Journal of Cystic Fibrosis 21 (2022) 873–877

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

2D Shear Wave Elastography, a promising screening tool for Cystic Fibrosis liver disease, shows a correlation between vitamin D and liver stiffness

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ARTICLE INFO

Article history:
Received 15 December 2021
Revised 24 May 2022
Accepted 17 June 2022
Available online 3 July 2022

Keywords:
Cystic fibrosis liver disease screening
2D Shear wave elastography
Liver stiffness
Vitamin D

ABSTRACT

Background: Liver disease in Cystic Fibrosis (CFLD) is an early complication of CF. Evidence of CFLD is often subclinical and screening is recommended. Screening includes a biochemical work-up and an ultrasound investigation. Non-invasive methods measuring liver stiffness such as shear wave elastography could be beneficial. This study describes the use of 2D Shear Wave Elastography (2D SWE) in screening for CFLD in a clinical setting and explores its correlation to other indicators of CFLD. Furthermore, a relationship between liver stiffness and nutritional status, lung function and glucose tolerance was explored.
Material and Methods: A retrospective cohort study was performed at a pediatric CF center. Information was gathered from the patients' charts and the Swedish national CF registry. The patients included had been evaluated for the presence of CFLD by ultrasound and 2D SWE during 2018-2020. Demographic data as well as data concerning nutritional status, lung function and glucose tolerance were collected.
Results: Fifty-one subjects were included with a median age of 11 years. Four children who had biopsy confirmed liver cirrhosis had significantly increased liver stiffness. There was a statistically significant negative correlation between liver stiffness and vitamin D levels and FEV1% predicted respectively. Children with abnormal glucose tolerance had increased liver stiffness compared to their normal glucose tolerant counterparts.
Conclusion: Measuring liver stiffness by 2D SWE is a reliable addition to CFLD screening with data comparable to the more conventional ultrasound investigation. Increased liver stiffness is associated with lower vitamin D levels, lower FEV1% predicted and abnormal glucose tolerance.

Background

Liver disease is a frequent and an early complication of Cystic Fibrosis (CF) with a cumulative incidence of 27-35%, most often diagnosed before the age of 18 years [1,2]. Many children with CF develop signs of liver abnormalities including hepatomegaly, steatosis and elevated liver enzymes and 5-10% of children with CF develop clinically significant liver disease with cirrhosis and portal hypertension [1,2]. CF related liver disease (CFLD) has been associated with severe genotypes, history of meconium ileus, malnutrition, CF related diabetes (CFRD) and male sex why a multifactorial etiology is probable [2,3,4,5]. CFLD is of high clinical relevance especially with the increasing survival of the CF population, and CFLD seems to increase both morbidity and mortality [6,7]. CFLD is often asymptomatic and therefore annual screening is recommended [8]. The screening for CFLD usually consists of abdominal examination, biochemical evaluations and ultrasound of the liver and the spleen with the addition of further investigations when indicated [8]. There is evidence that ultrasound investigations are more sensitive for detecting CFLD than biochemical measurements and the combination of an ultrasound and a biochemical work-up is often warranted [9]. However, a normal ultrasound does not exclude the existence of fibrosis [10]. Although liver biopsy has represented the gold standard for the diagnosis of fibrosis, it can be less reliable in CFLD because of the uneven distribution of lesions. Furthermore, a liver biopsy is an invasive procedure and not without complications. Therefore, additional methods for the evaluation of CFLD have been sought. One of these methods is elastography which measures the tissue stiffness or elasticity [11]. Differ-

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https://doi.org/10.1016/j.jcf.2022.06.009

ent types of elastographies are on the market, one being the transient elastography (TE or FibroScan) [11,12]. Various publications have revealed some benefits of the TE methods for CFLD screening [12,13]. A recent meta-analysis on the subject proposed a cutoff of 5.95 kPa for increased liver stiffness. Although the specificity of the TE was good (87%), the sensitivity was quite low (55%) [14]. The 2D Shear Wave Elastography (2D SWE) is another method for evaluating tissue stiffness. It is provided as an application on various ultrasound systems and with this technique a visual localization of the organ is present, in contrast to methods such as TE [11]. Less data is available on the 2D SWE technique and pediatric references are lacking.

