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PhD THESIS

USEFULNESS OF ULTRASOUND BASED ELASTOGRAPHIC METHODS FOR THE EVALUATION OF LIVER FIBROSIS

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KEY WORDS: elastography, liver fibrosis, chronic hepatopathies

INTRODUCTION

Chronic hepatopathies of different etiologies (viral chronic hepatitis B or C, alcoholic steatohepatitis, non-alcoholic steatohepatitis, autoimune or colestatic liver disease) are quite frequent in daily practice. The proportion of patients affected by chronic liver diseases varies in differerent geographical areas depending on the incidence of viral chronic B or C infection, depending on the alcohol consumption or on the prevalence of the obesity and metabolic syndrome

In these conditions, how can we evaluate and follow up these patients?

The severity of the liver fibrosis can be evaluated invasively using liver biopsy or non-invasively using biological tests or elastographic methods. Although hepatic biopsy is still considered the gold standard for the assessment of fibrosis and hepatic inflammation, due to its invasive nature and due to the fact that it is associated with some complications, their number has significantly decreased in favor of elastographic methods.

There are currently two types of elastographic techniques: ultrasound-based elastographic techniques and MRI elastography. The latter due to high costs is not used in current clinical practice in our country. The number of ultrasound-based elastographic methods increased significantly, each method having some limitations.

In this context, the aim of this research was to highlight the usefulness of ultrasound-based elastography in clinical practice.

SPECIFIC PART

2. AIMS

The first aim was to assess the feasibility of Transient Elastography (TE) using both probes (M or XL) in clinical practice and in overweight and obese patients, considering that this is the most frequent method used. The second aim was to quantify the value of TE in type 2 diabetic patients and to assess the usefulness of this method and its liver stiffness dynamics in patients with liver cirrhosis caused by C viral infection under interferon free treatment.

Another aim of this research was to assess the intra and interobserver reproducibility of a new point share wave elastography called ElastPQ.

Furthermore, I have identified the ElastPQ curving curve, the performance of this method for the evaluation of liver stiffness in patients with chronic viral hepatitis (B or C) and also in healthy subjects.

The final aim, was to assess the feasibility and the concordance between the newest ultrasound based elastographic methods (VTQ, ElastPQ, and SSI) and Transient Elastography.

3. MATERIAL & METHODS

The study included 4487 subjects, 2355 (52.5%) women and 2132 (47.5%) men, age between 17 and 85 years (mean age 55 years old). Subjects evaluation took place from January 2012 to June 2016 in the Department of Gastroenterology and Hepatology Timisoara.

The subgroup of 392 type 2 diabetic patients came from the Diabetes and Metabolic Outpatient Clinic, Timisoara and the subgroup of 225 subjects were from the Department of Gastroenterology and Hepatology Timisoara and from the Center of Digestive Diseases and Liver Transplantation, Fundeni Clinical Institute, Bucharest.

Two types of studies were performed, a retrospective one (January 2012- October 2014) and a prospective one (January 2013- June 2016) evaluated by various elastographic methods (Figure1).

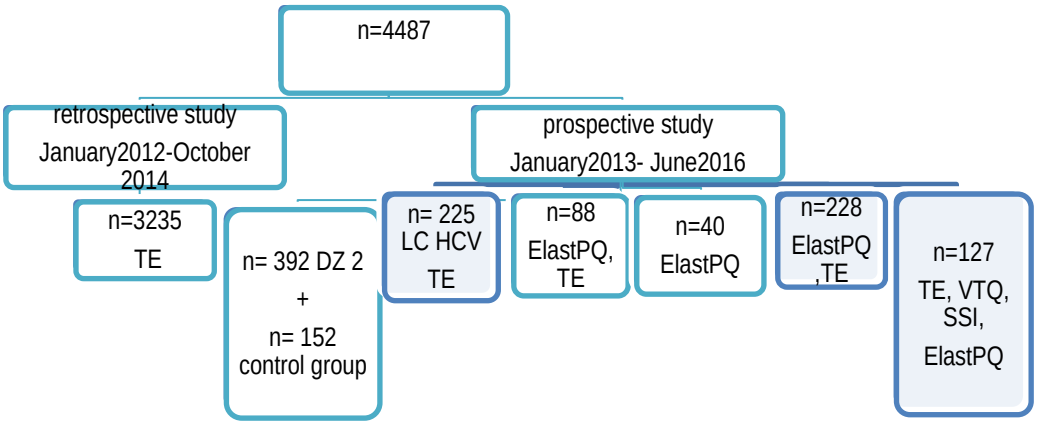

Figure 1: Characteristics of the study group, n-number of subjects, LC-liver cirrhosis

All the subjects included in the study were evaluated by ultrasound and did not have any visible focal liver lesions. From the study were excluded subjects with cardiac pacemakers, with obstructive jaundice, pregnant women and subjects that refused elastographic measurements.

