FibroScan®

Diabetology handbook

echosens™

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1 Introduction

Echosens™ is the world's #1 provider of non-invasive medical devices dedicated to assessment of chronic liver disease. Echosens™ significantly changed the practice of liver diagnosis with FibroScan®, the unique device using patented and validated VCTE™ [1] for liver stiffness assessment, and CAP™ [2-3] for steatosis quantification.

Since its first introduction in 2003 in Europe, numerous publications, in a large spectrum of chronic liver diseases, such as chronic viral hepatitis, alcoholic liver disease, or non-alcoholic fatty liver disease (NAFLD) [4-7], have demonstrated the performance of LSM by VCTE™ and CAP™ to assess fibrosis stage and steatosis grade, respectively. Hence, nowadays, LSM by VCTE™ and CAP™ are widely used as an alternative to the histological assessment of liver biopsy (LB) fragments that remains the reference method for staging and grading liver disease.

NAFLD is a growing public health problem reaching epidemic proportions and is considered as the most common cause of chronic liver disease worldwide. NAFLD encompasses a spectrum of histological changes that begin with simple steatosis (NAFL), which may gradually progress to the development of chronic inflammation (non-alcoholic steatohepatitis (NASH)), fibrosis, and ultimately cirrhosis. NAFLD and type 2 diabetes (T2DM) often coexist [8]. The prevalence of NAFLD is around 55% in T2DM patients [9] while, in comparison, NAFLD is detected in 24-25% of adults [10] in the general population but with notable differences across regions [11]. It has been reported that prevalence of advanced fibrosis in asymptomatic TD2M patients ranges between 5-7%. Consequently, early detection of NAFLD in T2DM population has become an urgent need, ideally by the mean of noninvasive markers.

The aim of this document is to provide a summary of the existing literature documenting the clinical use of LSM by VCTE™ and CAP™ in patients with Type 2 diabetes (T2DM).

2 Screening for NAFLD

2.1 Foreword

Considering the high prevalence of T2DM worldwide, expected to reach 7.7% of the world population by 2030, and also the high prevalence of NAFLD in diabetics, NAFLD related liver disease is about to become one of the leading cause 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 [12]. 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 NAFLD in the general population

Koehler et al. were the first to evaluate the prevalence of patients with abnormal LSM by VCTE™ values (≥ 8 kPa) in a cohort from the general population, as part of the Rotterdam study [13]. Among the 3041 participants measured by FibroScan®, 5.6% exhibited LSM by VCTE™ 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 of early targeting. Insulin resistance and T2DM to mitigate the risk of liver damage Harman et al. [14] 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 by VCTE™, 25.6% of patients had fibrosis defined by elevated liver stiffness ≥ 8 kPa, and 2.9% had cirrhosis. Presence of cirrhosis was significantly increased in obese patients with T2DM or hazardous alcohol use compared to the same categories of non-obese patients (odds ratio 9.4 [95% CI 2.2-40.9] for T2DM patients and 5.6 [95% CI 1.6-19.7] for patients with hazardous alcohol use, respectively, meaning that the number of new cases of cirrhosis diagnosed indicated that existing estimates of prevalence are likely to be underestimated

2.3 Screening for NAFLD IN T2DM patients

The use of FibroScan® in noninvasive screening strategies for early diagnosis of fibrosis and steatosis in diabetics has been evaluated in several studies:

Kwok et al. [15] evaluated the screening strategy for NAFLD in 1918 T2DM patients using FibroScan® with LSM by VCTE™ and CAP™ measurements. They revealed that around 70% of diabetic patients from primary care and hospital clinics had increased CAP™ suggestive of NAFLD, and that around 18% of diabetic patients had increased liver stiffness suggesting presence of advanced fibrosis. Biopsy was performed in a subgroup of 94 individuals for which there was a suspicion of advanced fibrosis or citrrhosis based on the FibroScan® examination; 56% had steatohepatitis and 50% had F3-4 disease. These results confirm that diabetic patients with high BMI and dyslipidemia are at particularly high risk and may be a high priority target for liver assessment.

