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The Potential Role of Transient Elastography in Assessing Patients with Primary Budd Chiari Syndrome

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1. Abstract

1.1. Background: Budd-Chiari Syndrome (BCS) is a rare disease defined as hepatic venous outflow obstruction at any level from the hepatic venules up to the cavo-atrial junction. Transjugular Intrahepatic Portosystemic Shunt (TIPS) is performed as a decompressive treatment in some patients.

1.2. Aim: To evaluate the potential role of Transient Elastography (TE) in assessing liver stiffness in patients with primary BCS.

1.3. Methods: Twenty one BCS patients and 10 patients with liver cirrhosis with different underlying etiologies underwent abdominal ultrasound and TE.

1.4. Results: Ninety-five percent of BCS patients had liver stiffness compatible with F4 with a median of 21 kPa, values which are usually obtained in patients with liver cirrhosis. Ten BCS and 10 cirrhotic patients underwent repeated TE with a median of 320 days between exams for BCS and 4.5 years for cirrhotic patients. The change of liver stiffness in BCS patients was 5.75 kPa (range -0.4 to 26.6), compared with-4.85 kPa (range -15.6 to 15.0) in cirrhotic patients (p-value = 0.0029). Change in liver stiffness from baseline to follow-up in BCS patients who underwent TIPS (n=4) was 0.2 kPa (range -0.4 to 15.3), whereas in patients without intervention (n=6) it was 6.75 kPa (range 1.3 to 26.6). The difference was not statistically significant.

1.5. Conclusion: Liver stiffness in BCS patients is dynamic progressive process with parameters of TE resembling liver cirrhosis. Even if TIPS seem to slow down the increment of liver stiffness, because of decreased liver congestion, it kept most patients with high score. The TE in BCS patients may be considered for monitoring for stable or upfront disease deterioration.

2. Introduction

Budd-Chiari Syndrome (BCS) is defined as hepatic venous outflow obstruction at any level from the hepatic venules up to the cavo-atrial junction, in the absence of congestive or restrictive heart disease. It occurs in 1 of 100,000 in the general population worldwide [1] and with annual incidence of 0.8 per million per year inhabitants [2]. The underlying etiologies for primary BCS vary. While intravascular thrombosis is more common in the West, membranous webs obstructing the inferior vena cava (IVC) are noticeable in Asia and

association with Behcet's disease is common in Turkey [3]. Thrombotic conditions commonly associated with BCS include polycythemia vera (PV), paroxysmal nocturnal hemoglobinuria, inherited deficiency of natural anticoagulants, e.g. protein C, protein S and anti thrombin or presence of factor V Leiden or prothrombin G20210A mutation [4, 5]. Currently, myeloproliferative diseases (MPD) with Janus kinase2 (JAK2) V617F gene mutation are the leading cause for BCS accounting for 25%-50% of cases [6, 7].

The clinical course of BCS varies from asymptomatic to fulminant hepatic failure. The latter is reported in 7% of cases, where as sub acute or chronic types occur in 45%-48% of patients. The occlusions of the hepatic veins lead to increased sinusoidal blood pressure with reduced sinusoidal and portal blood flow along with increased arterial blood flow in the microcirculation and centrilobular necrosis and fibrosis [8]. Prolonged occlusion results in progressive fibrosis and liver cirrhosis with portal hypertension [2]. Whether decompression leads to regression of liver fibrosis are still a matter of debate.

Doppler ultrasonography is the first line imaging modality for BCS diagnosis with a sensitivity of up to 85% [9-11].

Transient Elastography (TE) is a noninvasive tool for measuring liver stiffness [12-14]. It is based on calculating the speed of pressure-induced shear wave propagation through tissue subject to different biomechanical properties. Use of TE in the context of BCS was for the first time reported in assessing hepatic congestion 24 hours after endovascular interventions [15].

In the present study, we study the potential role of TE in assessing and monitoring patients with BCS.

