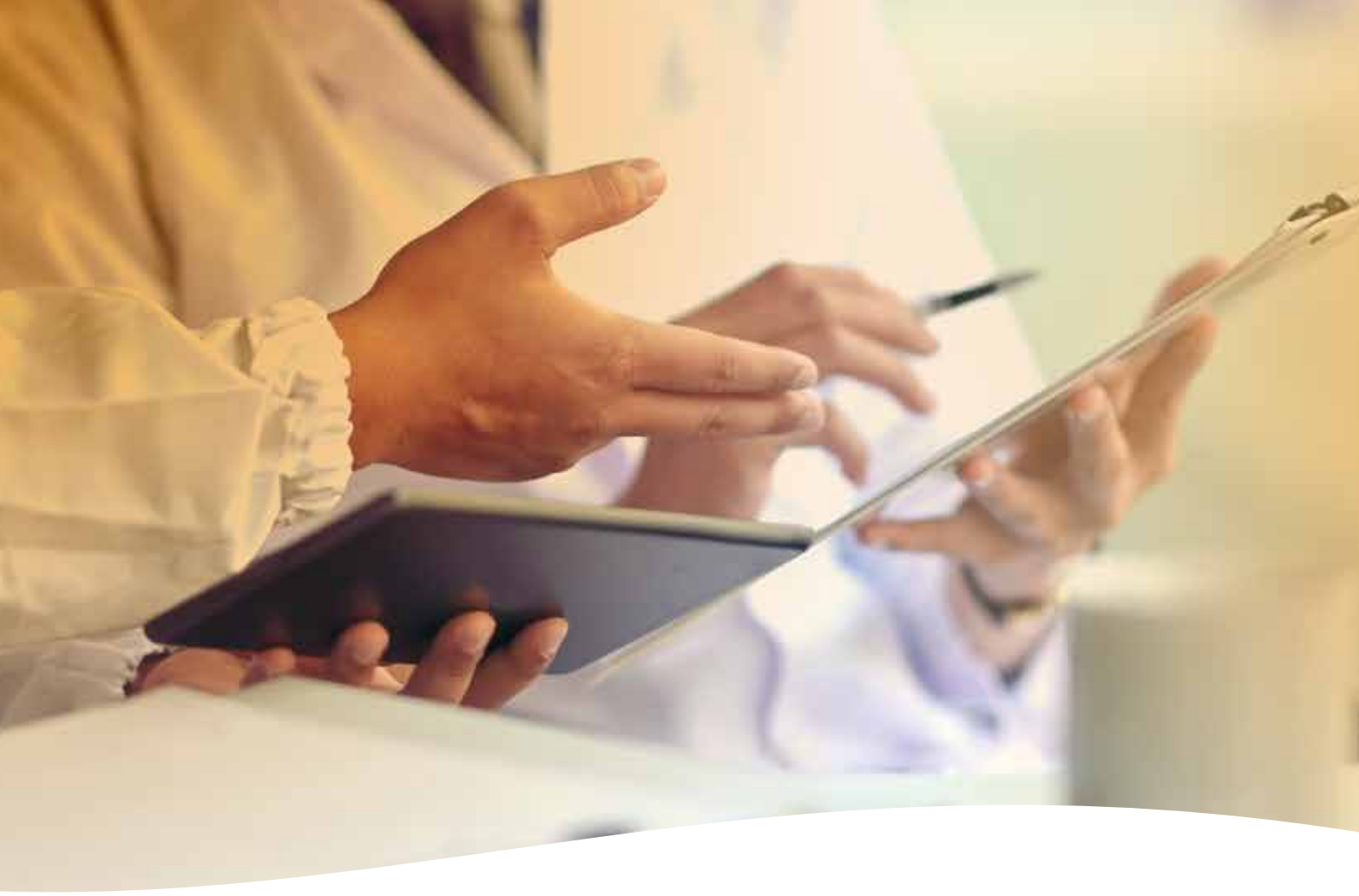


Diabetology and Endocrinology handbook

Usefulness of FibroScan® and its associated scores in patients with diabetes and metabolic risks

April 2023

FibroScan® by echosens

Contents

List of abbreviations

- LSM: Liver Stiffness Measurement
- CAP™: Controlled Attenuation Parameter
- VCTE™: Vibration-Controlled Transient Elastography
- T2DM: Type 2 Diabetes Mellitus
- NAFL: Non-Alcoholic Fatty Liver
- NAFLD: Non-Alcoholic Fatty Liver Disease
- NASH: Non-Alcoholic Steatohepatitis
- NFS: NAFLD Fibrosis Score
- NIT: Non-invasive test
- HCC: Hepatocellular Carcinoma

1 Introduction

The FibroScan® medical device allows non-invasive measurement of two biomarkers: liver stiffness measurement (LSM) which is based on the Vibration-Controlled Transient Elastography (VCTE™) technology[1] and Controlled Attenuation Parameter (CAP™)[2,3]. Many publications show the performances of LSM and CAP in assessing fibrosis stage and steatosis grade, respectively[4-7] in a large spectrum of chronic liver diseases, such as viral hepatitis, alcoholic liver disease, or non-alcoholic fatty liver disease (NAFLD). Additionally, new scores have been developed based on these FibroScan® measurements and routine clinical parameters (Fast™, Agile3+, and Agile 4) as an aid for the diagnosis of fibrotic NASH[8], advanced fibrosis, or cirrhosis[9], respectively in NAFLD subjects.

NAFLD encompasses a spectrum of histological changes that begin with simple liver steatosis (NAFL), which may gradually progress to the development of chronic inflammation (non-alcoholic steatohepatitis (NASH), fibrosis, and ultimately cirrhosis and its complications.

NAFLD is a growing public health problem reaching epidemic proportions and is considered as the most common cause of chronic liver disease worldwide. The prevalence of NAFLD in the general population is around 24-25% of adults[10] with notable differences across regions[11]. Also, NAFLD prevalence can increase up to 90% in morbidly obese patients[12].

As NAFLD and type 2 diabetes (T2DM) often coexist[13], the prevalence of NAFLD in these patients is higher, around 70% to 90% in T2DM patients[14], while approximately 30% to 40% of patients with diabetes have NASH[15]. The TD2M is the most important driver of mortality in patients with NAFLD, as the coexistence result in a worse metabolic profile and higher cardiovascular risks.[16,17]

The aim of this document is to provide a summary of the existing literature documenting the clinical use of LSM by VCTE™, CAP™, and FibroScan®-based scores in NAFLD/NASH patients with diabetes and other metabolic risk factors in primary care, endocrinology, obesity medicine, and gastroenterology practices.

2
Screening for NAFLD

2.1 Foreword

NAFLD related liver disease is becoming one of the leading causes of liver cirrhosis and its associated complications such as hepatocellular carcinoma (HCC), whose risk is estimated to be at 0.3% per year in NASH patients[18]. Furthermore, because over 50% of patients with advanced fatty liver disease have normal levels of liver enzymes, significant liver disease is missed when relying solely on abnormal liver blood test to identify it[19]. The diagnosis of NAFLD could be missed due to the lack of cost-effective, non-invasive diagnostic tools, and the absence of a clear consensus on the value of screening for NAFLD[20]. Altogether, this highlights the importance of early detection of NAFLD and the clinical need to identify at risk individuals for regular screening.

2.2 Screening for T2DM and metabolic risk factors in the general population

Koehler *et al.* evaluated the prevalence of patients with abnormal LSM values (≥ 8kPa) in a cohort from the general population, as part of the Rotterdam study[21]. Among the 3,041 participants measured by FibroScan®, 5.6% exhibited LSM value ≥ 8 kPa suggesting clinically relevant fibrosis. Presence of T2DM, especially with concomitant presence of steatosis, resulted in increased probabilities of having clinically relevant fibrosis, with an overall probability of 17.2%. These findings underline the significant role of these risk factors for liver fibrosis and stress the importance screening for significant fibrosis in patients with insulin resistance and T2DM to mitigate the risk of progression of liver damage.

