Profesional paper

IMPLEMENTATION OF SHEAR WAVE ELASTOGRAPHY AS A NEW METHOD IN THE CLINIC OF GASTROENTEROHEPATOLOGY – SKOPJE

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ABSTRACT

Despite the fact that liver biopsy is so far considered as " a golden standard" when diagnosing diffuse liver diseases, recently it has been replaced by non-invasive methods, such as serum markers of liver fibrosis and elastography, due to smallest amount of complications risk, and the likelihood for larger liver surface analysis.

Our study comprises 40 patients, with confirmed liver scarring, based on previous laboratory findings, clinical features, and abdominal ultrasound.

Based on the etiology and the stage of scarring, patients have been divided into three groups: patients with steatosis (alcoholic and non-alcoholic), patients with hepatitis, and patients with liver cirrhosis. Generally there has been established a positive correlation between elastography values and corresponding liver disease, except for small number of patients with more aggressive liver lesions than expected, resulting in higher elastography values.

Keywords: Shear wave elastography, serum markers of liver fibrosis, liver biopsy, liver - fibrosis

INTRODUCTION

The liver as one of the largest organs in the human body (except the fat tissue), performing a variety of metabolic functions, is known as "the human's chemical laboratory". The liver synthesizes essential materials like proteins, regulates levels of phospholipids and triglycerides, stores glucose as glycogen, and balance other complex metabolic pathways. Moreover, it's detoxifies the organism by eliminating toxins.

Liver fibrosis represents accumulation of connective tissue in the parenchyma, due to chronic hepatocellular lesion caused by excessive alcohol consumption, high-fat blood levels, genetic liver disorders, autoimmune diseases, viral infection (hepatitis B and C virus), hepatic vein thrombosis, decompensated heart failure and hepatotoxic drugs.

In acute liver lesions, parenchymal cells regenerate and replace necrotic cells. When liver lesions persist for a longer period, scarring occurs and the connective tissue destroys the specific lobular liver architecture, destroys particular vascular pattern and hepatocyte disfunctioning take place.

Diffuse liver lesion may advance to cirrhosis, with complications such as portal hypertension and hepatocellular failure. Cirrhosis and its complications represent a worldwide health burden. The word cirrhosis derives from the Greek word "khirros", meaning yellow-orange, named by Laënnec in the 19th century, because of the yellow-black and orange color of the scarred liver that he had noticed in autopsies. [1,2]

It has been considered that liver fibrosis is irreversible. In late 90s, it was discovered that advanced liver fibrosis is reversible, thus scientists were stimulated to create antifibrotic therapy and monitor changes in liver fibrosis by using non-invasive methods. [3,4]

Staging of liver fibrosis helps in assessing disease severity and its curability. In daily clinical practice, liver biopsy was considered as the only procedure for diagnosing diffuse liver scarring, as well as defining its degree. The risk of biopsy complications in severely ill patients, makes it more dangerous to repeat and monitor the treatment success. Another disadvantage of biopsy is that only a

small piece of the liver tissue is analyzed.

Great changes in modern hepatology occurred when non-invasive methods like serum markers of liver fibrosis and elastography were discovered, both of which are usefully providing staging of liver scarring.

The technique of elastography has been greatly developed since its start two decades ago, thus becoming an imaging method used in urgent cases too. It has been predicted to grow even more and to expand its use in medicine.

In the 90s, several groups of scientists in the United States, Europe, Japan, and Russia began to work in the field of elastography.