3. Material and Methods

3.1. Patients

Twenty-one patients with BCS were recruited from the liver units of several hospitals and Maccabi health maintenance organization (HMO) in Israel. Exclusion criteria were secondary BCS attributable to hepatic cell carcinoma. Patients with ascites were not included since the elastic waves of TE do not penetrate liquids [16]. All patients had contrast-enhanced CT before recruitment to ascertain diagnosis of primary BCS, to confirm the number of occluded hepatic veins and to distinguish them from collateral vessels. In 12/21 patients, all 3 hepatic veins were occluded, 7 patients had 2 veins occluded and in 2 patients only one vein was occluded. Ten of 21 patients had also an MRI, and in 4 of them had repeated MRI before the beginning of the study. Most of the MRI examinations were performed at sub acute or chronic phase of BCS and assessed the morphological changes of the liver with enlarged caudate lobe. Regenerative nodules were described in 4 BCS patient that underwent MRI. Gastro scope was performed in 20 of 21 participants and 11 patients (55%) had esophageal varices.

The control group comprised 10 patients with liver cirrhosis with diverse underlying etiologies and splenomegaly but without ascites that were part of the group served as controls in previous studies [17, 18]. The underlying causes for liver cirrhosis were: hepatitis C virus (HCV) (n=5), hepatitis B virus (HBV) (n=2), primary sclerosing cholangitis (PSC) (n=2) and non-alcoholic steato hepatitis (NASH) (n=1).

The study was approved by the Ethics Committee of the Tel Aviv Sourasky Medical Center, and all participants gave written informed consent according to the Declaration of Helsinki (0394-13-TLV).

3.2. Ultrasound and Doppler Analysis

Ultrasound and Doppler examination were performed in all participants as described previously [17, 18]. Special attention was given to liver and spleen size, enlargement of caudate lobe and liver echogenicity, presence of nodules in the liver and spleen and presence of ascites. Doppler examination assessed the flow in the portosystemic system, hepatic veins, inferior vena cava, in the intrahepatic or extrahepatic collaterals and in the TIPS, when present.

3.3. Transient Elastography (TE)

The TE was carried out by Fibroscan® (Echosens; Paris, France). Liver stiffness was expressed in kilopascals (kPa). and measurement translated for different degrees, e.g., mild fibrosis (F1), moderate fibrosis or more (F2), severe fibrosis (F3), and cirrhosis (F4) as reported elsewhere [14]. The results were given as the median of 10 subsequent measurements and defined as valid if the ratio of the interquartile range and median was less than 30%. All patients fasted at least 8 hours before the examination. Liver stiffness was measured 1.5-3cm below the liver capsule while the patient was supine in right lateral decubitus with the right arm placed overhead in maximal abduction to extend intercostal space for placing the transducer in the right intercostal space.

4. Statistical Analysis

Data are summarized by median and range. Pearson correlations were computed to assess the strength of the relationships between the continuous variables. The Wilcox on test was used to compare groups with respect to continuous variables.

5. Results

5.1. Clinical Characteristics

The clinical characteristics of the BCS patients are presented in (Table 1). Risk factors were found in 67% of the patients. All BCS patients received anticoagulants unrelated to etiology and only one patient received direct oral anticoagulant, e.g., rivaroxaban. Median duration of the disease was 5 years (range 0-16 years) at the time of the first TE examination. Median spleen size was 14.5 cm with a range of 7.5-22 cm at the time of the first abdominal ultrasound during the study.

Table 1: Clinical characteristics of patients with BCS.

Endovascular intervention	Spleen diameter (Median)	Risk factors	Median age (y) at diagnosis	Gender
TIPS-9	14.5 cm	PV with JAK2V617F- 4	Male - 23Y	Male-7
Hepatic Stent -1		Crohn's disease-5	Female-38Y	Female-14
		APLAS*-2		
		Factor V Leiden -1		
		Oral contraceptives-2		

5.2. Transient Elastography (TE)

The median liver stiffness in BCS patients was 21 kPa (range 5.7 to 69.1 kPa) with a compatible score of F4 similar to patients with liver cirrhosis.

Spleen size was weakly related to liver stiffness (r=0.31) and duration of disease (r=0.14).