Younossi *et al.*[17] performed a study in primary care and endocrinology outpatient clinics to screen patients for presence of NAFLD. Of the 7,555 patients screened the prevalence of T2DM, hypertension, and hyperlipidemia was 26%, 48% and 56%, respectively. Of the 103 patients referred to a FibroScan® procedure, 10% had LSM between 8kPa (presumed clinically significant fibrosis) and 12kPa (assumed advanced fibrosis or cirrhosis). Furthermore, 8% had LSM ≥12 kPa, suggesting possible cirrhosis; these patients had higher body mass index, liver enzyme levels, and were more likely to have comorbidities including diabetes and cardiovascular disease.

Vilar-Gomez *et al.*[22] performed a study in the United States which aimed at assessing the prevalence of individuals with at-risk NASH based on the Fast™ score (which combines LSM, CAP and AST) and a cut-off ≥ 0.35 (sensitivity 90%). The fibrotic NASH prevalence based on Fast ≥ 0.35 was 5.8% in the general population, increasing to 11.7% in patients with metabolic syndrome and to 22.5% in the subjects with T2DM.

> *It is important to note that most patients with NAFLD have likely not been identified and most of them are presumably being seen in the primary care practices without being diagnosed*
>
> *Younossi et al. Clinical and Translational Gastroenterology 2021*

TABLE 1

Fibrosis and Steatosis Assessment in T2DM Patients

	Fibrosis stage as detected by LSM (cut-off kPa)					Steatosis stage as detected by CAP™ (cut-off dB/m)			
Fibrosis-steatosis stage/ Publication = n patients	F0	F1	F2	F3	F4	S0	S1	S2	S3
Kwok *et al.*[23] = 1,884 (LSM), 1,799 (CAP)	**82.3%** (<9.3 kPa)			**17.7%** (≥9.3 kPa)		**27%** (<222 dB/m)	**5.1%** (222-232 dB/m)	**29.6%** (233-289 dB/m)	**38%** (≥290 dB/m)
Roulot *et al.*[24] = 669	**87.3%** (<9.3 kPa)		**3.3%** (≥8–9.4 kPa)	**7.3%** (≥9.5–12.9 kPa)	**2.1%** (≥13 kPa)	**25.4%** (<235 dB/m)	N/A	**49.9%** (>282 dB/m)	**23.8%** (>321 dB/m)
Lomonaco *et al.*[16] = 561	**79%** (<6.9 kPa)	**6%** (≥7.0–8.1)	**6%** (≥8.2–9.6 kPa)	**6%** (≥9.7–13.5 kPa)	**3%** (≥13.6 kPa)	**30%** (<273 dB/m)	**9%** (274–289 dB/m)	**7%** (290–301 dB/m)	**54%** (≥302 dB/m)
Ciardullo *et al.*[25] = 825	**76.2%** (<8.1 kPa)		**8.4%** (≥8.2–9.6 kPa)	**7.7%** (≥9.7–13.5 kPa)	**7.7%** (≥13.6 kPa)	**26.2%** (<273 dB/m)	**7.2%** (274–289 dB/m)	**8.3%** (290–301 dB/m)	**58.3%** (≥302 dB/m)
Sporea *et al.*[28] = 534	**72.6%** (<8.1 kPa)		**7.8%** (≥8.2–9.6 kPa)	**11.4%** (≥9.7–13.5 kPa)	**8.2%** (≥13.6 kPa)	**23.9%** (<273 dB/m)	**8.9%** (274–289 dB/m)	**6.9%** 290–301 dB/m)	**60.3%** (≥302 dB/m)

2.3
Screening for NAFLD IN T2DM patients

The burden of T2DM worldwide is expected to reach 7.7% of the world population by 2030[18]. The use of FibroScan® in noninvasive screening strategies for early diagnosis of fibrosis and steatosis in diabetics has been evaluated in several studies, as summarized in Table 1.

Kwok *et al.*[23] evaluated a screening strategy for NAFLD in T2DM patients from primary care and hospital clinics, with 70% patients having increased CAP suggestive of NAFLD, and 18% increased liver stiffness suggesting presence of advanced fibrosis, additionally they found that T2DM patients with VCTE ≥9.6 kPa had a longer duration of diabetes as compared to patients with T2DM and VCTE <9.6 kPa. A study in a French cohort by Roulot *et al.*[24] corroborates these results with similar steatosis and fibrosis rates. The diabetic population displayed a higher prevalence of overweight and obese individuals than the general population: 41.8% were overweight, 39.8% obese, compared to 37.9% and 14.4%, respectively, in the general population. Metabolic syndrome was present in 56.2% of T2DM patients compared to 20.7% in the general population.

Lomonaco *et al.*[16], Ciardullo *et al.*[25] and, Sporea *et al.*[26] used the cut-offs proposed by Eddowes *et al.*[27] for stratifying liver fibrosis (F≥2: 8.2 kPa, F≥3: 9.7 kPa, and F4>13.6 kPa) and steatosis (S1 (mild): 274 dB/m, S2(moderate): 290 dB/m, S3(severe): 302 dB/m)) stages. The publications show similar results with a prevalence of suspected liver fibrosis, LSM ≥8.2 kPa of 21%, 23.8% and 27.4% in the T2DM population. Moreover, severe steatosis (CAP ≥302 dB/m) was found in at least half the patients in all publications. The presence of fibrosis in Lomonaco *et al.* (cf. Figure 1) occurred in 10% of patients with mild steatosis (S1), 23% of those with moderate steatosis (S2), and 30% when steatosis was severe (S3). Sporea *et al.* associated by multivariate analysis female gender, BMI, waist circumference, elevated levels of AST, cholesterol, triglycerides, blood glucose, and high LSM with severe steatosis based on CAP ≥302 dB/m. In contrast, BMI, waist circumference, elevated levels of AST, HbA1c, and CAP were associated with advanced fibrosis based on LSM values ≥13.6 kPa.

Harman *et al.*[28] screened at-risk individuals (patients with hazardous alcohol use and presence of T2DM) in general practice for undetected cirrhosis using FibroScan® and studied the risk factors underlying these cases. Among the 899 patients that underwent LSM, 25.6% of patients had fibrosis (defined by LSM ≥ 8 kPa), and 2.9% had cirrhosis, defined by increased LSM, as well as histological, radiological, and biochemical methods. Presence of cirrhosis was significantly increased in obese patients with T2DM vs non-obese patients with T2DM (odds ratio 9.4 [95% CI 2.2-40.9]) and in obese patients with hazardous alcohol use compared to non-obese with hazardous alcohol use (5.6 [95% CI 1.6-19.7]). The number of newly diagnosed cirrhosis cases by screening with FibroScan® in primary care and referring to hepatologists doubled in this population, meaning the existing estimates of prevalence are likely to be underestimated.

> *Because almost 20% of the diabetic patients are at risk for compensated advanced chronic liver disease, it seems reasonable to screen all diabetic patients by liver elastography.*
>
> *Sporea et al. Journal of Clinical Medicine 2020*

2.4
Screening for NAFLD in overweight patients

As previously mentioned, TD2M and obesity are metabolic risk factors for NAFLD and its progression to NASH which could eventually lead to cirrhosis and hepatocellular carcinoma[29]. In patients with metabolic risk factors, T2DM, obesity and the presence of metabolic syndrome have been shown to be the key features associated with VCTE >7 kPa[30]. As such, it has been suggested that overweight and obese patients should be considered in priority for NAFLD screening in primary care and endocrinology setting[31].

A recent meta-analysis and systematic review by Quek *et al.* (cf. Figure 2) has estimated that 70 to 90% of the overweight population (BMI>25 kg/m²) may have NAFLD, and 33 to 50% to have NASH; additionally, this population presented clinically significant fibrosis (F2-F4) in 35 to 41% of patients. Furthermore, clinically significant fibrosis was observed in 20 to 27% of the obese population (BMI>30 kg/m²) with NAFLD, with almost 7% having advanced fibrosis (F3–4).