The subjects included in the study were divided in different subgroups (Figure 1) depending on the elastographic method and type of the study. All the subjects were evaluated by abdominal ultrasound before the elastographic measurements in order to exclude the presence of liver lesions and ascites.

Regardless of the elastographic method used (TE, ElastPQ, VTQ, SSI), the measurements were performed in fasting conditions (minimum 3 hours), the patient being in supine position with the right upper hand in maximum abduction and the measurements being performed in the right liver lobe. If the measurements were performed with two or more elastographic techniques, these were performed in the same session.

Ten liver stiffness measurements were performed using TE, VTQ, ElastPQ and three measurements for SSI. The median value was calculated and the result was expressed in meters/second (m/s) for VTQ or in kPa for the other elastographic techniques. For VTQ we consider failure those measurements that appeared as „ X-X-X” on the screen, while for

ElastPQ a value of „0.00” means that the system did not detect liver tissue. We defined valid liver stiffness values for ElastPQ if we could obtain 10 non-zero measurements.

Both TE and VTQ have well established quality criteria which consists of obtaining10 valid measurements with IQR < 30% and SR > 60%. For ElastPQ initially there were no quality criteria, a recent study (68) suggested that IQR / M ≤ 30% is the most important quality criterion if at least 5 measurements are obtained. On the other hand for SSI the manufacturer has not recommended the use of any criteria and EFSUMB (3) does not recommend a specific one because the results are discordant and limited.

In the subgroup of 392 diabetic patients assessed by TE, for a good differentiation between different stages of liver fibrosis I used the cut-off values proposed by Wong et al (153) in 2010: F2-F3 7-10.2kPa; F4 ≥ 10.3 kPa. On the other hand, in the subgroup where I evaluated the performance of ElastPQ taking TE as the reference method, I used the latest cut-off values published in the Tsochatzis meta-analysis (53): 7.0 kPa for significant fibrosis (F≥2), 9.5kPa for severe fibrosis (F≥3) and 12.0 kPa for liver cirrhosis (F=4).

4. RESULTS

4.1. FEASIBILITY OF TRANSIENT ELASTOGRAPHY (TE) WITH M AND XL PROBES IN CLINICAL PRACTICE AND IN OVERWEIGHT AND OBESE SUBJECTS

Out of 4487 subjects we evaluated the feasibility of Transient Elastography (TE) in clinical practice in 3235 subjects. In this subgroup I obtained valid measurements defined as IQR < 30% and SR ≥ 60%, in 62.2% (2015/3235) by using the M probe and in 80% (1011/1220) using the XL probe. The XL probe was used only when we could not obtain valid liver stiffness measurements with the M probe. Thus, using both probes we achieved a feasibility of 93.5%.

On the other hand, in overweight subjects we obtained reliable liver stiffness values in 89.9% (1039/1156): 63.1% (729) by M probe and 83.8% (746/890) in obese subjects: mostly by XL probe 65.4% (582). Thus, by using both probes in this category of subjects, reliable liver stiffness values were obtained in1785 subjects (87.2%).

4.2. VALUE OF TRANSIENT ELASTOGRAPHY (TE) IN TYPE 2 DIABETES MELLITUS PATIENTS

Out of 392 subjects with type 2 diabetes, reliable liver stiffness values were obtained in 76% (298/392). By using the cut-off values proposed by Wong et al. (22), significant fibrosis was found in 18.8% subjects with steatosis and in 13.8% liver stiffness values were suggestive for cirrhosis. Liver stiffness values suggestive for cirrhosis were significantly found in a higher proportion in subjects with moderate and severe steatosis (S2+ S3) than in subjects without steatosis or in those who presented mild steatosis (S0+ S1): 11.5% vs. 2.6%, p=0.0005

4.3. THE USEFULNESS OF TRANSIENT ELASTOGRAPHY (TE) IN MONITORING THE LIVER STIFFNESS VALUES IN SUBJECTS WITH HCV UNDERGOING INTERFERON FREE TREATMENT

A prospective study was conducted (December 2015 – September 2016) and the dynamic of liver stiffness values obtained by TE was evaluated in 225 subjects with liver cirrhosis, genotype 1b, at the beginning and at the end of treatment (EOT) undergoing interferon free treatment (Viekirax/Exviera + Ribavirină). In a subgroup of 170 subjects the dynamic of liver stiffness values was evaluated also at 12 weeks after EOT.

