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Noninvasive Measurement of Liver Fibrosis Using Transient Elastography in Pediatric Patients with Major Thalassemia Who Are Candidates for Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Although liver biopsy is an invasive procedure, it remains the gold standard technique for the evaluation of hepatic fibrosis in different patients, including those with major thalassemia (MT). Recently, noninvasive imaging techniques, such as transient elastography, have emerged. We investigated the effectiveness of TE, in comparison to liver biopsy, for the evaluation of liver fibrosis in pediatric patients with MT who were candidates for hematopoietic stem cell transplantation (HSCT). Eighty-three pediatric MT patients (48 boys and 35 girls), who were candidates for HSCT, were included in this study. The median age was 8 years. Liver stiffness was assessed for all patients, before transplantation, using both TE, measured in kilopascals (kPa) and liver biopsy, based on the Metavir score. The diagnostic accuracy of TE and liver biopsy were estimated using linear discriminated analysis (the area under the receiver operating characteristic curves [AUROCs]). The median TE score was 4.3 kPa (range, 3.5 to 5.2). The TE value did not differ among patients with different ferritin levels ($P = .53$). TE increased proportionally to Metavir fibrosis stages ($P < .001$) and the necroinflammatory grade ($P < .001$). The TE score also correlated to liver iron content ($P < .001$), liver size ($P < .003$), and Lucarelli risk classification (LRC) ($P < .001$). ROC curve analysis revealed moderate accuracy of the TE score for the diagnosis of fibrosis (AUROC = 73%) and for distinguishing individuals with a LRC III from those classified as I and II (AUROC = 82%). The TE score was also superior to Fibrosis-4 (AUROC = 61%) for the assessment of liver fibrosis and LRC differentiation. The results of this study demonstrated that TE can be a valuable method for assessing liver fibrosis and differentiating LRC III from the other 2 classes in pediatric patients with MT who have been selected for HSCT.

INTRODUCTION

Major thalassemia (MT), 1 of the most common genetic disorders worldwide [1,2], results from inadequate production or the absence of the beta chain of hemoglobin [3,4].

Although noncurative medical treatment has transformed MT from a lethal disease of childhood to a chronic disease of adulthood, hematopoietic stem cell transplantation (HSCT), with a high probability of event-free survival (80%) is currently the only curative treatment for MT patients [5–7]. However, HSCT is associated with the risk of transplantation-related mortality, graft-versus-host disease, and graft failure; therefore, selecting optimal transplantation candidates is extremely crucial. Also, considering the fact that MT patients are predisposed to liver fibrosis as a consequence of multiple blood transfusions, it is of utmost importance to classify the patients using the Lucarelli risk classification (LRC) before HSCT so that each patient will receive the appropriate conditioning regimen based on this classification. The LRC, which was first described in the late 1980s, is used as a prognostic system to predict transplantation outcomes in MT patients [8]. This classification consists of 3 risk factors: the quality of chelation therapy during the years before transplantation, hepatomegaly (>2 cm below the intercostal margin), and the presence of any portal fibrosis in the pretransplantation liver biopsy [7–9]. It is very important to use LRC before HSCT, as

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conditioning regimens and prognosis of this procedure are not the same in LRC class III patients and for those who fall into class I or II [8,10].

Although liver biopsy remains a gold standard for evaluating hepatic fibrosis, which is needed to determine the LRC, the invasiveness of biopsy and its related complications in MT patients have necessitated the application of novel, validated, noninvasive modalities for estimating the stage of hepatic fibrosis [4,11]. Several approaches, such as the Fibrosis-4 (FIB-4), the Lok index, the Fibro test, and the aspartate aminotransferase (AST)-to-platelet ratio index (APRI), have been used by investigators and compared with liver biopsy, showing varying degrees of accuracy in evaluating liver fibrosis. Another approach, transient elastography (TE), has also been used as a reliable, noninvasive tool for evaluating liver fibrosis, showing comparable results to liver biopsy, especially in patients with chronic viral hepatitis and cirrhosis [12,13]. However, studies on TE's performance assessing liver fibrosis in MT patients and especially its impact on determining the LRC are still scarce in the literature [14,15].

This study has 2 aims. The first is to investigate the efficacy of TE for the evaluation of liver fibrosis, compared with liver biopsy, in MT patients selected for HSCT. The second aim is to evaluate the predictive accuracy of TE in distinguishing MT patients characterized as LRC class III from the others.

METHODS

Participants and Study Design

Pediatric transplantation candidates diagnosed with MT who were referred to Shariati Hospital from October 2010 to February 2012 were enrolled in this study. A written informed consent was obtained from every patient's parents or legal guardians. Patients who did not give consent received the routine clinical care at our center. The study protocol was in accordance to the guidelines of the Declaration of Helsinki and was approved by the ethics committees of the Hematology-Oncology Research Center and Stem Cell Transplantation and the Digestive Diseases Research Institute.