FIGURE 1

A: Proportion of patients with T2DM (=591) screened in the outpatient clinical setting having liver steatosis (measured by CAP™) and with liver fibrosis (LSM by VCTE™)
B: Severity of liver fibrosis (LSM) in patients with T2DM divided into four stages: mild (F1), moderate (F2), severe or pre-cirrhosis (F3), and cirrhosis (F4).
C: Severity of liver steatosis in patients with T2DM divided into mild (S1), moderate (S2), and severe[16]

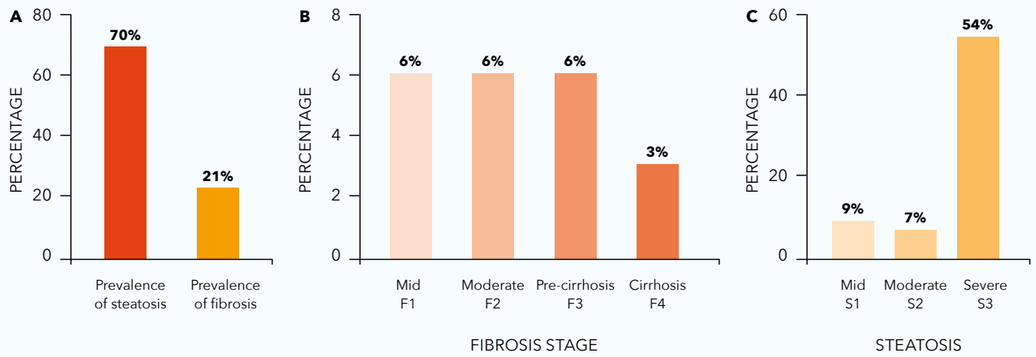
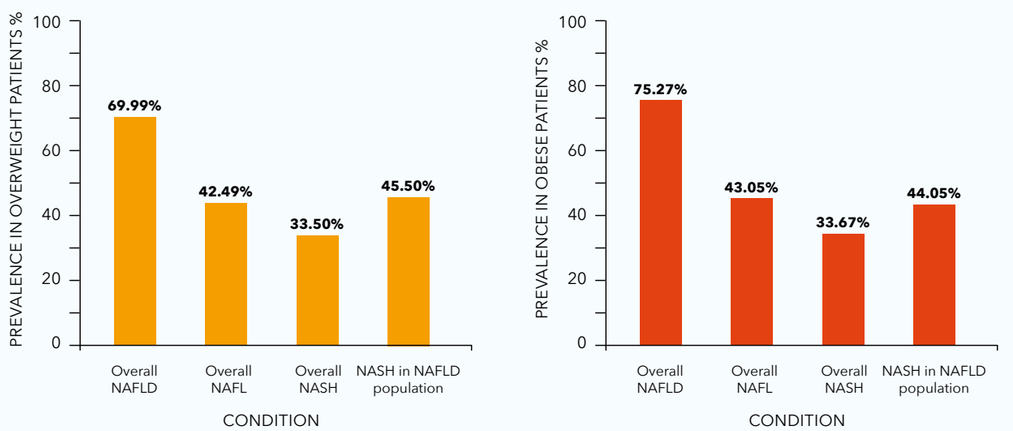


FIGURE 2

Prevalence of NAFLD, NAFL, and NASH in overweight and obese populations[31]



3

Clinical Care Pathways for Identification & Management of NAFLD

Due to the fact that patients with metabolic syndrome are mainly managed in primary care and endocrinology and/or diabetology settings, it is crucial to implement pathways to help screen these patients in these clinics, to identify those with NAFLD who are at higher risk of progression to advanced liver disease[17]. Recently, some major international liver and diabetology societies have issued specific guidelines proposing such types of pathways to optimize detection of NAFLD and referrals to liver specialists for more advanced cases.

3.1 International guidelines

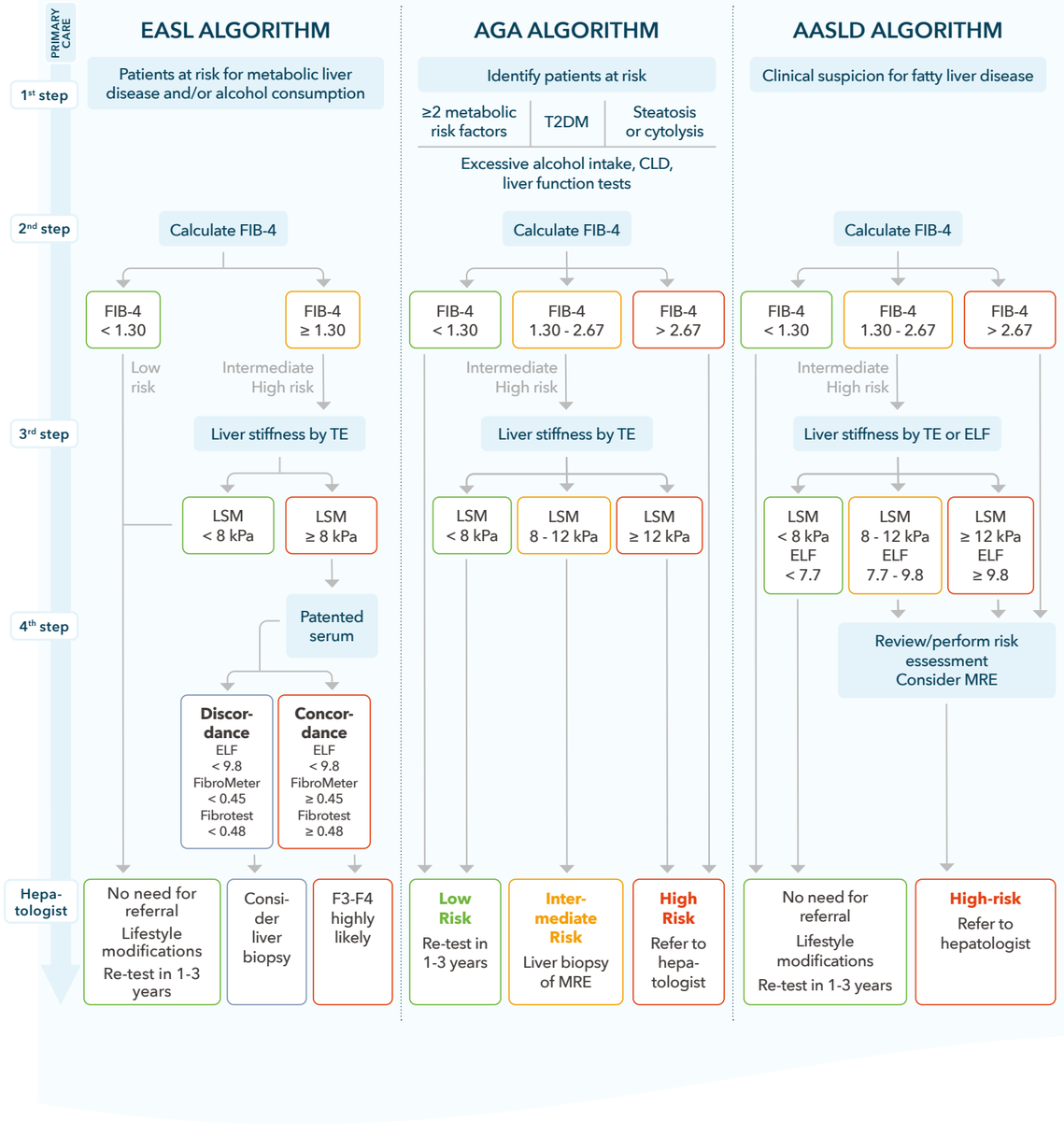
A multi-step sequential approach using different NITs (cf. Figure 3) has been proposed in multiple pathways. In 2021, the American Gastroenterological Association (AGA), in collaboration with members from professional societies, including the American Diabetes Association (ADA), American Osteopathic Association, Endocrine Society, and the Obesity Society[32] recommends to test all patients presenting liver risk factors (presence of T2DM or prediabetes, steatosis, obesity, alcohol consumption, abnormal transaminases…), by conducting standard tests to obtain key measures, followed by a simple FIB-4 test. This is in alignment with the more recent 2023 AASLD clinical guidelines[33] that also recommend screening patients with clinical suspicion of NAFLD, as well as the joint guidelines from the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO)[29] that recommend to test in priority patients with metabolic risk factors and/or alcohol consumption.