Ten of 21 BCS patients that were first included in the study had follow-up TE with a median of 320 days apart (range 90to 608 days) between exams. We then compared the change in liver stiffness from baseline to follow-up exam in patients with or without a previous endovascular intervention. As seen in Figure 1, the 4 patients with TIPS had a median stiffness change of 0.2 kPa (range -0.4 to 15.3), whereas the 6 patients without TIPS had a median change of 6.75 kPa (range 1.3 to 26.6). In those 4 BCS patients, endovascular interventions including TIPS or stent were previously carried out 2 months to16 years (median of 58.3 months) before participation in this study. The difference is not statistically significant (p-value=0.17 using the Wilcox on test) and the sample is too small to provide a statistically reliable result. The other 11 patients did not have follow-up exams since the elapsed time was too short.

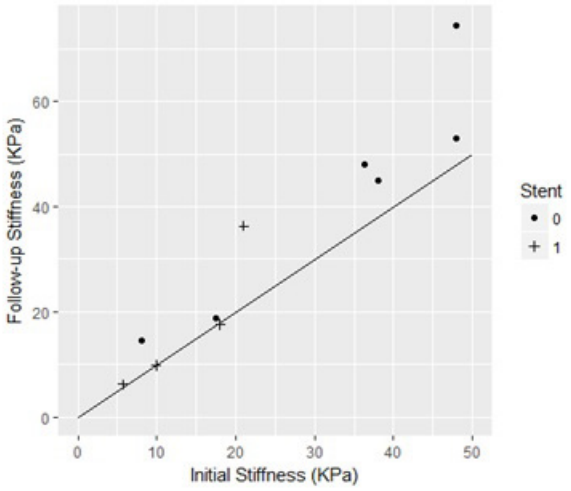

Figure 1: Follow-up versus initial liver stiffness measurement in 10 BCS patients. Those with a plus sign had a stent implanted. The line corresponds to no change in stiffness.

Median liver stiffness in the control group of cirrhotic patients was 19.7 kPa (range 12.2 to 35.3 kPa). The 10 cirrhotic patients had follow-up TE with a median of 4.5 years between exams (range 0.5 to 8 years).In 5 cirrhotic patients with hepatitis C, the repeat TE was performed between 3 months to 2 years after antiviral treatment was given and when no virus load was detected.

We next compared the change in liver stiffness in the 10 BCS patients and the 10 cirrhotic patients who had a repeat TE. As seen in Figure 2,the BCS patients had a median stiffness change of 5.75 kPa (range -0.4 to 26.6), whereas the cirrhotic patients had a median stiffness change of -4.85 kPa (range -15.6 to 15.0). The difference is statistically significant (p-value = 0.0029 using the Wilcox on test).

Albeit reduced liver stiffness in 8of 10 cirrhotic patients following specific therapy for underlying disease,only in 2 patients there was a change from F4 to F3.

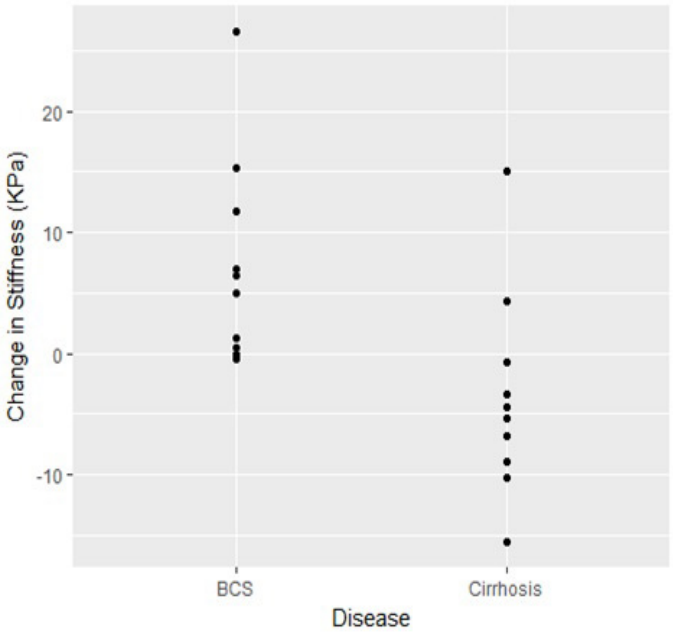

Figure 2: Change in liver stiffness from initial to follow-up measurement in 10 BCS patients and 10 cirrhotic patients.

