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## TITLE PAGE

### **TITLE: ASSESSMENT OF LIVER FIBROSIS BY TRANSIENT ELASTOGRAPHY (Fibroscan®) IN PATIENTS WITH A1AT DEFICIENCY**

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## **ABSTRACT**

Background: Alpha-1 antitrypsin deficiency (A1ATD) is a common genetic condition which predisposes to emphysema and liver disorders. It is estimated that 10-15% of homozygous individuals for the Z allele (PiZZ) may develop liver fibrosis. The optimal modalities to detect liver disease in PiZZ adult patients need to be defined. The aim of this prospective study was to perform a systematic noninvasive evaluation of the liver fibrosis by elastometry using Fibroscan® in a cohort of A1ATD patients with emphysema.

Methods: Patients followed in our respiratory unit were enrolled in this prospective study and underwent on the same day a physical examination, a biochemical profiling, an abdominal ultrasound (US) and a Fibroscan®.

Results: Twenty-nine PiZZ adults (19 male) were included. Median age was 50.4 yrs (21.5-67.2). Median serum A1AT level was 0.20 g/L (0.15-0.33). Liver Function Tests (LFT) were not normal in 2 patients and US was abnormal in 6 patients. Two patients had both abnormal LFT and US. Fibroscan® was technically feasible in 28/29 (97%) patients. Median liver stiffness was 4.5 kPa (2.8-32.8), and was > 7.2 kPa in 5/28 (18%) and > 14 kPa in 2/28 (7%) patients. Liver stiffness was increased in 2/2 (100%) patients with abnormal LFT and US, in 1/4 (25%) with abnormal LFT or US and in 2/22 (10%) patients with normal LFT and US.

Conclusions: Fibroscan® is an easy and repeatable tool which can be used in PiZZ patients to screen for the presence of significant liver fibrosis and to identify patients at higher risk to develop liver complications in the future and who may benefit from a closer surveillance.

## **KEYWORDS**

Alpha-1-antitrypsin deficiency, liver disease, fibrosis, cirrhosis, transient elastography, Fibroscan

## **ABBREVIATIONS**

Alpha-1 antitrypsin deficiency (A1ATD), liver function tests (LFT), ultrasound (US), Magnetic Resonance Elastography (MRE), Non Alcoholic Fatty Liver Disease (NAFLD)

## INTRODUCTION

Alpha-1 antitrypsin deficiency (A1ATD) is a common autosomal codominant genetic disorder which can cause severe pulmonary and/or liver diseases[1]. The molecular defect is a specific mutation of the SERPINA1 gene leading to the synthesis of an abnormal protein (mostly A1AT Z) that cannot be secreted and polymerizes in the endoplasmic reticulum of hepatocytes [2,3]. The inter-individual variability in the responses to intracellular stress induced by the accumulation of abnormal polymers, and in the mechanism allowing their degradation, is responsible for the different clinical manifestations of the liver disease which can vary from abnormal liver function tests (LFT), neonatal cholestasis to chronic hepatitis, cirrhosis and sometimes hepatocellular carcinoma [4–9]. It is estimated that 10-15% of homozygous individuals for the Z allele (PiZZ) may develop liver fibrosis.

So far, there is no approved specific treatment for the liver disease associated with A1ATD which accounts for 1-2% of annual liver transplantation in western countries [10]. Several complementary approaches dealing with increasing the autophagy process, silencing the expression of A1AT or preventing polymerization are currently in development and sometimes already in early clinical trials [11,12].

Liver involvement may be recognized late in the absence of systematic and complete liver evaluation. Furthermore, regular tests such as LFT and ultrasound (US) may be not sensitive enough to identify patients with early and reversible impairment. Liver biopsy, which was the gold standard in the diagnosis of most of liver diseases, has a morbidity in 0.5% patients (bleeding or pneumothorax) and a mortality of 0.02%, and can therefore not be recommended routinely in all patients [13]. For these reasons, noninvasive tests, either physical, such as measurement of liver stiffness by impulsive elastometry, or biological, with development of different scores (Fibrotest, Fibromètre, APRI, FIB-4, ELF, ...) have been developed to evaluate liver fibrosis and tend to replace the biopsy in many diseases either during the initial work-up or during the follow-up[14–20].

The aim of the present prospective study was to perform a systematic noninvasive evaluation of the liver fibrosis by elastometry using Fibroscan® in a cohort of A1-AT deficient patients with emphysema.

## **PATIENTS AND METHODS**

Adults patients with an A1AT deficiency (A1ATD) and followed in our respiratory unit were enrolled prospectively in this study. Patients with an acute respiratory decompensation were excluded from the study. Twenty-eight patients PiZZ were included in this study. Four patients (2 with PiSZ and 2 with PiZ null) were screened but excluded because the risk of liver involvement is unclear in this setting.

Informed consent was obtained for all patients. This study was approved by the Ethical Review Board of South East IV (CPP Sud-Est IV) on 7<sup>th</sup> April 2011, ID RCB Number 2011-A00264-37 and was registered as NCT01455298 on <https://clinicaltrials.gov>.