In this study we describe the use of 2D SWE in the screening for CFLD in a clinical setting at a pediatric CF center. We explored the correlation of liver stiffness to other indications of CFLD. Furthermore, we investigated the relationship between liver stiffness and nutritional status, lung function and glucose tolerance respectively.

Material and method

A retrospective cohort study was performed at a pediatric CF center in Lund Sweden. The patients included were those who had been evaluated for CFLD by ultrasound and 2D SWE between 2018 and 2020. Exclusion criteria were liver and lung transplantations. The study was approved by the local ethical review board (EPN 2018/54).

Data were collected from the results of the annual review assessments as registered in the patients' charts and the Swedish national CF registry. These included age, gender, specific CFTR mutations, height (z score), weight (z score), serum calcifediol (vitamin D) and bacterial colonization with *Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Achromobacter xylosoxidans, Burkholderia cepacia complex and* non-tuberculous mycobacteria (NTM).

Results from the liver disease screening were also collected. The liver function tests Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Glutamyl transferase (GT) were registered along with the results from the ultrasound and 2D SWE of the liver. An ultrasound is performed once a year from the age of 5 at the CF center as a part of the annual assessment. 2D SWE was added to CFLD screening at our center in 2017. The ultrasound is performed by pediatric radiologists, and, at the same visit, further evaluation of the liver is done using the 2D SWE from Canon/Toshiba Aplio i70. In subjects who had undergone a liver biopsy, the results from the pathology assessments were registered. The use of ursodeoxycholic acid was noted as well.

The results of the lung function measurements were recorded, including the forced expiratory volume in 1 second percent predicted (FEV1% predicted) and the lung clearance index (LCI). FEV1% predicted values are obtained at the annual assessment via spirometry using the Global Lung Function Initiative equations [15]. At the CF center multiple breath washout (MBW) is performed on Exhalyzer-D with 3 consecutive measurements per patient resulting in an average LCI value representing ventilation inhomogeneity [16].

The results from oral glucose tolerance tests (OGTT) were collected, and the status of glucose tolerance defined. Abnormal glucose tolerance (AGT) includes CFRD, impaired glucose tolerance (IGT) an indeterminate glycemia (INDET) [17]. CFRD is defined as a fasting blood glucose ≥ 7 mmol/L (126 mg/dl) and/or a 120-minute blood glucose value ≥ 11.1 mmol/L (200 mg/dl). IGT means a fasting blood glucose < 7 mmol/L (126 mg/dl) and a 2-hour blood glucose value ≥7.8 mmol/L (140 mg/dl), but <11.1 mmol/L (200 mg/dl). INDET is represented by a fasting blood glucose < 7 mmol/L (126 mg/dl) and a 120-minute blood glucose value of < 7.8 mmol/L (140 mg/dl), but at least one intermediate (at 30, 60 or 90 minutes during the OGTT) blood glucose value ≥ 11.1 mmol/L (200 mg/dl).

Statistical analysis was performed using IBM SPSS Statistics version 26 (IBM Svenska AB, Stockholm, Sweden). Continuous data were analyzed for normality of distribution and non-parametric tests chosen for their statistical analysis. Correlations were calculated using Spearman's correlation test. The Mann-Whitney U test was performed for comparison of two independent variables. The Kruskal-Wallis test was used for comparison of more than two independent variables. Level of significance was set at a p-value ≤0.05.

