Ultrasound in Med. & Biol., Vol. 42, No. 9, pp. 2146–2155, 2016

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2016.04.016

● *Original Contribution*

ULTRASOUND AND POINT SHEAR WAVE ELASTOGRAPHY IN LIVERS OF PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

Anders Batman Mjelle,* Anesa Mulabecirovic,* Trygve Hausken,*† Roald Flesland Havre,* Odd Helge Gilja,*† and Mette Vesterhus*‡

*National Centre for Ultrasound in Gastroenterology, Department of Medicine, Haukeland University Hospital, Bergen, Norway; †Department of Clinical Medicine, University of Bergen, Bergen, Norway; and ‡Norwegian PSC Research Center, Division of Cancer Medicine, Surgery and Transplantation, Department of Transplantation Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway

(*Received* 12 *October* 2015; *revised* 21 *April* 2016; *in final form* 26 *April* 2016)

Abstract—Point shear wave elastography (pSWE) is an ultrasound-based method for non-invasive quantification of liver fibrosis. The objective of this study was to explore liver pSWE in patients with primary sclerosing cholangitis (PSC) for assessment of fibrosis. Fifty-five non-transplant patients with PSC (38 males, 17 females; mean age: 46.4 y) were included and compared with 24 matched controls. Median (range) PSC duration was 8.1 (0–33) y. Ultrasonographic scanning followed by liver stiffness measurement by pSWE was performed using a conventional ultrasound system (Philips iU22). Signs of liver fibrosis on B-mode were identified in 21 patients (38%). Splenomegaly was found in 19 patients (35%) and ascites in two patients (4%). Successful pSWE measurements were achieved in the right liver lobe of all individuals and in the left liver lobe of 36 patients (65.5%). PSC patients had significantly higher median shear wave velocity (SWV) than controls in the right liver (median [range] SWV 1.26 [0.73–2.57] m/s vs. 1.09 [0.88–1.25] m/s, $p < 0.001$). SWV measured in the left liver lobe and spleen did not differ between PSC patients and controls. Our findings indicate that PSC patients have increased median SWV, indicating more fibrosis compared with controls; however, a wide range of SWV values were obtained among PSC patients, possibly reflecting the various stages in disease development. (E-mail: mette.vesterhus@helse-bergen.no) **© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).**

Key Words: **Primary sclerosing cholangitis, Point shear wave elastography, Non-invasive, Liver fibrosis, Elastography, Ultrasound.**

INTRODUCTION

Primary sclerosing cholangitis (PSC), a chronic inflammatory disease affecting the biliary tree, leads to liver fibrosis and cirrhosis over time, with a reported median transplant-free survival time of 12–21 y (Boonstra et al. 2013; Broomé et al. 1996). Medical therapy with proven benefit is lacking, and PSC is a frequent indication for transplantation.

A major challenge in PSC is the lack of valid prognostic markers and biomarkers of disease activity (Hirschfield et al. 2013; Karlsen et al. 2014). Fibrogenesis is an important pathogenetic pathway in PSC and a target of treatment in several clinical trials. A serum marker panel of fibrosis, the enhanced liver fibrosis (ELF) test, was reported to distinguish mild from advanced disease in PSC by an area under the curve of 0.81 and to predict prognosis independently of other biomarkers, underscoring the importance of accurate liver fibrosis estimation in PSC (Vesterhus et al. 2015). However, for other etiologies of liver fibrosis, some studies indicate an improved performance of ultrasound elastography compared with ELF or an incremental value of the combination of the ELF test and liver stiffness evaluation by ultrasound elastography (Cobbold et al. 2010; Wahl et al. 2012). Hence, better methods for the diagnosis, grading and monitoring of liver fibrosis are warranted.

Ultrasound elastography is a technique measuring liver stiffness as an expression of fibrosis and has emerged as an important tool in the diagnosis and follow-up of liver fibrosis and cirrhosis, largely replacing