On the same day, all patients underwent a physical examination (with determination of Body Mass Index (BMI) and daily alcohol consumption), a biochemical profiling (which AST, ALT, GGT, ALP, INR, platelet count), an ultrasound (with determination of hepatomegaly, steatosis, dysmorphism and splenomegaly) and a transient elastography (Fibroscan®). Normal ranges were respectively 9-45 IU/L for AST, 9-65 IU/L for ALT, 12-64 IU/L for GGT, 35-130 IU/L for ALP.

Measurement of liver stiffness by transient elastography was performed using a Fibroscan® with a M probe as previously described [16,21]. The results were expressed in kilopascals (kPa). Measures were considered reliable when they fulfilled all the following criteria:  $\geq 10$  valid measurements,  $\geq 60\%$  success rate and interquartile range / median ratio (IQR/M)  $\leq 30$ .

Fibrosis was considered significant in case of liver stiffness  $> 7.2$  kPa. Cirrhosis was defined by liver stiffness  $> 14$  kPa and/or US signs of cirrhosis (hepatic dysmorphism with splenomegaly) [17].

APRI and FIB-4 scores were calculated for all patients and patients with APRI  $> 1$  and/or FIB-4  $> 3.25$  were considered to have severe fibrosis[22,23].

Statistical analysis was performed using SPSS software, version 23.0 (IBM, Armonk, NY). Categorical variables were expressed as percentages and compared with the Chi-square or Fischer's exact tests. Continuous variables were expressed as median (ranges) and compared using the Mann-Whitney's test. A p value less than 0.05 was considered statistically significant.

## **RESULTS**

The clinical characteristics of patients are shown in Table 1. Twenty-nine patients, 19 males and 10 females, were enrolled in this study. Median age was 50.4 yrs (21.5-67.2). Median serum A1AT level was 0.20 g/L (0.15-0.33). Diagnosis of respiratory emphysema was performed 65 months (15-288) prior to this evaluation. Twenty-three patients were on augmentation therapy.

Median BMI was 22.6 (18.0-31.2). Five patients were overweight (BMI 25-30) and one was obese (BMI >30). One patient had excessive daily alcohol consumption (>21 units per weeks), 16 patients were occasional drinkers.

The biological and ultrasonography findings are shown in table 1. LFT were abnormal in 3 (10%) patients. Median ASAT, ALT, GGT, ALP and total bilirubin were respectively 28 IU/L (19-91), 23 IU/L (17-62), 33 IU/L (12-237), 72 IU/L (43-148), 11 µmol/L (11-52).

The abnormalities revealed by abdominal US were hepatomegaly in 6 patients, steatosis in 2 patients, hepatic dysmorphism in 1 patient and splenomegaly in 1 patient. In one patient with dysmorphic hepatomegaly, steatosis and splenomegaly, the radiological evaluation was in favor of cirrhosis.

Impulsive elastometry was possible in 28/29 (97%) patients. The patient who failed Fibroscan® evaluation had complete normal LFT, US and FIB-4 and APRI values. Median liver stiffness was 4,5 kPa (2.8-32.8) (Table 1), and was >7,2 kPa in 5/28 (18%) and >14 kPa in 2/28 patients (7%). FIB-4 and APRI scores were respectively >3.25 and >1 only in the two patients with Fibroscan® value >14 kPa.

When possible, Fibroscan® was increased in 2/2 (100%) patients with abnormal LFT and US, in 1/4 (25%) with normal LFT and abnormal US and in 2/22 (10%) patients with normal LFT and US (figure 1). Median Age, gender, median BMI and alcohol consumption was not different between the group of patients with significant fibrosis  $\geq$ F2 estimated by Fibroscan® and the group without fibrosis ( $p>0.05$ ). Median AST, ALT, GGT were significantly higher in patients with significant fibrosis but remain in the normal range (Table 2). Median ALP, total bilirubin and platelet count were not different between the 2 groups.

## **DISCUSSION**

The best strategy to identify PiZZ A1ATD individuals with liver impairment remains unclear. It has been shown that an increase in ALT has a low sensitivity to identify A1ATD adults with liver disease [24], however the mean levels of liver enzymes were more elevated in patients with portal hypertension but frequently within normal range [25]. We found the same result in our study with a median value of transaminases in the normal range but 2-fold higher in the group of patient with significant fibrosis identified by Fibroscan®. In another study, ALT and GGT levels were similar to patient without liver disease and lower than patients with Non Alcoholic Fatty Liver Disease (NAFLD) [26].

Our results show that, in a cohort of PiZZ adult patients, Fibroscan® can identify in a non invasive way, complementary to LFT and US, 17% of patients with suspected significant fibrosis ( $\geq$ F2) and 7% of patient with cirrhosis ( $\geq$ F4). These results are consistent with those of a recent study where a systematic liver evaluation with liver biopsy was performed in 23 patient candidates for lung transplantation [27]. Morer et al. have shown that 13% of patients had moderate fibrosis (F2) and 8% severe fibrosis (F3 or F4). In another study, the prevalence of severe fibrosis or cirrhosis was 17,5% in PiZZ A1ATD patients who presented with either abnormal transaminases or abnormal platelet count or abnormal US [28].