Although most patients with NAFLD and NASH have traditionally been diagnosed and managed by hepatologists, the recent availability of noninvasive diagnostic procedures is expanding the role of other health care professionals likely to see patients with these conditions, particularly gastroenterologists, endocrinologists, obesity medicine specialists, and primary care providers.

Sporea et al. Journal of Clinical Medicine 2020

FIGURE 3

Referral pathway proposed by the European Association for the Study of the Liver (EASL), the American Gastroenterology Association (AGA), and the American Association for the Study of Liver Disease (AASLD) to noninvasively assess advanced liver fibrosis[30]



All the above mentioned organizations propose as a second line test a LSM examination by VCTE/FibroScan® for patients with indeterminate FIB-4 results[32]. The 2021 EASL guidelines[34] further recommend a third line assessment using patented serum tests and liver biopsy. Finally, all associations recommend to refer the patients belonging to the "high risk groups" to a liver specialist.

Patients with diabetes are at higher risk for NASH and advanced fibrosis and should be screened for clinically significant fibrosis (stage ≥2). In the primary care setting, vibration-controlled elastography (VCTE™) is favored as initial secondary assessments due to cost considerations.

Rinella, et al. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease

Regarding the patient's management, the American Association of Clinical Endocrinology (AACE), focuses on the management of patients with NAFLD with diabetes, to prevent the progression to NAFLD related cirrhosis. They suggest the "low risk groups" to be managed by diabetologists and endocrinologists outside tertiary care[15]. The joint NAFLD guidelines from the EASL, EASD and EASO on the management of NAFLD also recommended to monitor these "low risk" patients with simple NAFL without worsening of metabolic risk factors, every 2 to 3 years. This monitoring should include routine biochemistry, assessment of comorbidities and non-invasive monitoring of fibrosis[35]. Furthermore, AASLD recommends that patients with pre-diabetes, T2DM or two or more metabolic risk factors should be assessed every 1 to 2 years. Finally, the European guideline on obesity care in patients with gastrointestinal and liver diseases (Joint European Society for Clinical Nutrition and Metabolism/United European Gastroenterology guideline) mentions that all patients with obesity should be assessed for T2DM, and that CAP could be used to verify the diagnosis of NAFLD instead of liver biopsy[36].

NAFLD is a major public health problem that will only worsen in the future, as it is closely linked to the epidemics of obesity and type 2 diabetes mellitus. Given this link, endocrinologists and primary care physicians are in an ideal position to identify persons at risk on to prevent the development of cirrhosis and comorbidities. To stage the risk of fibrosis in persons with NAFLD, clinicians should prefer the use of VCTE as best validated to identify advanced disease and predict liver-related outcomes.

Cusi et al. AACE Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings; Endocrine Practice 2022

3.2
Validation of the clinical pathways in primary care

This sequential approach detailed in the guidelines is now being widely tested in real clinical practice.

Tomah *et al.*[20] developed an algorithm aimed at supporting diabetologists and primary care providers for screening T2DM patients for NAFLD and advanced fibrosis. They suggest the hepatologist to perform the FibroScan® examination once the patient has been referred by a previous FIB-4 or NFS result. This study concluded that increased awareness about NASH and its complications is warranted among diabetologists, and an interdisciplinary approach is needed for the care of T2DM patients and NAFLD, starting with early identification and higher quality referrals.

Mansour *et al.*[19] validated the use of at least a two-step assessment (FIB-4 followed by LSM by VCTE™) of liver fibrosis/cirrhosis into routine annual diabetes review of 467 patients with T2DM. The results showed that 43% of the patients referred for FibroScan® had significant fibrosis (defined by LSM≥8 kPa) and 22.4% had cirrhosis (defined by LSM≥15 kPa). The use of this pathway represented a 7-fold increase in comparison from the standard care in the detection of advanced liver disease compared with standard care in place before the implementing the clinical algorithm.

4

Assessment of T2DM severity and of cardiovascular risk with Fibroscan®

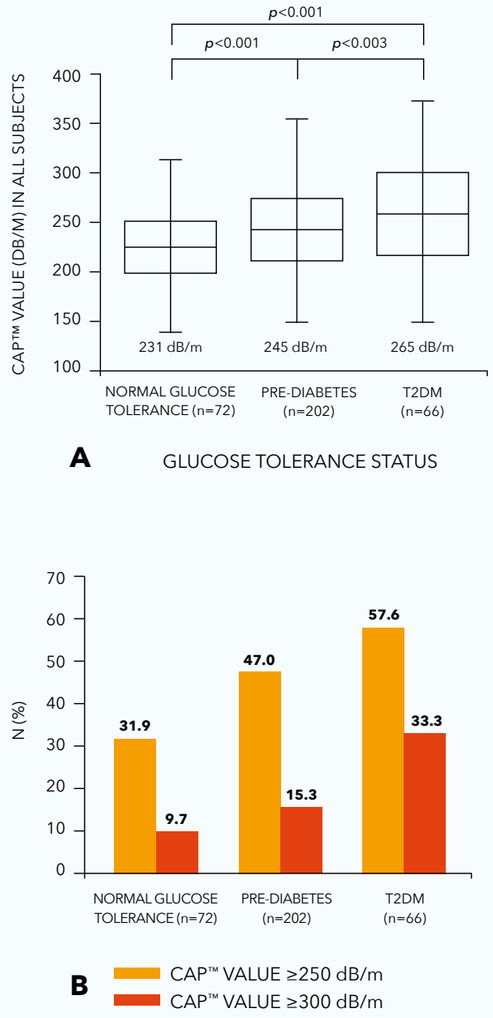
Chon *et al.*[37] were the first to evaluate the link between severity of NAFLD detected by CAP™, and the glucose tolerance profile, in a cohort of 340 patients divided in 3 groups (T2DM patients, prediabetics, and patients with normal glucose tests). They showed that the presence and severity of NAFLD detected by CAP™ was increasing with the glucose tolerance status and was significantly different within the three groups (cf. Figure 5).

Conversely, by multivariate analysis, CAP™ was also found to be associated with T2DM: subjects with CAP ≥ 300 dB/m were found to have a 2.8-fold higher risk of having T2DM than those with CAP < 250 dB/m [p=0.017]. At last, CAP was also strongly correlated with insulin resistance, a known marker of T2DM. Hence CAP may represent an additional parameter that can supplement the traditional variables representing metabolic risk, for evaluation of T2DM.

FibroScan® could be further used to risk stratify for diabetes specific complications such as cardiovascular ones, as suggested by Lombardi *et al.* who performed a study in 472 NAFLD patients using LSM by VCTE™. Elevated LSM (>8.7 kPa) was significantly correlated with presence of carotid plaques in a multivariate model. This cut-off was also independently linked to higher carotid arterial stiffness values in patients under the age of 50[38]. A recent Brazilian article reports the results of the Rio de Janeiro Type 2 diabetes and NAFLD cohort of 400 patients with a median follow up of 5.5 years. Increased LSM (>9.6 kPa) was an independent predictor of Cardiovascular Events and all-cause mortality. In the same cohort, steatosis as assessed by CAP™ (CAP>296 dB/m) seemed to have a protective factor for all cause of cardiovascular mortality. Both parameters seem to have dual opposite effects and may be useful for risk stratification of cardiovascular outcomes if these results are confirmed.

FIGURE 4

Prevalence (A) and severity (B) of NAFLD detected by CAP™, by glucose tolerance status[37]



5

Monitoring effect of interventions

The Joint European Society for Clinical Nutrition and Metabolism and the United European Gastroenterology guidelines recommends monitoring of fibrosis progression or regression in patients with NAFLD by non-invasive procedures[36]. Thus, the effect of therapeutic interventions on T2DM subjects has also been evaluated by the mean of FibroScan® in several studies.

5.1 Lifestyle intervention

Weight loss/Lifestyle Management

The 2019 ADA guidelines recommend as a first line of therapy a comprehensive lifestyle management, including weight loss and physical activity[39]. The 2023 AASLD guidelines also recommend the use of CAP™ by FibroScan® for the point-of-care assessment of hepatic steatosis which can be used as a monitoring tool for evaluating lifestyle changes.