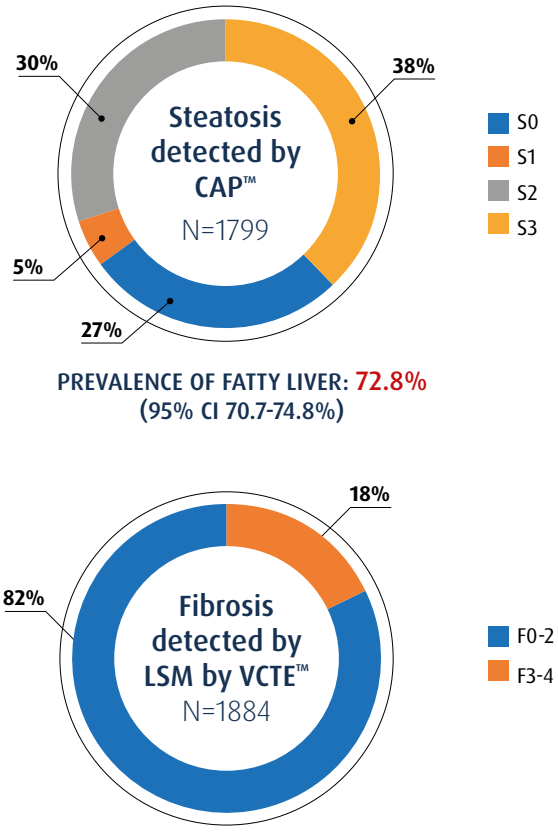

FIGURE 1: PREVALENCE OF SIGNIFICANT STEATOSIS AND ADVANCED FIBROSIS DETECTED BY FIBROSCAN® IN A T2DM COHORT OF 1918 PATIENTS [15]

A similar study was conducted in a French cohort by Roulot et al. [16] with quite similar steatosis and fibrosis rates: 75% of diabetic patients showed increased CAP™ ≥236 dB/m suggestive of steatosis; 12.7% had LSM by VCTE™ ≥ 8 kPa suggestive of significant fibrosis and 2.1% had LSM by VCTE™ ≥ 13 kPa suggestive of cirrhosis.

Sporea et al. performed FibroScan® (with LSM by VCTE™ only) and ultrasound examinations to noninvasively evaluate fibrosis and steatosis in a group of 340 T2DM patients [12]. Using the FibroScan® LSM by VCTE™ cut-off values proposed by Wong et al. [17], significant fibrosis and advanced fibrosis (F2/F3 patients)-, LSM by VCTE™ ≥ 7 kPa) was found in 18.8% patients with steatosis, while 13.8% had cirrhosis (F4, LSM by VCTE™ ≥10.3 kPa). By multivariate analysis, obesity, steatosis, higher ALT, hypertriglyceridemia were independently associated with LSM by VCTE™ values ≥ 7 kPa, suggestive of significant liver fibrosis.

> *"Liver stiffness assessment in Type 2 diabetic patients should be performed systematically to identify those with significant liver fibrosis."*
>
> *Sporea et al. Journal of Gastrointestinal and Liver Disease 2016*

Sobhonslidsuk et al. [18] performed a very similar work on an Asian cohort of 141 diabetics and 60 control patients. Fatty liver was diagnosed (by ultrasound) in 82 (60.7%) diabetic patients. LSM by VCTE™ values revealed that 22 diabetic patients (16.1%) had fibrotic stages of at least significant fibrosis, which was more common in diabetic patients than in normal subjects (16.1% vs 1.7%, p=0.002).

2.4 International guidelines

The need for NAFLD screening among diabetics is now also recommended in some international guidelines: joint NAFLD guidelines from the EASL, EASD and EASO on the management of NAFLD recommended to monitor patients with NAFL without worsening of metabolic risk factors, every 2–3-years. This monitoring should include routine biochemistry, assessment of comorbidities and non-invasive monitoring of fibrosis [19].

Moreover AASLD NAFLD guidelines 2017 [20] also mention the FibroScan® (VCTE™) as a valuable tool to detect advanced fibrosis in T2DM patients.

Recently, the American Diabetes Association (ADA) also recommended that T2DM patients or prediabetes patients with elevated liver enzymes or fatty liver should be evaluated for the presence of NASH and liver fibrosis [21].

> *"There should be a high index of suspicion for NAFLD and NASH in patients with type 2 diabetes. Clinical decision aids such as NAFLD Fibrosis Score or FIB4 or vibration controlled transient elastography (VCTE™) can be used to identify those at low or high risk for advanced fibrosis (bridging fibrosis or cirrhosis)".*
>
> *Chalasani et al. AASLD Practice Guidance from the American Association for the Study of Liver Diseases; Journal of Hepatology 2017*

3
Staging Type 2 diabetes with FIBROSCAN®

Chon et al. [22] 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 3 groups (cf Figure 2).