Figure 1 represents the dynamics of publications related to ultrasound elastography between 1995 – 2015 y, while numerous publications within one year (2007-2008), indicate the enormous use of elastography in numerous clinical trials around the world, in patients with diffuse changes in the liver parenchyma.[5]

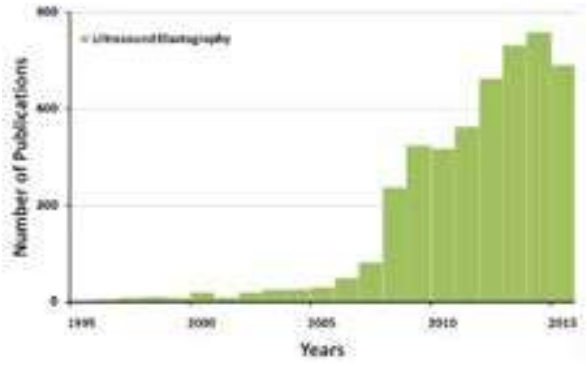

Figure 1. Dynamics of publications related to ultrasound elastography according to PubMed database in between 1995-2015. [36]

It must be stressed that ultrasound elastography represents a major field of elastography, compared with other imaging techniques such as magnetic and mechanic resonance imaging. [6,7]

Even though lot of studies began to assess focal liver lesions, elastography has not been recommended for such use, as a result of its limitations in the depth of penetration. Besides being used as an alternative method of liver biopsy in staging liver fibrosis, it is also used for predicting complications in patients with cirrhosis. [8,9,10,11]

Chronic liver scarring is a consequence of abnormal growth of extracellular matrix, produced by fibroblasts during the process of fibrinogenesis and fibrinolysis. Hence the liver loses its elasticity and becomes stiffer.

Ultrasound elastography measures liver stiffness in a non-invasive manner. The method measures the reaction of the tissue via an external mechanical device (Fibroscan), or acoustic radiation force impulse monitored by ultrasound (US), or magnetic resonance imaging (MRI).

There are two ultrasound elastography techniques widely used for assessing liver elasticity: Strain and Shear Wave Elastography (SWE). Both methods use mechanical vibrations in the liver parenchyma and monitor its changes. They differ in the manner of using external mechanical vibrations and how they measure liver elasticity [12,13,14]. SWE is considered as a dynamic method, which directly measures elasticity unlike the semiquantitative method of Strain Elastography, which measures liver elasticity by comparing it to other structures.

In strain elastography, tissue displacement is measured by using mechanical compression (with an ultrasound transducer, cardiac pulsation, and respiration). Tissue displacement is measured and converted to strain image thus providing displacement percentage [15]. Fibrous tissue shows greater stiffness. Fibrous tissue displaces less than normal parenchyma and strain images from fibrotic tissue will indicate less strain relative to normal tissue (Fig 2)

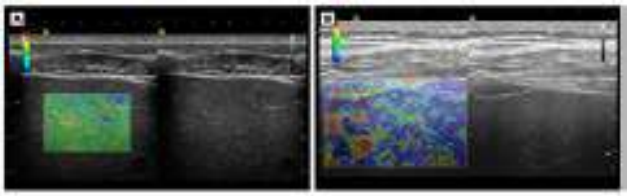

Figure 2 .Strain Elastography showing healthy liver parenchyma (A) and liver cirrhosis (B). [37]

Shear Wave Elastography- shear waves may be created by external compression and by vibrations caused by the transducer, as well as by acoustic radiation force impulse (ARFI). Shear waves expand everywhere, including biological tissues. They can be generated in the tissue itself when an external force is used, deforming the tissue. [11-15] Measurements of tissue elasticity are based on the travel speed of shear wave and the density of the material through which shear waves travel.

Several methods are used for performing Shear Wave Elastography, such as Transient Elastography (TE, Figure 3), Point Shear Wave Elastography (point SWE, Figure 4),

and 2D SWE (2D- SWE, Figure 5). The methods differ in the manner of shear wave generation and from the place where measurements are taken.

Compared to transient elastography or fibroscan, which generates shear waves via vibrations caused by the sound when it hits the liver tissue, Point Shear Wave and 2D SWE use internal acoustic force- ARFI for generating shear waves.

Shear Wave techniques (TE and ARFI) measure the wave speed traveling through the tissue. Thus, speed is converted to kilopascal, a unit of Young's modulus.