Franco *et al.* (2020)[40] evaluated the effect of different lifestyle interventions: aerobic and anaerobic physical activity programs, a Low Glycemic Index Mediterranean Diet (LGIMD), and their combination on CAP by FibroScan®. The results showed that LGIMD combined with aerobic physical activity program (PA1) had the highest effect on reduction of CAP, compared to the other interventions (see Figure 5), as well as having a positive effect in intrahepatic markers of liver damage, insulin resistance and BMI.

The results are also in line with more recent publications, such as the study from Calabrese *et al.*[41] from 2022, in which they concluded that a combination of a Mediterranean diet and a physical activity program contributes to the composition of the gut microbiota in NAFLD patients (all overweight or obese), by reducing the characteristic dysbiosis present in these patients, increasing the resilience of microbial communities inhabiting the gut, reducing the CAP parameter assessing liver steatosis.

Finally, Zaharia *et al.*[42] followed patients with T2DM and NAFLD during a 12-week low calorie diet. Weight was reduced by 9%, One in three participants normalized their HbA1c (< 6.5%), and liver fat (measured by CAP) decreased by 20% (326 ± 64 vs 263 ± 56 dB/m), alongside with decreased liver stiffness, measured by LSM.

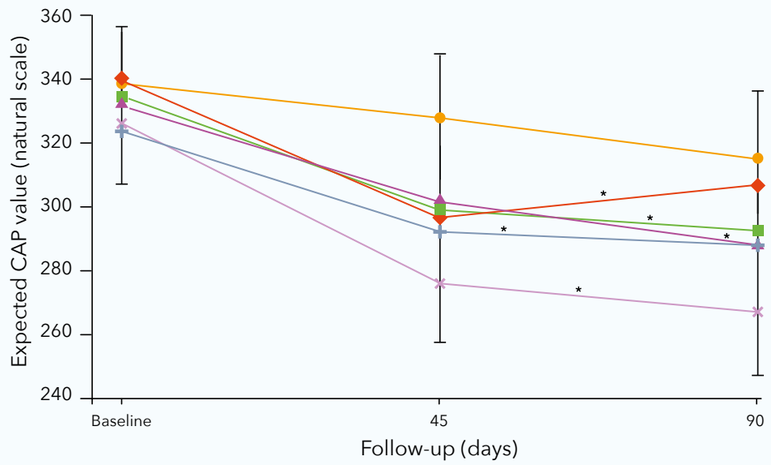
Surgical Interventions

NAFLD/NASH is increasingly accepted as a comorbid condition benefitting from bariatric surgery[33], thus, this therapeutic interventions have been demonstrated to reduce body weight, HbA1c, insulin resistance, and has even resulted in partial or full remission of T2DM in certain individuals[20].

Gollisch *et al.*[43] have evaluated the effect on fibrosis and steatosis (assessed by LSM and CAP, respectively) of an innovative treatment of T2DM aiming at improving glucose control and weight loss (EndoBarrier gastrointestinal liner) on a group of 20 patients with a 13 months follow up period. Overall, during the course of treatment, LSM reduced from 10.4 kPa (IQR 6.0–14.3) to 5.3 kPa (IQR 4.3–7.7, $p < 0.01$). Regarding the group of patients with elevated LSM at baseline (n = 13), LSM decreased from 12.9 kPa (IQR 10.3–15.1) to 5.8 kPa (IQR 4.8–8.8, $p < 0.01$), and normalized in most patients (8/13). CAP values also significantly improved during EndoBarrier treatment from 343 dB/m (IQR 326-384) to 317 dB/m (IQR 269-375, $p < 0.05$).

FIGURE 5

Diet and Physical Activity Effects on NAFLD: Expected CAP values by Treatment and Time.



C: control diet
LGIMD: Low Index Mediterranean Diet
PA1: Aerobic Physical Activity
PA2: Combined Physical Activity[40]
PA1+LGIMD
PA2+LGIMD

CAP: Controlled Attenuation Parameter FibroScan®
*p<0.05 45 days vs baseline and 90 days vs baseline

5.2 Pharmacotherapies

Some medications approved for T2DM have shown benefits for the treatment of NAFLD/NASH and should be taken into consideration in some situations under specific circumstances[33]. Their impact on FibroScan® biomarkers is discussed below, for each category of medication.

Thiazolidinediones (TZDs)

Lee *et al.*[46] investigated the effects of a 24 weeks treatment by lobeglitazone on T2DM patients with NAFLD (identified by CAP ≥ 250 dB/m). They showed that at the end of the treatment lobeglitazone improved hepatic steatosis, as assessed by CAP (which decreased from 313.4 to 297.8 dB/m, p=0.016), and liver enzyme profiles, as assessed by aminotransferase and γGTP levels, but not liver fibrosis (assessed by LSM).

Lavynenko *et al.*[47] compared the efficacy of a triple therapy (metformin/exenatide/pioglitazone) versus a stepwise conventional therapy (metformin → glipizide → glargine insulin) in T2DM patients that had a 6 year follow up with sequential FibroScan® examinations using CAP and LSM for monitoring steatosis and fibrosis, respectively. At the end of the study, 69% of patients who received the conventional therapy had a grade S2/S3 steatosis (CAP > 269 dB/m) versus 31% in triple therapy (P = .0003). Additionally, 26% of subjects who received the conventional therapy had stage F3/F4 fibrosis (LSM> 8 kPa) in comparison to 7% in triple therapy (P = .04). These results confirmed already reported effects of pioglitazones on reducing hepatic steatosis and fibrosis in T2DM patients with biopsy proven NASH.

GLP1 Receptor Agonists

The class of Glucagon-like peptide-1 receptor agonists (GLP-1RAs) antidiabetic agent has also demonstrated efficacy in improving NAFLD. Tan *et al.*[48] assessed liver fibrosis using LSM in T2DM patients, in which 262 were liraglutide users and 1,503 non-users. After a 12-month follow-up liraglutide use tended to be associated with a reduced prevalence of advanced fibrosis when compared to the non-users (3.1% vs. 6.1%, P = 0.218).

Similarly, Newsome *et al.*[49] conducted a study in 320 biopsy proven NASH patients to determine the efficiency of the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide. Among patients with biopsy-confirmed NASH and fibrosis, a significantly higher percentage of patients had NASH resolution with once-daily semaglutide when compared with placebo (40% in the 0.1-mg group, 36% in the 0.2-mg group, 59% in the 0.4-mg group, and 17% in the placebo group). However, the study did not show a significant between-group difference in the percentage of patients with an improvement in fibrosis stage, assessed by LSM.