Hemoglobin electrophoresis or mutation analyses were performed on all patients to confirm the diagnosis of MT. Patients with cardiovascular diseases; cirrhosis; human immunodeficiency virus; viral hepatitis, including hepatitis B or hepatitis C; and any other chronic liver disease were excluded from the study. All patients underwent both a liver biopsy (before transplantation) and TE with a maximum interval of 3 months between the 2 procedures. The same individual performed all TE examinations in the 83 patients. The TE operator, as well as the gastroenterologist performing the biopsy, were blinded to the results of the other procedure. Laboratory evaluations including a complete blood count and platelet counts, as well as serum ferritin, AST, alanine aminotransferase (ALT), alkaline phosphatase, bilirubin (total and direct), albumin levels, and coagulation tests such as partial prothrombin time (PTT), prothrombin time (PT), international normalized ratio (INR) and bleeding time (BT), were measured in all patients.

All patients were classified based on the following LRC criteria: the quality of chelation therapy given before HSCT, the presence of hepatomegaly (palpable liver more than 2 cm below the costal margin), and the presence of any portal fibrosis on biopsy. Regular chelation therapy was defined as the use of deferoxamine 40 mg/kg for 8 to 12 hours each day, at least 5 days a week, starting less than 2 years from the time blood transfusions started. The absence of hepatomegaly and liver fibrosis, along with regular iron chelation before transplantation, categorizes an individual as class I, presenting with 1 or 2 of the 3 criteria defines class II, and having all 3 criteria characterizes class III [7–9].

Transient Elastography

TE was performed using Fibroscan502 (5 MHz, EchoSens, Paris, France). The S and M probes were used based on the manufacturer's guidelines: the S probe was used when the thoracic parameter was $\leq$ 75 cm, and the M probe was used when the thoracic parameter was >75 cm. With the patient lying in a dorsal decubitus position, and with maximal abduction of the right arm, the probe was placed on the patient's skin, overlying the right lobe of the liver, through the intercostal spaces. The median value of 10 valid measurements was recorded for each subject. The recorded value was considered valid if the interquartile range (IQR) was less than 30% of the median reading. The results were presented in kiloPascals (kPa).

Table 1
Characteristics of Patients

Variable	Value
Age, yr	8 (5-11)
Gender	48 male, 35 female
BMI (kg/m^2)	14.7 (13.8-16.1)
Ferritin (ng/mL)	1764 (1000-2311)
ALT (IU/L)	24 (15-36)
AST (IU/L)	28 (22-35)
ALP (IU/L)	396 (317-490)
Bilirubin total (mg/dL)	1.5 (.9-1.9)
Bilirubin direct (mg/dL)	.4 (.2-.5)
Prothrombin time (sec)	13.4 (12-14)
Albumin (g/dL)	3.9 (3.5-4)
TE scores (kPa)	4.3 (3.5-5.2)
METAVIR stage, n (%)	
F0 (no fibrosis)	14 (16.9)
F1 (portal fibrosis without septa)	50 (60.2)
F2 (portal fibrosis with few septa)	7 (8.4)
F3 (numerous septa without cirrhosis)	12 (14.4)
F4 (cirrhosis)	0
METAVIR grade, n (%)	
A0 (no activity)	65 (78.31)
A1 (mild activity)	18 (21.69)
A2 (moderate activity)	0
A3 (severe activity)	0
Iron load by atomic absorption spectrometry, × times more than normal	9 (5-15.7)
Liver size, mm	111 (100-130)
LRC, n (%)	
1	15 (18.1)
2	46 (55.4)
3	22 (26.5)

ALP indicates alkaline phosphatase.
Date presented as median (IQR) or n (%), as appropriate.

Liver Biopsy

Liver biopsy samples were obtained before transplantation, using a 16-gauge AceCut biopsy needle (TSK Laboratories, Tochigi-ken, Japan).

The biopsy specimens were considered adequate if they were at least 20 mm in length and contained 10 or more portal tracts. Fibrosis stage and necro-inflammatory grades were scored, based on the METAVIR system, by an expert liver pathologist.

Liver iron concentration (LIC) was quantified using atomic absorption spectrometry (Varian SpectrAA 20, Belrose, Australia). The presence of any fibrosis on biopsy was considered as a risk factor for LRC.

FIB-4 and APRI were also compared to liver biopsy results. FIB-4, which is based on simple variables such as age, AST, ALT, and platelet counts, was calculated using the following formula: age (years) · AST [U/L]/(platelets [10^9/L](ALT [U/L])$^{1/2}$), whereas APRI was calculated as (AST/upper limit of normal range)/platelet count (10^9/L) · 100.

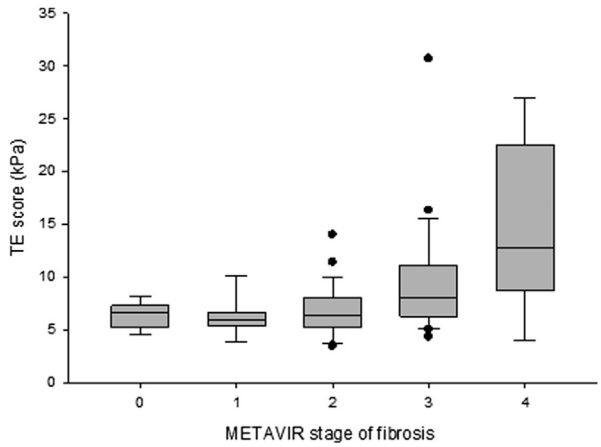

Figure 1. Correlations of TE score with METAVIR stage of fibrosis.