Table 1
Demographic and clinical data of the study population

Age in years, median (range)	11 (5-18)
Female n (%)	23 (45)
Homozygous Δ F508 n (%)	25 (49)
FEV1% predicted, median (range)	90.6 (44.4-115.8)
LCI, median (range)	7.8 (5.8-18.5)
Height z-score, median (range)	-0.27 (-2.99-1.8)
Weight z-score, median (range)	-0.3 (-2.98-2.1)
Chronic colonization * (%)	13 (25)

* *P. aeruginosa, S. maltophilia, A. xylosoxidans, B. cepacia complex* or NTM

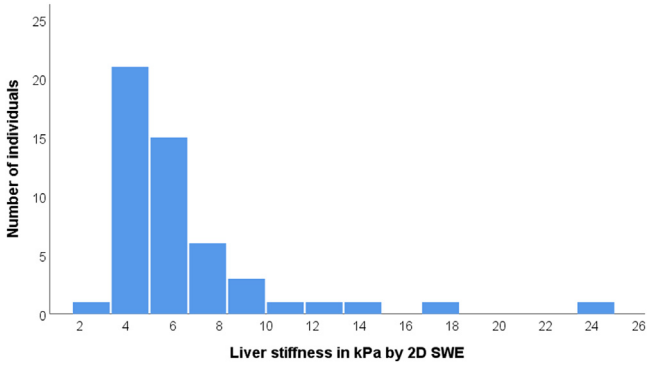

Figure 1. Liver stiffness in kPa measured by 2D SWE in 51 children.

Results

During this period 65 children and adolescents were registered at the CF center. Fifty-one of them (78%) were included in the study. The median age was 11 years (range 5-18 years) and 23 (45%) were female. Twenty-five participants (49%) were homozygous and 12 (23.5%) were heterozygous for the ΔF508 mutation. Almost all the participants had pancreatic insufficiency (98%). Eleven patients (21.6%) were receiving treatment with ursodeoxycholic acid at the time of the evaluations. Chronic colonization with *P. aeruginosa* was found in 6 patients (11.8%) and in 7 individuals (13.7%) other chronic bacterial colonization was present. Demographic and clinical data of these 51 individuals are shown in Table 1.

In 6 individuals (11.7%) the liver was described as nodular or fibrotic on ultrasound. In 9 individuals (17.6%) it was described as echogenic or with signs of steatosis and in 4 cases (7.8%) it was described as enlarged without other abnormalities. Thirty-two patients (62.7%) had a normal ultrasound of the liver.

The median number of measurements per session of 2D SWE was 10 (range 6-13). The median value for elastography measurements or liver stiffness was 5.2 kPa (range 3.2-23.8; SD 3.6; CV 55%). (Figure 1). A positive correlation was found between liver stiffness and age (r (51)= 0.452, p=0.001).

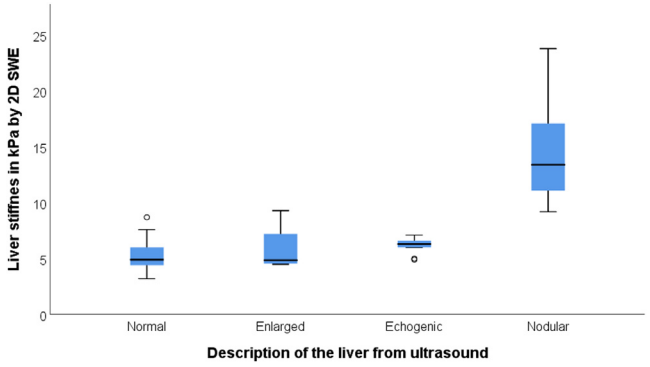

Figure 2. Liver stiffness measurements by 2D SWE in 51 children with CF, sub grouped by ultrasound findings (p=0.001).

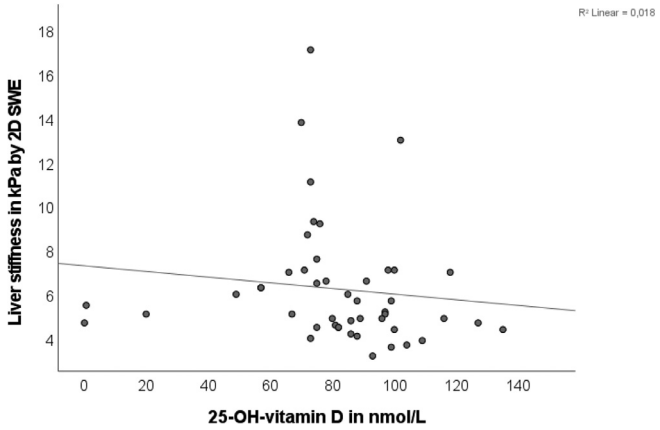

Figure 3. Increased stiffness of the liver correlates with lower vitamin D levels (n=48; p= 0.014).