SGLT2 Inhibitors

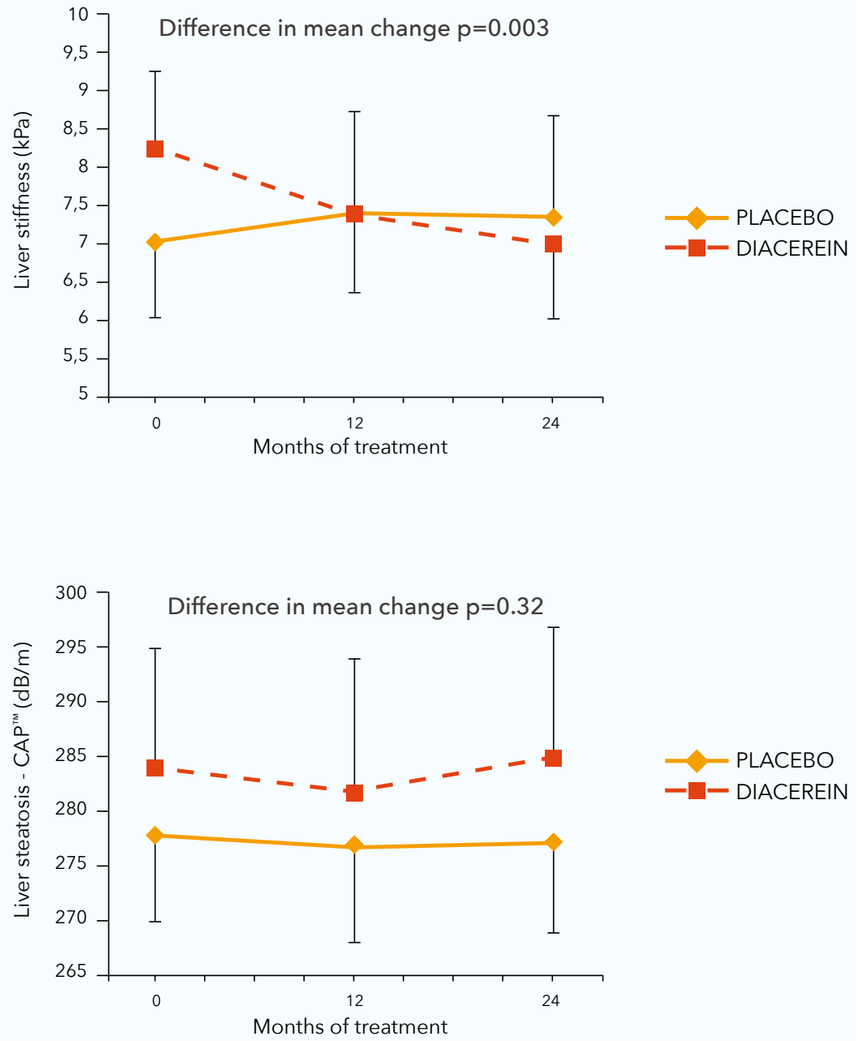
Based on the first data available using FibroScan®, the use of SGLT-2i seems to impact both LSM and CAP; hence the effects of dapaglofizin, a sodium-glucose co-transporter-2-inhibitor, on hepatic steatosis and fibrosis assessed by LSM and CAP was evaluated on patients with T2DM and NAFLD[50]. A significant decrease of both LSM (9.45 to 8.1 kPa) and CAP (314 to 290 dB/m) was reported after 24 weeks in the group of treated patients, also associated with a decrease of liver enzymes and visceral fat.

Other Treatment Options

Leite *et al.*[51] assessed the effect of diacerein, a symptomatic slow-acting drug in osteoarthritis, on 69 diabetic patients with NAFLD (2 years treatment with 100 mg/day, with a placebo group of 35 patients). Diacerein significantly reduced LSM by a mean decrease in liver stiffness of 1.0 kPa, while patients in the placebo group had a mean increase in liver stiffness of 0.5 kPa (adjusted mean difference: −1.6 kPa; 95% CI: -2.6 to −0.5 kPa; p = 0.003), whereas no significant change in liver steatosis measured by CAP was observed in both groups (Figure 6).

FIGURE 6

Change in LSM (left) and in CAP™ (right) by VCTE™ during 2-year treatment with placebo and diacerein. Bars represent standard errors of the mean.[51]



6

Type 2 diabetes and chronic viral hepatitis

Numerous studies have reported an increased risk of T2DM in chronic hepatitis C (HCV) patients[52]. Noninvasive evaluation of degree of fibrosis in T2DM patients combined with chronic HCV infection has been performed[53]. LSM was found to be higher in patients affected by both T2DM and HCV than in patients with HCV alone ($p<0.05$), suggesting higher fibrosis levels due to impaired IGF-1 secretion associated with insulin resistance.

In a recent Chinese study, 2330 HBV patients including 671 patients with concomitant HBV and T2DM were assessed with LSM by VCTE™. The prevalence of F3/F4 (LSM> 9kPa) and F4 (LSM≥ 12kPa) was 3 times higher in patients with chronic hepatitis B combined with T2DM in comparison to HBV antiviral-treated patients. Presence of T2DM was independently associated with fibrosis progression assessed by LSM and with occurrence of HCC. Risk of HCC increased by 4% for every 1kPa increment in liver stiffness[54].

7

Conclusion

As summarized in this document, LSM by VCTE™, CAP™ and FibroScan®-based scores have been shown to be of clinical utility for the management of patients with diabetes and metabolic risks factors. First, FibroScan® can be used to detect NAFLD related liver damage at an early stage in high risk populations such as T2DM patients, as fibrosis remains the main prognostic factor for liver related events. Second, it can also be used to monitor the disease progression/regression following the interventions on steatosis and fibrosis such as lifestyle modifications, pharmacotherapies or even surgery. Third, the prognostic value of LSM for cardiovascular events needs to be further explored as it could become a valuable biomarker for assessing cardiovascular risk.