The measurements of shear wave velocity are taken from a small area (usually 5-10 mm of point shear wave) or points of sequential measurements (2D-SWE). [15-25]

Figure 3 Transient Elastography showing the measurement of liver stiffness in kilopascals (kPa).[38]

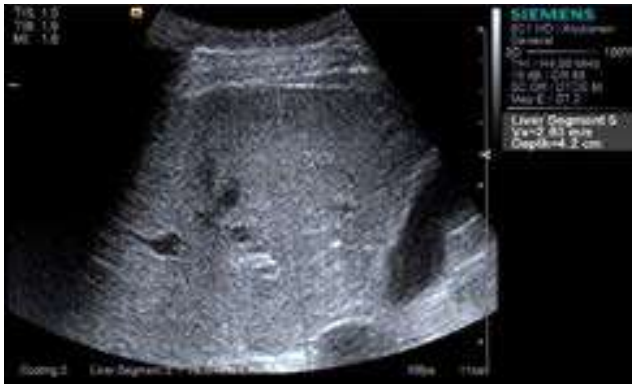

Figure 4 Point-Shear Wave Elastography assessment in the right liver lobe in a 36-year-old woman with pulmonary arterial hypertension. [39]

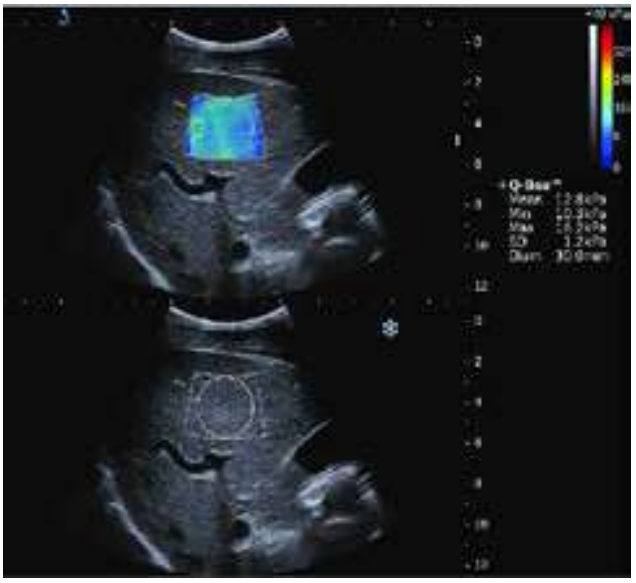

Figure 5 2D SWE measurement in the liver of a 43-year-old man with fibrosis stage F4. [40]

Similar to fibroscan, Point SWE measurements are performed with minimum pressure with a transducer in the intercostal space on the right side. The patient must holds the breath during the procedure - he is in the inspiratory phase. The values are reported either as the velocity of the shear wave (m/s) or converted in kilopascal (kPa).

Point Shear Wave Elastography simultaneously shows the velocity of shear waves and the black-and-white ultrasound image.

Point SWE has been proven as very useful for diagnosing hepatic fibrosis in patients with chronic infection with C and B virus, alcoholic and non-alcoholic diseases of the liver. [28,29,30,31,32]

A meta-analysis comprising nine studies with overall 518 patients with chronic liver diseases, assessed the diagnosing performance of Point SWE for staging liver fibrosis. The final optimum values for diagnosing liver fibrosis with their respective sensitivity and specifics were as follows: Point SWE provides a comparison of measurements in different places in the left and right lobe of the liver. The highest values are noted in the left lobe of the liver, but the accuracy of Point SWE seems to be higher in the right lobe compared to the left lobe. [27]

The sensitivity of Point SWE for staging F2 fibrosis is approximately 75 %, while for diagnosing cirrhosis is approximately 90%. Specificity is approximately 85 and 87%. [26,27]

Compared to Point SWE which produces a black-and-white liver imaging, 2D SWE is in color. It is also used in patients with ascites, and measurements are made under the right rib as well as from other sides of the liver.