Four patients (7.8%) with liver cirrhosis, confirmed by biopsy, had significantly increased liver stiffness compared to all the other patients with a median value of 15.45 kPa (13.0-23.8) (p=0.001). The liver biopsies had not been performed in relation to the 2D SWE measurements. In 3 patients the liver biopsies preceded the 2D SWE measurements by 1-3 years. In one patient the biopsy was done one month after the 2D SWE evaluation. Two individuals had periportal fibrosis on biopsies, stages 1 and 2-3 respectively, and their levels were both 6.3 kPa. These biopsies were performed 2 years before the 2D SWE in one patient and 7 months after the 2D SWE measurement in the other one. The 6 patients who had signs of fibrosis on ultrasound had increased liver stiffness compared to those who had a normal ultrasound, echogenic liver, or hepatomegaly (H (3)=19.3, p=0.001) (Figure 2).

In respect to liver function tests, the only correlation found was between liver stiffness in kPa and ALT levels (r(49)=0.331, p=0.021), but when the patients who were treated with ursodeoxycholic acid were omitted, this correlation was no longer statistically significant. A negative correlation was found between 2D SWE levels and height (r (51)= -0.949, P=0.001) and weight (r(51)= -0.707, p=0.054), respectively, but the latter did not reach statistical significance. There was a statistically significant negative correlation between 2D SWE levels and vitamin D levels (r (48)= -0.352, p= 0.014) (Figure 3). The correlation remained statistically significant while controlling for height (r (43)= -0.343, p= 0.018) and age (r (45)= -0.323, p= 0.027) respectively. Furthermore, there was a statistically significant negative correlation between liver stiffness and lung function as measured by FEV1% predicted (r (48)= -0.299, p= 0.039). However, no correlation was found between liver stiffness and lung function as measured by LCI (r (41)=0.021, p=0.87). There was no significant correlation found between vitamin D levels and FEV1%predicted (r (45)= -0.155, p= 0.3). Also there was no difference in 2D SWE values between individuals with and without bacterial colonization (H (2)= 3.99, p=0.14).

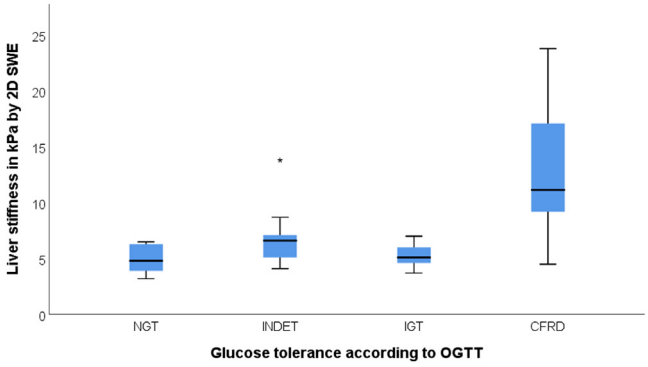

Figure 4. Liver stiffness of 39 children as measured by 2D SWE in kPa for NGT (n=10), INDET (n=13), IGT(n=10) and CFRD(n=6) (p=0.006).

Thirty-nine of the 51 patients were eligible for defining glucose tolerance, either by an OGTT or a previous CFRD diagnosis. The remaining 12 children had not done an OGTT due to young age. Ten children had normal glucose tolerance, 13 had INDET, 10 had IGT and 6 had CFRD. Children with AGT had significantly higher 2D SWE levels (M place = 22.47) than children with normal glucose tolerance. (M place = 12.85; U= 216, p=0.021). Within the different categories of AGT there was a statistically significant difference of liver stiffness between CFRD, IGT, INDET and normal glucose tolerance (H (3)=12.4, p=0.006) (Figure 4).