Out of 225 subjects, reliable liver stiffness measurements were obtained in 93.7%, so the final analysis included 211 subjects. The mean liver stiffness value has significantly decreased after interferon free treatment: 26.4 ± 11.7 vs. 23.5 ± 13.3 kPa (p=0.01). In a subgroup of 170 subjects, all with sustained viral response (SVR) the liver stiffness values were also evaluated at 12 weeks post EOT. The mean liver stiffness values were significantly lower at 12 weeks post EOT versus the values obtained at baseline: 21.3±11kPa (95% IC:20.1-24.9) vs. 27.4±11.9kPa (95% IC:25.2-29.6) (p<0.0001) and versus those obtained at EOT: 21.3±11 kPa (95% IC: 20.1-24.9) vs. 23.7±13.3kPa (95% IC: 23.5-24.2) (p<0.0001).

4.4 THE REPRODUCIBILITY OF A POINT SHARE WAVE ELASTOGRAPHY ELASTPQ

A prospective study (December 2015 - June 2016) was conducted and the intra and interobserver reproducibility of the latest point share wave elastography was evaluated in a group of 88 subjects (44.3% women, 55.7% men). All the subjects were evaluated also by TE and were classified in cirrhotic and non-cirrhotic subjects if the value obtained with TE ≥12 kPa vs. TE<12kPa (23).

An expert in abdominal ultrasound, defined as the first operator (> 1000 examinations) and experience in elastography (> 500) and a beginner in abdominal ultrasound defined as the second operator (100 examinations) and limited experience in elastography (50 measurements) but with no experience in ElastPQ, performed the examinations. The intra and interobserver reproducibility was studied in 50 subjects, 12 subjects being in both groups.

The intraobserver reproducibility was excellent, ICC of 0.97 (95% CI: 0.94-0.98). Absence of cirrhosis was associated with a lower ICC, while sex, age, higher BMI and presence of cirrhosis defined by TE seemed not to affect liver stiffness values obtained with ElastPQ.

The interobserver reproducibility was excellent (ICC = 0.89, 95% IC: 0.82-0.94). The ICCs were smaller in women and subjects > 65 years old. Also their respective 95% LOAs had a wider range.

Table 1. Agreement between operators using medians calculated from different numbers of LSMs

Liver stiffness	Operator 1 median (IQR)	Operator 2 median (IQR)	ICC (95% CI)
3 LSM	5.13 (4.79)	4.91 (5.9)	0.922 (0.862-0.956)
5 LSM	5.66 (6.51)	4.7 (5.1)	0.951 (0.913-0.972)
10 LSM	5.4 (5.71)	5.15 (5.66)	0.952 (0.915-0.973)

LSM denotes liver stiffness measurement, IQR- interquartile range, ICC interclass correlation coefficient, CI confidence interval

4.5. THE LEARNING CURVE OF ELASTPQ

Using the same cohort of 50 subjects in which the interobserver reproducibility was studied I evaluated also the ElastPQ learning curve. It seems that the second operator with limited experience in liver elastography obtained similar results with the elastography expert after the 30th subject. The performance of the second operator was fair, obtaining an AUROC of 0.735, 95% CI (0.557-0.913), (p = 0.01).

4.6. ELASTPQ IN SUBJECTS WITHOUT LIVER PATHOLOGY

The value of ElastPQ was studied in a cohort of 40 subjects without known liver pathology (Ag.Hbs , Ac.anti HCV negative) and with a normal abdominal ultrasound. The aim of this study was to determine liver stiffness values in this category of subjects.

The mean liver stiffness in these „healthy" subjects was 4.24 ± 0.96 kPa, 95% CI (3.93 - 4.56). There were no significant differences between the mean value obtained in men and women and between the BMI categories.