METHODS AND MATERIALS

This study provides the results of measurements with the non-invasive SWE method in 40 patients with different liver pathologies, and different age and sex. The study was carried out in the Clinic of Gastroenterohepatology in Skopje.

Patients who are scanned with SWE, belong to the age group from 18 to 80 years old, and they primarily underwent basic and biochemical analyses of the liver and one of the imaging methods: either abdominal ultrasound or computer tomography of the abdomen. Clinical features, high liver enzyme values, and changes in the liver structure, which can be noted in the imaging methods were main indications for SWE performance.

Even though Point SWE can be performed in patients with ascites and obesity, numerous studies have demonstrated that obtained values are not reliable. Furthermore, SWE cannot be performed in patients with cardiovascular or malignant diseases. Nevertheless, it can be performed in pregnant patients and during the period of lactation.

The implementation of non-invasive methods for diagnosing diffuse liver diseases such as serum markers of liver fibrosis in the Institute of Immunology, fibroscan in the Clinic of Infectious Diseases, and Point SWE in the Clinic of Gastroenterohepatology has significantly alleviate the diagnosis and subsequent treatment of patients with hepatitis B and C infection.

Starting from 2017, in our clinic has been implemented the new method of SWE which is a Real-Time Elastography, and SWE measurement or Point SWE which is 2D. It is performed with the ARIETTA V70 Hitachi Aloka device and convex C251 (1.8 - 5.0 MHz) transducer.

It is a quantitative method that measures the velocity of wave expansion in the liver tissue, thus showing liver elasticity. Every change of elasticity represents morphological changes in the liver parenchyma.

The method is non-invasive and lasts for 15 to 30 minutes. The measurements are taken according to the recommendations of EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology).[33]

The result is automatically displayed as a mean value of 10 measurements of the wave velocity moving through the tissue (shear wave velocity - Vs), with a quality index that expresses the percentage of efficient measurement (VsN) which cannot be lower than 50% (Figure 6).

The result provides staging of fibrosis from F0 to F4. There is no liver fibrosis if the SWE value is lower than 5.8 kPa. When the results is from 5.9 to 7.2 kPa, it indicates F1 value or initial stage of fibrosis. When the value amount is between 7.3-9.5 kPa then fibrosis is progressive or F2-F3. In the case of cirrhosis, the measured values are from 9.6-12.5 kPa or even higher.

Usually, measurements must not be very deep in the liver parenchyma, but not less than 1.5cm away from the liver capsule, and away from blood vessels.

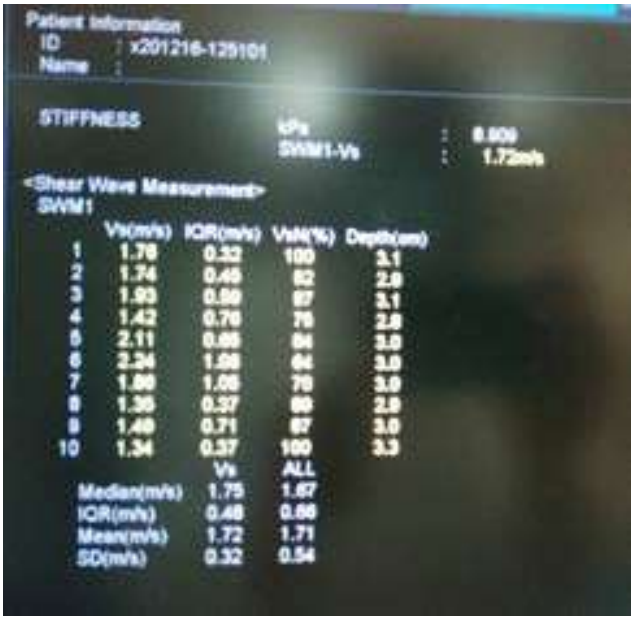

Figure 6. Results of SWE in a patient with liver fibrosis of the F2 scale.