Discussion

CFLD is a diagnostic and a therapeutic challenge. Its most serious forms, cirrhosis and the following complications, constitute a major source of morbidity in children and adolescents with CF. The assessment of CFLD and disease progression is complicated, and no single method seems completely sufficient. The evolution of fibrosis in CFLD is an important aspect in clinical surveillance and the inherent procedural risks of liver biopsies call for the exploration of other, less invasive, methods. In this study we have examined one of these methods, *i.e.,* the 2 SD SWD alongside ultrasound investigations. In our clinical practice we experienced the need to find more sensitive methods for detecting and evaluating the progression of CFLD in children, and with the goal of gathering further experience we added the 2D SWE method to our CFLD screening protocol.

Calvopina et al investigated the potential of Supersonic SWE (SSWE) in a prospective study and found that liver stiffness was significantly higher in children with CFLD compared to those without CFLD and concluded that the method had good diagnostic accuracy especially when combined with biochemistry measurements [18]. A cutoff at 6.85 kPa for liver stiffness was proposed by the authors and a cut-off at 9.05 for the differentiation between mild and serious disease. In our sample, the children who had cirrhosis confirmed by biopsy had substantially increased liver stiffness measured by 2D SWE (median value of 15.45 kPa), supporting this conclusion despite the technical differences between SSWE and 2D SWE [18].

Few studies have examined the use of 2D SWE in the evaluation of CFLD. *Yavuz et al* revealed in their prospective study that children with CF had increased liver stiffness, measured by 2D SWE, compared to healthy controls and reason that liver involvement can occur much earlier than detectable by ultrasound alone [19].

Levitte et al compared 2D SWE to Magnetic Resonance (MR) elastography and found a significant correlation between these two methods. Additionally, they found that GT was a relevant biochemical marker in CFLD [20]. MR elastography is not routinely used at our CF center and the sole visual comparison was therefore with the abdominal ultrasound. In our cohort no specific biomarker was convincingly useful but the fact that some children were already treated with ursodeoxycholic acid could be an explanation to the lack of evidence in this aspect. Periodic inflammation of the liver with elevated liver enzymes could also lead to increased liver stiffness but it does not necessarily lead to liver fibrosis. This is one of the reasons why the diagnosis of CFLD can be complicated [3].

An advantage of investigating liver stiffness by 2D SWE is its non-invasive nature and the possibility of combining the investigation with a standard ultrasound, which is often more easily accessible than MR elastography. Furthermore, the numerical results given in kPa can be helpful individually in the surveillance of disease progression, despite the lack of validated references. The study of *Gominon et al* indicated that liver stiffness increases with time and that the slope of worsening detected by elastography can predict CFLD [21]. This is an important aspect of this methodś potential in individual clinical surveillance. Longitudinal data for the 2D SWE and other similar methods are still needed to further evaluate their role in the monitoring of disease progression in CFLD. However, the disadvantage of the 2D SWE method is that it is subject to the same shortcomings as the liver biopsies because of the heterogenous distribution of the fibrosis in the early stages of the disease.

Some authors have addressed the issue of CFLD and nutrition. Essential fatty acid deficiency and liver steatosis have shown to be correlated and malnutrition seems to be a relevant risk factor for CFLD [1,5]. Vitamin D deficiency has been linked to inferior lung function and CFRD but similar associations to CFLD have not previously been demonstrated to the authorsḱnowledge [22,23]. We found vitamin D deficiency to be associated with increased liver stiffness which might be an indication of suboptimal nutritional status and as such associated with CFLD. Seasonal differences in vitamin D level could affect the results if most of the blood sampling were taken during summer or early autumn. However, the annual visits and thereby blood sampling are evenly spread throughout the year so this bias is very unlikely in our cohort. It would be interesting to see if similar findings were present in Mediterranean countries. Whether vitamin D levels are linked to CFLD remains as an observation from this small study without definitive conclusions, but it could surely be an interesting field in future research on CFLD.Whether CFLD is related to a deterioration in the lung function remains to be solidified. Some papers have revealed an association between CFLD and worsened lung function while others have demonstrated the opposite [24,25]. The reason for the diverse findings on this matter might in part be explained by variable definitions of CFLD. In our study the correlation of increased liver stiffness, demonstrated by 2D SWE, and lower FEV1% predicted did not consider any specific definition of CFLD and there is no causal relationship claimed but it is still an interesting notion and worth further investigations in the future.