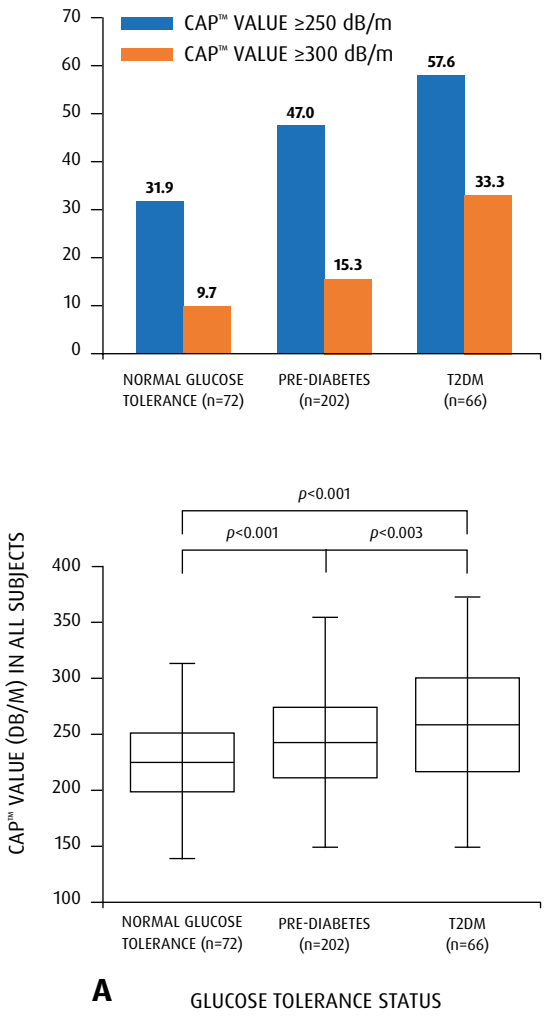

FIGURE 2: PREVALENCE (A) AND SEVERITY (B) OF NAFLD DETECTED BY CAP™, BY GLUCOSE TOLERANCE STATUS

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 insulino-resistance (IR), a known marker of T2DM. Hence CAP™ may represent an additional parameter that can supplement the traditional variables representing metabolic risk, for evaluation of NAFLD risk.

The relationship between the presence of NAFLD and complications of diabetes has also been assessed by Yeung et al. [23]. They investigated the correlation between NAFLD and albuminuria, a marker of chronic kidney disease, in a T2DM cohort of 1763 patients. After adjusting with other cofounders, advanced fibrosis assessed by VCTE™ was associated with increased risk of albuminuria in obese patients with T2DM (odd ratio =1.52, p =0.039).

4
Monitoring effect of therapeutic interventions

The effect of therapeutic interventions on T2DM subjects has also been evaluated by the mean of FibroScan® in several studies.

Gollisch et al. [24] have evaluated the effect on fibrosis and steatosis (assessed by LSM by VCTE™ 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 by VCTE™ 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 liver stiffness at baseline (n = 13), liver stiffness reduced from 12.9 kPa (IQR 10.3–15.1) to 5.8 kPa (IQR 4.8–8.8, $p < 0.01$), and liver stiffness normalized in most patients (8/13) by the time of EndoBarrier explantation. CAP™ values also significantly improved during EndoBarrier treatment from 343 dB/m (IQR 326-384) to 317 dB/m (IQR 269-375, $p < 0.05$).

More recently several clinicians have evaluated the impact of T2DM therapies on LSM by VCTE™ and CAP™: Lee et al. [25] investigated the effects of a 24 weeks treatment by lobeglitazone (a thiazolidinedione) on T2DM patients with NAFLD (identified by CAP™ ≥ 250 dB/m). They showed that lobeglitazone treatment 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 (based on LSM by VCTE™). On the contrary, treatment by diacerein (an anti-inflammatory drug) seemed to affect LSM by VCTE™ only, and not CAP™, as reported by Leite et al. [26] who assessed the effect of this drug (2 years treatment with 100 mg/day) on 69 diabetic patients with NAFLD, with a placebo group of 35 patients. VCTE™ was performed at baseline, and after 12 and 24 months of follow up. Diacerein significantly reduced LSM by VCTE™ by 1.6 kPa (95% CI: -2.6 to -0.5 kPa, p=0.003) vs placebo group during treatment, whereas no significant change in liver steatosis measured by CAP™ was observed in both groups (Cf Figure 3).

Other treatments options seem to impact both LSM by VCTE™ and CAP™; hence the effects of dapaglofizin, a sodium-glucose co-transporter-2-inhibitor, on hepatic steatosis and fibrosis evaluated by LSM by VCTE™ and CAP™ by VCTE™ was evaluated on patients with T2DM and NAFLD [27]. There was a significant decrease of both LSM by VCTE™ (9.45 to 8.1 kPa) and CAP™ (314 to 290 dB/m) after 24 weeks in the group of treated patients, associated with decrease of liver enzymes and visceral fat in the same group.