RESULTS

In recent years, in the Clinic of Gastroenterohepatology-Skopje, numerous elastographies were performed. Most patients with liver diseases of various etiologies underwent liver biopsy, and final pathohistological values have demonstrated a close similarity with elastography values and other non-invasive methods.

In this study, 40 patients were analyzed, divided into 3 groups: 16 patients with viral hepatitis, 9 patients with alcoholic and non-alcoholic steatosis, and 15 patients

with liver cirrhosis.

Figure 7 Concordance of Shear Wave Elastography values with liver scarring of different etiologies.

DISCUSSION

Liver diseases of different etiologies are increasing in our country and abroad especially viral liver diseases such as hepatitis B and C, with high morbidity and mortality. Adequate and fast diagnosis is very important for the prevention of liver scarring progression and its treatment.

One of the most common infections in the world is Hepatitis B infection with cirrhosis and hepatocellular carcinoma as complications. According to World health organization (WHO), 1/3 of the world population has serologic evidence of former or current Hepatitis B virus infection. 40% of the world population has had contact with a carrier of the disease or they are carriers of Hepatitis B virus. [34,35]

Hepatitis C causes acute disease, which may go away unnoticed, or cause long-term chronic disease and cause complications such as cirrhosis and hepatocellular carcinoma. Unlike Hepatitis B, after the acute phase where 90% of patients are completely cured, 80% of Hepatitis C patients, result in chronic diseases. [34,35]

The Clinic of Gastroenterohepatology diagnoses and treats many patients with these diseases. Staging hepatic fibrosis is very important for further treatment and for preventing the disease progression. Liver biopsy was and is still considered a “golden standard” for diagnosing liver fibrosis of various etiologies. The attempt to avoid complications that may be caused by this procedure gave birth to the idea for inventing non-invasive methods for diagnosing liver fibrosis.

In recent years, a major significance was given to the accuracy of serum marker of liver fibrosis. Serum markers of hepatic fibrosis represent fragments of extracellular matrix produced by liver stellate cells during the process of fibrinogenesis and fibrinolysis. They are divided into direct and indirect markers of liver fibrosis.

Indirect markers of liver fibrosis refer to biochemical serological tests that indicate liver functioning but do not reflect the metabolism of the extracellular matrix. Serum Aminotransferase values, platelets, coagulation factors, gamma-glutamyl transferase, total bilirubin, alfa 2 macroglobulin, and alfa 2 globulin are individual markers that are combined in serological panels for monitoring liver fibrosis changes.

Direct serological markers of liver fibrosis are produced by stellate cells during the process of extracellular matrix formation due to pathological alterations in the liver. Some of them like procollagen type 3 amino-terminal peptide, hyaluronic acid, laminin, and collagen type 4 are determined in our Institute of Immunology with the chemiluminescence method.

Shear Wave Elastography, combined with serological markers of liver fibrosis are continuing to replace the invasive methods for diagnosing patients with chronic liver diseases.

Our study comprises 40 patients of both sexes between 18 and 80 years of age, with liver scarring of different etiology. In 7 out of 9 patients with liver steatosis, the values of elastography correspond to liver scarring and are F0-F1, and 2 patients have F2 and F3 values. In 14 out of 16 patients with hepatitis of infectious or autoimmune etiology note the values F1-F2, while in two patients the value F3 is noted (with a more aggressive disease). 2 out of 15 patients with cirrhosis had elastography values of F3-F4, while in 13 patients elastography values are F4.

CONCLUSION

The analyses of patients’ results indicate concordance of elastography values with the degree of liver scarring of different etiology. In patients with liver steatosis, elastography values are F0-F1. In patients with Hepatitis B, C, or autoimmune diseases, the values are F2-F3. The F4 elastography value indicates major liver scarring, i.e., cirrhosis.

In our Clinic, this method is used with growing intensity, and it is providing an exact diagnosis of patients with

chronic liver diseases of different stages and etiologies, with results comparative with those provided with invasive methods.

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