Recently, a pilot study has shown that liver stiffness evaluated by Magnetic Resonance Elastography (MRE) was significantly higher in eleven A1ATD patients compared to controls (2.6 vs 2.2 kPa) and was similar to patients with NAFLD (2.6 vs 2.7 kPa) [26]. As expected, MRE value was higher in patients according to the degree of fibrosis on histological evaluation. An MRE threshold of  $\geq 3.0$  kPa provided 88.9% accuracy with 80% sensitivity and 100% specificity to detect the presence of any fibrosis. MRE seems to be a promising technique to evaluate fibrosis in many diseases [29] however the availability, the duration and the cost of the procedure could be a brake on expansion of this modality, at least in a short period of time. On the contrary, Fibroscan® is an easy, rapid and somewhat costless procedure which has shown its interest in the most frequent liver diseases (chronic viral hepatitis, alcoholic liver disease, NAFLD, autoimmune hepatitis) [30]. Even if the threshold to identify significant fibrosis or cirrhosis may vary according to the etiology, the different values are overall in the same range. To date, there is no data regarding the performance of Fibroscan® on A1ATD patients, probably because of its rarity. We were worried about the possible difficulties to perform Fibroscan® in patients with severe emphysema and thoracic distension but in our cohort the failure rate was only 3% *ie* in the normal range[31].

The absence of liver biopsy is the major limitation of our study. However because of the absence of specific treatment in case of liver involvement in one hand and on the other hand the risk of complications and the possible sampling error we decided to avoid this procedure which will not have changed the clinical management. In the future, soon hopefully, in case of specific treatment of the liver impairment, these patients would benefit from a biopsy to confirm or not the liver impairment as a pretherapeutic work-up. Currently, patients with either abnormal LFT or US but also with abnormal Fibroscan® are included in a program with a close monitoring in the liver clinic.

In conclusion, Fibroscan® is a well-known easy and repeatable tool and our results suggest that it can also be used in PiZZ patients to screen for the presence of significant liver fibrosis and to

identify patients at higher risk to develop liver complications in the future and who may benefit from a closer surveillance.

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## TABLES

**Table 1:** Clinical, biological, ultrasonography and elastometry characteristic of the patients

(biological and elastometry values are expressed with median)

Characteristic	Value	Range
<i>Clinical</i>		
Number of patients	29	
Male, n (%)	19 (66)	
Age at evaluation (median)	50.4	21.5-67.2
Serum A1AT level (g/L) (median)	0.20	0.15-0.76
Emphysema, n (%)	28 (97)	
Augmentation therapy, n (%)	23 (79)	
Excessive alcohol consumption, n (%)	1 (3)	
BMI (median)	22.6	18.0-31.2
BMI >25, n (%)	6 (21)	
<i>Biological</i>		
AST, IU/L	28	19-91
ALAT, IU/L	23	14-62
GGT, IU/L	33	12-237
ALP, IU/L	72	43-148
Total bilirubin, $\mu\text{mol/L}$	11	7-52
Hb, g/L	151	130-173
Platelets, G/L	255	125-394
<i>Ultrasonography</i>		
Hepatomegaly, n (%)	6 (21)	
Steatosis, n (%)	2 (7)	
Dysmorphism, n (%)	1 (3.5)	
Splenomegaly, n (%)	1 (3.5)	
<i>Elastometry</i>		
Liver stiffness, kPa	4.6	2.8-32.8
Success rate, %	80	60-100
IQR/med, %	22	7-29

**Table 2:** Biological results according to the value of Fibroscan®

(all biological data are expressed with median (range))

	Fibroscan® > 7.2 kPa	Fibroscan® ≤ 7.2 kPa	
n	5	23	
AST, IU/L	41 (22-91)	25 (19-40)	p=0.027
ALT, IU/L	45 (23-56)	21 (14-45)	p=0.002
GGT, IU/L	55 (34-194)	29 (12-62)	p=0.004
ALP, IU/L	96 (45-148)	72 (43-104)	p=0.239
total bilirubin, μmol/L	11 (9-52)	11 (7-20)	p=0.264
platelet median, G/L	212 (125-394)	268 (140-374)	p=0.215

## **LEGENDS FOR FIGURE**

**Figure 1** : Flow chart describing the results of liver function tests and liver imagery in the 28 patients with interpretable Fibroscan®.

(LFT were considered elevated if one of the different parameters (AST, ALT, GGT or ALP) was upper the limit of the normal range. US was considered abnormal in case of the presence of one of the following items (hepatomegaly, steatosis, hepatic dysmorphism or splenomegaly). Fibroscan was considered abnormal when the stiffness was  $> 7.2$  kPa).