Address correspondence to: Mette Vesterhus, Department of Medicine, Haukeland University Hospital, Jonas Lies vei 49, N-5021 Bergen, Norway. E-mail: mette.vesterhus@helse-bergen.no

liver biopsy in hepatitis B and C (Cosgrove et al. 2013; Ferraioli et al. 2015). The status of liver biopsy as the gold standard for liver fibrosis assessment has long been challenged because of its invasiveness and risk of serious complications, as well as the substantial sampling error and inter-observer variation between pathologists (Castera and Pinzani 2010; Cholongitas et al. 2006; Thampanitchawong and Piratvisuth 1999). Liver biopsy is generally not indicated in PSC for either diagnosis or follow-up because of the patchy disease distribution and consequent sampling bias, except in cases of suspected small-duct disease or autoimmune hepatitis overlap (Chapman et al. 2010; European Association for the Study of the Liver 2009). Ultrasound elastography has the advantages of being non-invasive and repeatable and offers the possibility of investigating several regions of the liver, thus reducing sampling bias. Guidelines for the use of elastography in clinical practice have been published (Bamber et al. 2013; Cosgrove et al. 2013); however, reports on elastography in PSC are scarce (Corpechot et al. 2006; Hagstrom et al. 2012; Righi et al. 2012).

Interestingly, a recent publication reported that baseline values of transient elastography (TE), as well as the change in liver stiffness measured by TE, are associated with clinical outcome in PSC (Corpechot et al. 2014). Point shear wave elastography (pSWE) is a more recent technology than TE, with the advantage of being incorporated into high-end ultrasound equipment, allowing B-mode ultrasound guidance of elastography measurements and an integration of liver stiffness measurement with a full evaluation of the liver. Some studies of pSWE in patient populations with chronic liver disease of heterogeneous etiologies have included PSC patients in small numbers insufficient for sub-analysis (Righi et al. 2012). To our knowledge, there are no studies exploring pSWE in PSC alone. In this study, we aimed to evaluate liver stiffness in PSC patients and compare them with healthy controls using ultrasound pSWE.

METHODS

Patient population and data collection

The protocol was in accordance with the Declaration of Helsinki and approved by the Regional Committee for Health and Research Ethics in Western Norway. Patients invited to participate in the study belonged to a known cohort of non-transplanted PSC patients in western Norway. Informed written consent was obtained from each patient enrolled. PSC patients with a histologically confirmed diagnosis of autoimmune hepatitis (AIH) were classified as PSC–AIH overlap. Patients were examined, and patient records were searched for information on clinical data, including ascites, encephalopathy, esophageal varices, variceal bleeding and inflammatory bowel disease status at the time of serum extraction. On the day of ultrasound and elastography, blood was sampled and biochemical analyses were performed using the standard routine laboratory protocols, including C-reactive protein, hemoglobin, leukocytes, platelets, creatinine, total bilirubin, albumin, International Normalization Ratio, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and γ-glutamyl transferase. The Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4) scores of fibrosis were calculated using published algorithms (Sterling et al. 2006; Wai et al. 2003). Mayo risk scores were calculated using the algorithm for the revised Mayo risk score (Kim et al. 2000). Blood samples were not taken from healthy controls.

B-Mode ultrasound examination

Immediately before pSWE examination, all patients underwent B-mode ultrasound scanning of the liver and spleen. All examinations were performed by a single operator (M.V.) using a standardized scanning protocol on a Philips iU22 (Philips Healthcare, Andover, MA, USA) scanner. Scores were registered for liver capsule regularity, parenchyma heterogeneity, liver angle appearance, presence of ascites, gallbladder stones or polyps and the presence of bile duct variability or sludge. Measures were taken for liver size in a sagittal section in the medioclavicular line; gallbladder length, width and area; spleen length and width; and portal vein diameter. Splenomegaly was defined as spleen length >12 cm.

Point shear wave elastography

Liver and spleen stiffness was measured in the fasting condition by pSWE using a conventional ultrasound system (ElastPQ, iU22, Philips Healthcare) equipped with a convex probe (C5-1). For liver measurements, patients and controls were examined in the supine position with their right arm maximally abducted. A 0.5×1.5-mm region of interest was placed 2–6 cm deeper than the liver capsule in hepatic tissue, avoiding large vessels or bile ducts (Fig. 1). Right lobe measurements were made in an intercostal position, whereas left liver lobe measurements were performed in a subcostal epigastric position, with sampling from the central portion of the left liver lobe. Spleen stiffness was measured by pSWE from a left-side intercostal position. All pSWE measurements were acquired in relaxed mid-breath hold with minimal scanhead pressure being applied. A valid measurement was defined as the median value of 10 acquisitions, provided the requirement for a success rate $\geq 60\%$ was also fulfilled. The acquisitions were performed during separate breath holds in the same general area within one segment, avoiding visible bile ducts and blood