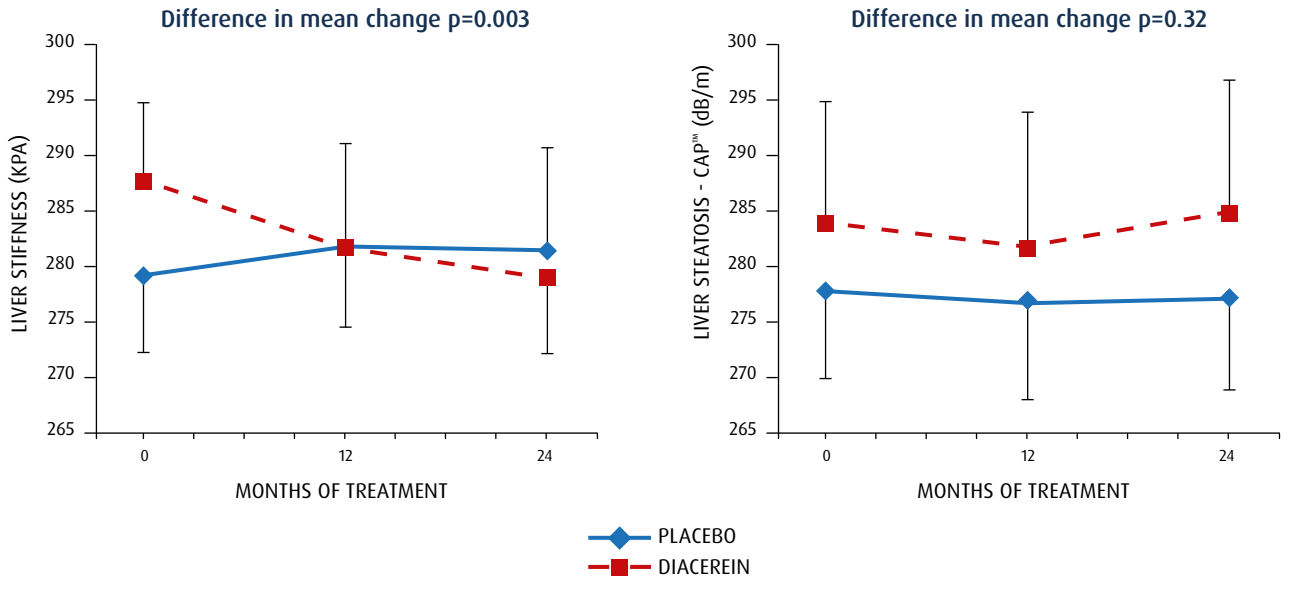

FIGURE 3: CHANGE IN LSM BY VCTE™ (LEFT) AND IN CAP™ (RIGHT) BY VCTE™ DURING 2-YEAR TREATMENT WITH PLACEBO (BLUE) AND DIACEREIN (RED). BARS REPRESENT STANDARD ERRORS OF THE MEAN.

5 Type 2 diabetes and chronic hepatitis c

Numerous studies have reported an increased risk of T2DM in chronic hepatitis C patients [28]. Noninvasive evaluation of degree of fibrosis in T2DM patients combined with chronic HCV infection has been performed [29]. LSM by VCTE™ 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 probably due to impaired IGF-1 secretion associated with insulinoresistance.

6 FIBROSCAN® and Type 1 diabetes

Whereas the prevalence of NAFLD measured by ultrasonography (US) ranges from 50 to 70% in patients with T2DM, it is also present 40–50% in patients with type 1 diabetes (T1DM) [30]. Recent studies showed increased risk of cardiovascular disease, chronic kidney disease (CKD), retinopathy, and symmetrical polyneuropathy in patients with T1DM and NAFLD [31, 32]. Association between T1DM and AIH has been reported in 1-10% of patients [33]: presence of chronic hepatitis C associated with T1DM has also been reported in Egyptian children [34]. These observations support early diagnosis and treatment of hepatic fibrosis in patients with T1DM.

Prevalence of hepatopathies among children and adolescents with T1DM has been evaluated by Elkabbany et al. [35] by noninvasively measuring LSM by VCTE™ in a group of 100 Egyptian children and adolescents. 31 of patients were found to have one or more hepatic abnormalities (HCV, AIH, NAFLD...) among which 24 had LSM by VCTE™ values suggesting F0/F1 fibrosis and 7 F2/F3 fibrosis stages, suggesting that LSM by VCTE™ provides a valuable non-invasive method for detection of liver fibrosis as well as monitoring the severity of fibrosis in T1DM.

7 Conclusion

As summarized in this document, LSM by VCTE™ and CAP™ have been shown to be of clinical utility for the management of patients with diabetes: first to detect NAFLD related liver damage at an early stage in T2DM patients with metabolic risk factors, keeping in mind that fibrosis remains the main prognostic factor for decompensation. Second, to assess effect of therapeutic interventions (pharmacologic or surgical treatment for diabetes) on steatosis and on fibrosis. Third, as an aid by the means of CAP™ to stage severity of diabetes and risk stratify patients for its associated complications.

8 References

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