References

1. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, Christidis C, Ziol M, Poulet B, Kazemi F, Beaugrand M, Palau R. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound in Medicine and Biology 2003; 29: 1705–13
2. Sasso M, Beaugrand M, Ledinghen V de, Douvin C, Marcellin P, Poupon R, Sandrin L, Miette V. Controlled attenuation parameter (CAP): a novel VCTE guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound in Medicine and Biology 2010; 36: 1825–35. [DOI: 10.1016/j.ultrasmedbio.2010.07.005]
3. Sasso M, Audiere S, Kemgang A, Gaouar F, Corpechot C, Chazouilleres O, Fournier C, Golsztejn O, Prince S, Menu Y, Sandrin L, Miette V. Liver Steatosis Assessed by Controlled Attenuation Parameter (CAP) Measured with the XL Probe of the FibroScan: A Pilot Study Assessing Diagnostic Accuracy. Ultrasound in Medicine and Biology 2016; 42: 92–103. [DOI: 10.1016/j.ultrasmedbio.2015.08.008]
4. Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. Journal of Hepatology 2011; 54: 650–9. [PMID: 21146892 DOI: 10.1016/j.jhep.2010.07.033]
5. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, Herrmann E. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008; 134: 960–74. [DOI: 10.1053/j.gastro.2008.01.034]
6. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol, 2015. (vol 63). Available from: URL: http://www.ncbi.nlm.nih.gov/pubmed/25911335; http://www.sciencedirect.com/science/article/pii/S0168827815002597#
7. Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, Ledinghen V de, Kumar M, Lupsor-Platon M, Han KH, Cardoso AC, Ferraioli G, Chan WK, Wong VW, Myers RP, Chayama K, Friedrich-Rust M, Beaugrand M, Shen F, Hiriart JB, Sarin SK, Badea R, Jung KS, Marcellin P, Filice C, Mahadeva S, Wong GL, Crotty P, Masaki K, Bojunga J, Bedossa P, Keim V, Wiegand J. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. Journal of Hepatology 2017; 66: 1022–30. [PMID: 28039099 DOI: 10.1016/j.jhep.2016.12.022]
8. Newsome PN, Sasso M, Deeks JJ, Paredes A, Boursier J, Chan WK, Yilmaz Y, Czernichow S, Zheng MH, Wong VW, Allison M, Tsochatzis E, Anstee QM, Sheridan DA, Eddowes PJ, Guha IN, Cobbold JF, Paradis V, Bedossa P, Miette V, Fournier-Poizat C, Sandrin L, Harrison SA. FibroScan-AST (Fast™) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. The Lancet Gastroenterology & Hepatology 2020; 5: 362–73. [PMID: 32027858 DOI: 10.1016/s2468-1253(19)30383-8]
9. Sanyal AJ, Foucquier J, Younossi ZM, Harrison SA, Newsome PN, Chan W-K, Yilmaz Y, Ledinghen V de, Costentin C, Zheng M-H, Wong VW-S, Elkhashab M, Huss RS, Myers RP, Roux M, Labourdette A, Destro M, Fournier-Poizat C, Miette V, Sandrin L, Boursier J. Enhanced diagnosis of advanced fibrosis and cirrhosis in individuals with NAFLD using FibroScan-based Agile scores. Journal of Hepatology 2022. [PMID: 36375686 DOI: 10.1016/j.jhep.2022.10.034]
10. Araujo AR, Rosso N, Bedogni G, Tiribelli C, Bellentani S. Global epidemiology of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: What we need in the future. Liver Int 2018; 38 Suppl 1: 47–51. [DOI: 10.1111/liv.13643]
11. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, Bugianesi E. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018; 15: 11–20. [PMID: 28930295 DOI: 10.1038/nrgastro.2017.109]
12. Batman B, Altun H, Simsek B, Aslan E, Namli Koc S. The Effect of Laparoscopic Sleeve Gastrectomy on Nonalcoholic Fatty Liver Disease. Surg Laparosc Endosc Percutan Tech 2019; 29: 509–12. [PMID: 31107849 DOI: 10.1097/sle.0000000000000672]
13. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64: 73–84. [PMID: 26707365 DOI: 10.1002/hep.28431]
14. Targher G, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. Gut 2020; 69: 1691–705. [PMID: 32321858 DOI: 10.1136/gutjnl-2020-320622]
15. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, Kashyap S, Mechanick JI, Mouzaki M, Nadolsky K, Rinella ME, Vos MB, Younossi Z. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings. Endocrine Practice 2022; 28: 528–62. [PMID: 35569886 DOI: 10.1016/j.eprac.2022.03.010]
16. Lomonaco R, Godinez Leiva E, Bril F, Shrestha S, Mansour L, Budd J, Portillo Romero J, Schmidt S, Chang K-L, Samraj G, Malaty J, Huber K, Bedossa P, Kalavalapalli S, Marte J, Barb D, Poulton D, Fanous N, Cusi K. Advanced Liver Fibrosis Is Common in Patients With Type 2 Diabetes Followed in the Outpatient Setting: The Need for Systematic Screening. Dia Care 2020: dc201997. [PMID: 33355256 DOI: 10.2337/dc20-1997]
17. Younossi ZM, Pham H, Felix S, Stepanova M, Jeffers T, Younossi E, Allawi H, Lam B, Cable R, Afendy M, Younoszai Z, Afendy A, Rafiq N, Alzubaidi N, Ousman Y, Bailey M, Chris Z, Castillo-Catoni M, Fozdar P, Ramirez M, Husain M, Hudson E, Schneider I, Golabi P, Nader F. Identification of High-Risk Patients With Nonalcoholic Fatty Liver Disease Using Noninvasive Tests From Primary Care and Endocrinology Real-World Practices. Clin Transl Gastroenterol 2021; 12: e00340. [PMID: 33825721 DOI: 10.14309/ctg.0000000000000340]
18. Sporea I, Mare R, Lupusoru R, Sima A, Sirli R, Popescu A, Timar R. Liver Stiffness Evaluation by Transient Elastography in Type 2 Diabetes Mellitus Patients with Ultrasound-proven Steatosis. Journal of Gastrointestinal & Liver Diseases 2016; 25: 167–74. [DOI: 10.15403/jgld.2014.1121.252.lsf]
19. Mansour D, Grapes A, Herscovitz M, Cassidy P, Vernazza J, Broad A, Anstee QM, McPherson S. Embedding assessment of liver fibrosis into routine diabetic review in primary care. JHEP Reports 2021; 3: 100293. [PMID: 34179738 DOI: 10.1016/j.jhepr.2021.100293]
20. Tomah S, Alkhouri N, Hamdy O. Nonalcoholic fatty liver disease and type 2 diabetes: where do Diabetologists stand? Clinical diabetes and endocrinology 2020; 6: 9. [PMID: 32518675 DOI: 10.1186/s40842-020-00097-1]
21. Koehler EM, Plompen EP, Schouten JN, Hansen BE, Darwish Murad S, Taimr P, Leebeek FW, Hofman A, Stricker BH, Castera L, Janssen HL. Presence of diabetes mellitus and steatosis is associated with liver stiffness in a general population: The Rotterdam study. Hepatology 2016; 63: 138–47. [DOI: 10.1002/hep.27981]
22. Vilar-Gomez E, Vuppalanchi R, Mladenovic A, Samala N, Gawrieh S, Newsome PN, Chalasani N. Prevalence of High-risk Non-alcoholic Steatohepatitis (NASH) in the United States: Results from NHANES 2017-2018. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association 2021. [PMID: 34958922 DOI: 10.1016/j.cgh.2021.12.029]
23. Kwok R, Choi KC, Wong GL, Zhang Y, Chan HL, Luk AO, Shu SS, Chan AW, Yeung MW, Chan JC, Kong AP, Wong VW. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut 2016; 65: 1359–68. [DOI: 10.1136/gutjnl-2015-309265]
24. Roulot D, Roudot-Thoraval F, G NK, Kouacou N, Costes JL, Elourimi G, Le Clesiau H, Ziol M, Beaugrand M. Concomitant screening for liver fibrosis and steatosis in French type 2 diabetic patients using Fibroscan. Liver International 2017; 37: 1897–906. [DOI: 10.1111/liv.13481]
25. Ciardullo S, Monti T, Perseghin G. High Prevalence of Advanced Liver Fibrosis Assessed by Transient Elastography Among U.S. Adults With Type 2 Diabetes. Diabetes Care 2020; 44: 519–25. [PMID: 33303638 DOI: 10.2337/dc20-1778]
26. Sporea I, Mare R, Popescu A, Nistorescu S, Baldea V, Sirli R, Braha A, Sima A, Timar R, Lupusoru R. Screening for Liver Fibrosis and Steatosis in a Large Cohort of Patients with Type 2 Diabetes Using Vibration Controlled Transient Elastography and Controlled Attenuation Parameter in a Single-Center Real-Life Experience. J Clin Med 2020; 9: 1032. [DOI: 10.3390/jcm9041032]
27. Eddowes P, Sasso M, Allison M, Tsochatzis E, Anstee Q, Sheridan D, Guha NI, Cobbold JF, Deeks J, Paradis V, Bedossa P, Newsome PN. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Non-alcoholic Fatty Liver Disease. Gastroenterology 2019; 156: 1717–30. [PMID: 30689971 DOI: 10.1053/j.gastro.2019.01.042]
28. Harman DJ, Ryder SD, James MW, Wilkes EA, Card TR, Aithal GP, Guha IN. Obesity and type 2 diabetes are important risk factors underlying previously undiagnosed cirrhosis in general practice: a cross-sectional study using transient elastography. Alimentary Pharmacology & Therapeutics 2018; 47: 504–15. [PMID: 29210096 DOI: 10.1111/apt.14463]
29. Blond E, Disse E, Cuerq C, Drai J, Valette PJ, Laville M, Thivolet C, Simon C, Caussy C. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease in severely obese people: do they lead to over-referral? Diabetologia 2017; 60: 1218–22. [DOI: 10.1007/s00125-017-4264-9]
30. Canivet CM, Boursier J. Screening for Liver Fibrosis in the General Population: Where Do We Stand in 2022? Diagnostics (Basel, Switzerland) 2023; 13: 91. [DOI: 10.3390/diagnostics13010091]
31. Quek J, Chan KE, Wong ZY, Tan C, Tan B, Lim WH, Tan DJH, Tang ASP, Tay P, Xiao J, Yong JN, Zeng RW, Chew NWS, Nah B, Kulkarni A, Siddiqui MS, Dan YY, Wong VW-S, Sanyal AJ, Noureddin M, Muthiah M, Ng CH. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. The Lancet Gastroenterology & Hepatology 2022. [DOI: 10.1016/S2468-1253(22)00317-X]
32. Kanwal F, Shubrook JH, Adams LA, Pfotenhauer K, Wai-Sun Wong V, Wright E, Abdelmalek MF, Harrison SA, Loomba R, Mantzoros CS, Bugianesi E, Eckel RH, Kaplan LM, El-Serag HB, Cusi K. Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2021; 161: 1657–69. [PMID: 34602251 DOI: 10.1053/j.gastro.2021.07.049]
33. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE, Loomba R. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology (Baltimore, Md.) 2023. [PMID: 36727674 DOI: 10.1097/HEP.0000000000000323]
34. European Association for the Study of the Liver, Clinical Practice Guideline Panel, Chair, EASL Governing Board representative, Panel members. Reply to: Correspondence on "EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update". J Hepatol 2021. [PMID: 34742599 DOI: 10.1016/j.jhep.2021.10.008]
35. Marchesini G. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Journal of Hepatology 2016; 64: 1388–402. [PMID: 27062661 DOI: 10.1016/j.jhep.2015.11.004]
36. Bischoff SC, Barazzoni R, Busetto L, Campmans-Kuijpers M, Cardinale V, Chermesh I, Eshraghian A, Kani HT, Khannoussi W, Lacaze L, Léon-Sanz M, Mendive JM, Müller MW, Ockenga J, Tacke F, Thorell A, Vranesic Bender D, Weimann A, Cuerda C. European guideline on obesity care in patients with gastrointestinal and liver diseases - Joint ESPEN/UEG guideline. Clinical nutrition (Edinburgh, Scotland) 2022. [PMID: 35970666 DOI: 10.1016/j.clnu.2022.07.003]
37. Chon YE, Kim KJ, Jung KS, Kim SU, Park JY, Kim do Y, Ahn SH, Chon CY, Chung JB, Park KH, Bae JC, Han KH. The Relationship between Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease Measured by Controlled Attenuation Parameter. Yonsei Medical Journal 2016; 57: 885–92. [DOI: 10.3349/ymj.2016.57.4.885]
38. Lombardi R, Petta S, Pisano G, Dongiovanni P, Rinaldi L, Adinolfi LE, Acierno C, Valenti L, Boemi R, Spatola F, Craxi A, Fargion S, Fracanzani AL. FibroScan Identifies Patients With Nonalcoholic Fatty Liver Disease and Cardiovascular Damage. Clin Gastroenterol Hepatol 2020; 18: 517–9. [DOI: 10.1016/j.cgh.2018.11.011]
39. American Diabetes Association. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes-2019. Dia Care 2019; 42: S34-S45. [PMID: 30559230 DOI: 10.2337/dc19-S004]