6. Discussion

In this work, we found that 95% of the patients with BCS, unrelated to underlying etiology, had high values of liver stiffness measured at TE, similar to patients with liver cirrhosis.

Four of 21 BCS patients (19%) had PV with JAK2V617F mutation. Notably, treatment with cytoreductive therapy e.g., hydroxyurea along with anticoagulants and anti aggregants was not able to halt the progressive increment in liver stiffness measured by TE. In patient number 4, the high level of liver stiffness measured at TE anticipated clinical deterioration with liver failure and indeed this patient is programmed for liver transplantation.

BCS has rarely been associated with inflammatory bowel disease [19-22]. However, 5 of our 21 BCS patients (24%) had Crohn's disease

where 3 of them were on TNF alpha antagonist treatment. Such association can be explained by the prothrombotic state caused by uncontrolled inflammation during flares in Crohn's disease and perhaps by fibrosis reported to be related to treatment with anti TNF–α antagonist [23, 24]. The later reported to be associated with pulmonary fibrosis in patients with rheumatoid arthritis.

Two patients in our cohort had antiphospholipid syndrome. The association between antiphospholipid syndrome and BCS is not clear [25]. Factor V Leiden mutation was present in one of the patients and may have been a risk factor, as reported previously [10]. In 29% of our BCS patients, the etiology was still unknown.

In 8of the 10 BCS patients that had a follow up TE, liver stiffness increased. The later could be attributed to increased congestion and perhaps fibrosis. It is assumed that the increased liver stiffness developed during the first few weeks after hepatic vein occlusion and probably depends on the extent of initial vein occlusion. Though it is still not clear why the course of BCS is progressive when hepatic decompression happens through collaterals or when endovascular procedures are performed. It is hypothesized that the collaterals that formed are not efficient at impeding chronic ischemia [26]. In our study, in BCS patients with TIPS the progression of liver stiffness did occur but was slower in different to other groups. In the Hong-Wei Wang study, liver stiffness measured at 2 days after TIPS insertion was significantly decreased when assessed by Real-time Shear Wave Elastography but remained stable at 3 months though still in the cirrhotic range [27]. Another group reported that repeated TE measurement years after TIPS detect decreased value [28].

In sharp contrast with BCS, in 80% of cirrhotic patients, liver stiffness declined following treatment for underlying disease even if 70% of the cirrhotic patients remained with F4. In 3 control patients with HCV cirrhosis, a follow- up values of TE was compatible with F2-F3 after treatment. Indeed, liver fibrosis was shown to reduce following suppression of HCV and HBV [29], likewise in treated patients with autoimmune hepatitis [30] or abstinence of alcohol in alcoholic liver cirrhosis which could be related to reduce inflammation.

The question that one would ask is whether the increased liver stiffness in patients with BCS is irreversible. It may occur that in response to injury due to vascular thrombosis, the sinusoidal endothelial cells activate quiescent hepatic stellate cells HSC) with proliferative contractile myofibroblast phenotype that produce extracellular matrix in the liver, producing fibronectin, TGF-β1 and PDGF [31].

The contribution of increased liver congestion during the years, albeit collateral development should not be ignored as it is known that congestion by itself could increase liver stiffness [27].

We are aware of the major limitation of the work by the lack of liver biopsies. Yet liver biopsy in BCS is not routinely performed as it does not change management and it is still invasive procedure. Another limitation is the small group of patients. However, the fact that the liver stiffness was high in almost all our BCS patients gives us confidence that a larger group would not alter our results. The sample size of the cirrhotic patients is small but it reflects the parameters of liver stiffness known in cirrhotic patients worldwide [13, 14].

To note that only 48% of BCS patients had a second TE and at variable time gaps. However, we did find that in 80% of patients, the liver stiffness increased even when the repeat examination was done after a short interval. This raises a doubt about the effectiveness of the treatment given today to the patients with BCS.

In summary, liver stiffness in BCS patients is a dynamic progressive process despite the application of specific therapy to the underlying disease.

TE can serve as a surrogate modality to assess progression of liver stiffness in BCS patients and in cases where target therapy is implemented.

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