Singh et al present in their longitudinal review from Australia that CFLD is associated with inferior lung function, nutritional problems and endocrine comorbidities including osteoporosis and CFRD [25]. These findings are supported by our results both in terms of lung function, nutritional status, vitamin D levels and CFRD. CFRD is a common and a serious complication of CF affecting 1-2% of children under the age of 10 and 10-20% of individuals in the second decade of life [26]. Although CFRD is rare before the age of 10, abnormal glucose tolerance is present from a young age [27]. There is strong evidence for an association between inferior lung function and CFRD and even other forms of abnormal glucose tolerance. The decline in lung function often precedes the CFRD diagnosis and the period of AGT has been gaining more attention in CFRD research [28]. *Minicucci et al* demonstrated in their paper that patients with CFLD had more than 11-fold increased risk for developing CFRD as compared to individuals without CFLD. They suggest earlier CFRD screening for individuals with signs of CFLD [29]. Other studies have also demonstrated this relationship [4,30]. Here we present that children and adolescents with abnormal glucose tolerance and not only CFRD, have increased liver stiffness demonstrated by the 2D SWE method. This could indicate a partial common pathogenic pathway for CFRD and CFLD, but given the retrospective nature of our study design, no causal relationship could be established. During the evolvement of CFRD from AGT, possible associated disease progression in other organs should be studied as it may be of an importance. Early screening with OGTT for children with signs of liver involvement is supported by our findings and seems at least warranted even for other reasons such as the declining lung function in the years before CFRD diagnosis.

The main weaknesses of this study include its retrospective design and the limited number of subjects. The 2D SWE measurements were performed by different pediatric radiologists and although all of them are highly qualified there is always the possibility of interinvestigator variability in the interpretations. Furthermore, the examination was combined with an ultrasound which could give rise to some bias in the evaluation. The fact that there are various techniques available to measure liver stiffness makes comparison between different studies somewhat difficult. The reference values from one technique is not applicable to another one and since the different CF centers and radiology departments have access to different equipment, the gathering of data for meta-analysis and multi center studies is complicated. The lack of reference values for children for the 2D SWE method and the lack of validation and standardization for the different techniques is also troublesome.

In conclusion, measuring liver stiffness by 2D SWE is feasible in clinical practice, and it can be performed in conjunction with the more standard ultrasound investigation. Increased liver stiffness is associated with lower vitamin D levels, inferior lung function and abnormal glucose tolerance. Whether a common pathophysiological pathway explains these relationships remains the aim for future studies to explore further.

Credit author statement

All authors have made substantial work in to this paper.

Helga Elidottir: Study design. Ethical application. Study protocoll. Recruiting patients. Writing most of the paper. Statistics with assistance.

Stefanie Diemer: Ethical applications and study protocoll with Helga. Consent forms and participant information. Critical review of the paper.

Erik Eklund: Helgas superior supervisor in phD studies. Critical review and corrections of the study protocol, ethical application and this paper.

Christine Hansen: Helgas co-supervisor in phD studies. Study protocoll. Recruiting patients. SPSS statistics work with Helga. Critical review and corrections of the whole process and this paper.

Declaration of Competing Interest

Authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors would like to thank all the participants and the pediatric CF team at Lund CF center. Dr.Kristina Vult von Steyern is to thank for expert information on the 2DSWE technical issues and we thank our colleagues at the pediatric radiology department in Lund for their outstanding and innovative work for children with CF.

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