40. Franco I, Bianco A, Mirizzi A, Campanella A, Bonfiglio C, Sorino P, Notarnicola M, Tutino V, Cozzolongo R, Giannuzzi V, Aballay LR, Buongiorno C, Bruno I, Osella AR. Physical Activity and Low Glycemic Index Mediterranean Diet: Main and Modification Effects on NAFLD Score. Results from a Randomized Clinical Trial. Nutrients 2020; 13: 66. [PMID: 33379253 DOI: 10.3390/nu13010066]

41. Calabrese FM, Disciglio V, Franco I, Sorino P, Bonfiglio C, Bianco A, Campanella A, Lippolis T, Pesole PL, Polignano M, Vacca M, Caponio GR, Giannelli G, Angelis M de, Osella AR. A Low Glycemic Index Mediterranean Diet Combined with Aerobic Physical Activity Rearranges the Gut Microbiota Signature in NAFLD Patients. Nutrients 2022; 14. [PMID: 35565740 DOI: 10.3390/nu14091773]

42. Zaharia OP, Kupriyanova Y, Karusheva Y, Markgraf DF, Kantartzis K, Birkenfeld AL, Trenell M, Sahasranaman A, Cheyette C, Kössler T, Bódis K, Burkart V, Hwang J-H, Roden M, Szendroedi J, Pesta DH. Improving insulin sensitivity, liver steatosis and fibrosis in type 2 diabetes by a food-based digital education-assisted lifestyle intervention program: a feasibility study. Eur J Nutr 2021. [PMID: 33839905 DOI: 10.1007/s00394-021-02521-3]

43. Gollisch KS, Lindhorst A, Raddatz D. EndoBarrier Gastrointestinal Liner in Type 2 Diabetic Patients Improves Liver Fibrosis as Assessed by Liver Elastography. Experimental and clinical endocrinology & diabetes 2017; 125: 116–21. [DOI: 10.1055/s-0042-118961]

44. Agarwal L, Aggarwal S, Shalimar, Yadav R, Dattagupta S, Garg H, Agarwal S. Bariatric Surgery in Nonalcoholic Fatty Liver Disease (NAFLD): Impact Assessment Using Paired Liver Biopsy and Fibroscan. Obes Surg 2020; 31: 617–26. [PMID: 33052552 DOI: 10.1007/s11695-020-04977-4]

45. Liu SY-W, Wong VW-S, Wong SK-H, Wong GL-H, Lai CM-S, Lam CC-H, Shu SS-T, Chan HL-Y, Ng EK-W. A prospective 5-year study on the use of transient elastography to monitor the improvement of non-alcoholic fatty liver disease following bariatric surgery. Sci Rep 2021; 11: 5416. [PMID: 33686111 DOI: 10.1038/s41598-021-83782-0]

46. Lee YH, Kim JH, Kim SR, Jin HY, Rhee EJ, Cho YM, Lee BW. Lobeglitazone, a Novel Thiazolidinedione, Improves Non-Alcoholic Fatty Liver Disease in Type 2 Diabetes: Its Efficacy and Predictive Factors Related to Responsiveness. Journal of Korean medical science 2017; 32: 60–9. [DOI: 10.3346/jkms.2017.32.1.60]

47. Lavynenko O, Abdul-Ghani M, Alatrach M, Puckett C, Adams J, Abdelgani S, Alkhouri N, Triplitt C, Clarke GD, Vasquez JA, Li J, Cersosimo E, Gastaldelli A, DeFronzo RA. Combination Therapy with Pioglitazone/Exenatide Metformin Reduces the Prevalence of Hepatic Fibrosis and Steatosis: The Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT) Trial. Diabetes Obesity Metabolism 2022. [PMID: 35014145 DOI: 10.1111/dom.14650]

48. Analyse prospective de la prévalence et des causes de discordances entre FibroScan® et Fibrotest lors de leur utilisation combinée en première intention pour l'évaluation non invasive de la fibrose chez les malades atteints d'hépatite chronique C (HCC) [Prospective analysis of the occurrence and causes of discrepancies between FibroScan® and Fibrotest used in combination for first line fibrosis assessment in patients with chronic hepatitis C]; 2005; September 29-30; Bordeaux, France, 2005

49. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, Sanyal AJ, Sejling A-S, Harrison SA. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. The New England Journal of Medicine 2020; 384: 1113–24. [PMID: 33185364 DOI: 10.1056/NEJMoa2028395]

50. Shimizu M, Suzuki K, Kato K, Jojima T, Iijima T, Murohisa T, Iijima M, Takekawa H, Usui I, Hiraishi H, Aso Y. Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease. Diabetes, obesity & metabolism 2018; 21: 285–92. [DOI: 10.1111/dom.13520]

51. Leite NC, Viegas BB, Villela-Nogueira CA, Carlos FO, Cardoso CRL, Salles GF. Efficacy of diacerein in reducing liver steatosis and fibrosis in patients with type 2 diabetes and non-alcoholic fatty liver disease: A randomized, placebo-controlled trial. Diabetes Obes Metab 2019; 21: 1266–70. [DOI: 10.1111/dom.13643]

52. Hammerstad SS, Grock SF, Lee HJ, Hasham A, Sundaram N, Tomer Y. Diabetes and Hepatitis C: A Two-Way Association. Frontiers in endocrinology 2015; 6: 134. [DOI: 10.3389/fendo.2015.00134]

53. Cao LH, Lu FM, Lu XJ, Zhu LY. Study on the relationship between insulin growth factor 1 and liver fibrosis in patients with chronic hepatitis C with type 2 diabetes mellitus. Journal of cellular biochemistry 2018; 119: 9513–8. [DOI: 10.1002/jcb.27267]

54. Mak L-Y, Hui RW-H, Lee C-H, Mao X, Cheung K-S, Wong DK-H, Lui DT-W, Fung J, Yuen M-F, Seto W-K. Glycemic burden and the risk of adverse hepatic outcomes in patients with chronic hepatitis B with type 2 diabetes. Hepatology 2022. [PMID: 36130882 DOI: 10.1002/hep.32716]

55. Cardoso, Claudia R L *et al.* "Prognostic impact of liver fibrosis and steatosis by transient elastography for cardiovascular and mortality outcomes in individuals with nonalcoholic fatty liver disease and type 2 diabetes: the Rio de Janeiro Cohort Study." Cardiovascular diabetology vol. 20,1 193. 24 Sep. 2021, doi:10.1186/s12933-021-01388-2

because liver health matters