4.7. THE PERFORMANCE OF ELASTPQ IN PATIENTS WITH B AND C CHRONIC HEPATOPATHIES

The performance of ElastPQ was studied in 228 subjects with chronic hepatopathies (26% HBV, 74 % HCV) taking TE as the reference method. In the final analysis 205/228 (89.9%) subjects were included, with valid measurements using both elastographic methods. The ElastPQ performance in predicting different stages of hepatic fibrosis in chronic hepatitis B and C using TE as a reference method is shown in Table 2

Table2. The performance of ElastPQ for differentiation of fibrosis degrees, considering TE as the reference method in a cohort with mixed patient (HBV and HCV)

Fibrosis stage	Cut-off	AUROC	Se (%)	Sp (%)	PPV(%)	NPV (%)	AC (%)
F≥2	>7.2kPa	0.94 CI(0.92-0.97)	84.6 % CI(77.8-90.2)	96.7% CI(88.7-99.6)	98.4% CI(94.3-99.8)	72.8% CI(61.8-82.1)	90%
F≥3	>8.5kPa	0.97 CI(0.95-0.99)	88.4% CI(81.7-93.4)	98.6% CI(92.8-100)	99.1% CI(95.3-100)	83.1% CI(73.7-90.2)	92%
F=4	>8.9 kPa	0.97 CI(0.95-0.99)	92.9% CI(86.9-96.6)	93.4% CI(84.8-96.9)	93.8% CI(87.7-97.5)	91.3% CI(83.6-96.2)	93%

4.8 THE FEASIBILITY AND CONCORDANCE BETWEEN VTQ, ELASTPQ, SSI AND TE FOR THE EVALUATION OF LIVER FIBROSIS

At the end of the PhD thesis the feasibility of four shear wave elastographic methods (TE, VTQ, ElastPQ, SSI) was evaluated in a cohort of 127 subjects with diffuse chronic hepatopathies of different etiologies (Table 3).

Table 3. Feasibility of four elastographic methods

Elastographic method	Feasibility	p
ElastPQ vs. TE	85.8% vs. 87.4%	0.84
ElastPQ vs. VTQ	85.8% vs. 92.1%	0.16
ElastPQ vs. SSI	85.8% vs. 95%	0.02
TE vs. SSI	87.4% vs. 95%	0.05
TE vs. VTQ	87.4% vs. 92.1%	0.30
VTQ vs. SSI	92.1% vs. 95%	0.49

p<0.05 statistical significance

Thus, in the final analysis were included only 82/127 subjects (64.5%) with valid and reliable measurements obtained by all four methods. The concordance between liver stiffness values obtained by ElastPQ, VTQ and SSI with the TE considered as the reference method is reported in Table 4.

Table 4. Concordance between ElastPQ, VTQ and SSI versus ETU

	Precision coefficient (Pearson r)	Accuracy coefficient (Cb)	Concordance correlation coefficient (CCC)
ElastPQ	0.74	0.86	0.64
VTQ	0.80	0.89	0.72
SSI	0.86	0.95	0.82

CONCLUSIONS:

1. The feasibility of Transient Elastography in clinical practice using both probes (M and XL) is in general population approximately 93% and 87% in overweight and obese subjects.

2. Significant fibrosis obtained by using Transient Elastography, in subjects with type 2 diabetes mellitius and moderate steatosis is over 30%, suggesting the systematic need for the evaluation of this category of subjects.

3. Transient Elastography assessment allowed evidence of a decrease in mean EOT values in approximately 60% of subjects with HCV cirrhosis after interferon-free antiviral treatment and about 75% at 12 weeks of EOT (compared with initial pretreatment values, in patients with SVR).

4. ElastPQ has an excellent intra and interobserver reproducibility which is not influenced by the presence of obesity.

5. Obtaining 5 reliable measurements using ElastPQ is sufficient in clinical practice.

6. Minimal experience in elastography, but experience in abdominal ultrasound is required for obtaining reliable liver stiffness.

7. The mean liver stiffness values assessed by ElastPQ in subjects without known liver pathology is 4.24 ± 0.96 kPa and is not influenced by gender and body mass index.

8. ElastPQ is an accurate method for predicting significant fibrosis (VPP: 98.4% obtained for a cut-off value of 7.2 kPa) and for exclusion liver cirrhosis (VPN: 91.3% for a cut-off value of 8.9 kPa)

9. The feasibility of the newer elastographic methods based on ultrasound (ElastPQ, VTQ, SSI) is at least similar or even superior to the Transit Elastography, an internationally validated method.

10. The concordance between ElastPQ, VTQ, and SSI versus Transition Elastography varied from moderate for ElastPQ and VTQ elastography to excellent for SSI elastography.

11. Ultrasound based elastography (ETU, ElastPQ, VTQ, SSI) seems to be a promising method both in diagnosing the severity of fibrosis and monitoring subjects with chronic viral hepatopathies but also in screening hepatic fibrosis in type 2 diabetics, being an alternative to liver biopsy.