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Shear Wave Elastography Detects Asymptomatic Changes of the Liver among Diabetes Mellitus Type 2 Patients

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Abstract

Damage to the liver is a common clinical consequence of chronic diabetes mellitus type 2 (DM2). This study evaluates whether ultrasound shear wave elastography and hemodynamics of the portal vein and the hepatic artery can complement traditional clinical work-up data for the monitoring of liver health among DM2 patients.Methods: Sixty-four (64) participants (31 controls and 33 patients with confirmed type 2 diabetes mellitus) between 21 to 74 years of age were recruited. Liver size, stiffness and hemodynamics of the portal vein and the hepatic artery were evaluated. Glycated hemoglobin (HbA 1c), aspartate aminotransferase (AST), alanine a minotransferase (ALT), and alkaline phosphatase (ALP) were monitored. Student's t-test was employed with significance attained at $p < 0.05$.Results: Asymptomatic significant differences were detected among DMT2 patients: (1) Largest Liver size (p=0.04); (2) Higher liver stiffness (p=0.04); (3) Higher alkaline phosphate levels (p=0.03); (4) Higher HbA1c levels (<0.001) and (7) presence of moderate to severe liver fibrosis. DM2 F1 stage has higher liver stiffness (0.006) and HbA1c levels (<0.001).

Index terms—

1 Introduction

ccording to the International Diabetes Federation, in 2019, diabetes affects 463 million people around the world. It is a source of major concern that this prevalence is expected to increase to 700 million by 2045. 1 Detrimental effects on liver health such as steatosis or fatty liver are common clinical consequences of chronic diabetes mellitus type 2 (DM2). More than 70% of adult patients with DM2 develop steatosis or non-alcoholic fatty liver disease (NAFLD), with significant anatomical and physiological detrimental effects. [2][3][4] In fact, NAFLD is a worldwide epidemic of great financial impact with an estimated prevalence as high as 30% of the worldwide population, most likely due to the fact that obesity and diabetes are risk factors of this fatal condition when left untreated. [5][6][7] Nonalcoholic steatohepatitis (NASH) usually precedes NAFLD, as the liver becomes inflamed and fibrosis develops. [8][9] Fibrosis is characterized by an excess of connective tissue that produces an increase in liver density, which in turn, eventually leads to organ dysfunction. Liver fibrosis can worsen into cirrhosis and cancer. Unfortunately, as is the case for NAFLD, liver fibrosis can also be asymptomatic. Therefore, a gap in standard clinical algorithms for the long-term management of DM2 is to be able to monitor liver health with a cost-effective approach.

Even though liver enzymes are used as screening for liver disease, they may not correlate with severity of disease. 10 Liver biopsy is considered the gold standard to confirm liver pathology, but this is an expensive diagnostic tool. In addition, it is a high risk invasive procedure with unwarranted potential side effects. 11 In contrast, shear wave hepatic elastography is a non-invasive and a cost-effective diagnostic tool that measures the elasticity and hardening of liver tissue across the organ. [12][13][14] We aim to determine whether the use of shear wave hepatic elastography can complement traditional clinical work-up data for the monitoring of liver health among DM2 patients.

2 II.

3 Material and Methods

4 a) Subjects

Sixty-four (64) participants (31 controls and 33 patients with confirmed type 2 diabetes mellitus) between 21 to 74 years of age were recruited in two clinical sites: a university based endocrinology hospital clinic in Puerto Rico and an endocrinology clinic, associated with a Puerto Rican school of medicine. The recruitment was carried out with the following exclusion criteria: previous hepatic disease, hyperlipidemia, right upper quadrant trauma, chronic kidney disease, morbid obesity, alcoholism, and cardiac disease. The study adhered to the approved research protocol by the Protection of Human Research Participants Office of the Medical Sciences Campus, University of Puerto Rico (protocol number A9000113). All participants signed and provided written informed consent prior to recruitment. All sonographic images were made by one of the authors (BLRC) who is an experienced sonographer; and were independently evaluated by the same diagnostic radiologist who is the president of the Radiological Society of Puerto Rico (GBO).

5 b) Laboratory test results

Laboratory test results were obtained from medical records: blood levels of glycated hemoglobin (HbA 1c), hepatic enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase [ALP]. Laboratory test report were obtained within a time window of 6 months of the ultrasound imaging session. For the purpose of this study, HbA 1c levels were used to confirm diabetes, whereas ALT, AST and ALP levels were used as indicators of liver function.

6 c) Sonographic imaging of the liver

A real time abdominal sonogram study was performed to evaluate liver anatomy and hemodynamics of the portal vein and hepatic artery, with a Logiq E9 ultrasound machine (GE Healthcare, Milwaukee, Wisconsin, USA) with a C1-6-VN 2D convex probe. Hepatic ultrasound images and craniocaudal measurements were obtained with the patient in a left anterior oblique position (15^{o} -20^{o}) with the right arm placed above the head. The scan was performed in the anterior axillary region (AAR). The craniocaudal measurement of the right liver lobe (RLL) was traced from the highest right hemi-diaphragm visualized in the ultrasound image to the inferior tip of the right lobe, as parallel as possible to the anterior wall of the liver. 15 Ultrasound images of the main portal vein (MPV) and hepatic artery (HA) were also obtained in oblique position to evaluated MPV vein diameter (cm), MPV velocity (cm/seg), MPV pulsatility index ($PI = V_2 / V_1$), HA velocity (cm/seg) and HA resistive index($RI = V_1 - V_2 / V_1$).

For liver stiffness, RLL images were obtained with study participants placed in a left anterior oblique position (15°-20°), with the right arm placed above the head and with the skin exposed from the hip to the xiphoid process. The intercostal right upper quadrant was scanned to obtain a longitudinal image of a given region of interest (ROI) in the segment VIII of the liver, at a depth of $<$ 8 cm under the skin to avoid blood vessels, shadowing areas and anatomical boundaries between organs. Patients were asked to hold breath and avoid deep inspiration while elastography measurements were taken. Mean values (in kPa) are reported. The presence and degree of fibrosis was identified following METAVIR Scale classification for GE LogiqE9: Healthy liver F0 ($<$ 5.48 kPa), Normal to Mild fibrosis F1 (5.48 -8.29 kPa), Mild to Moderate fibrosis F2 (8.29 -9.40 kPa), Moderate to severe fibrosis F3 (9.40 -11.9 kPa), and Cirrhosis F4 ($>$ 11.9 kPa).

7 d) Statistical Analysis

Data shown is expressed as mean $\pm$ standard deviation unless otherwise specified. Analyses were performed with XLSTAT-Biomed software (Version 2018.5, Add in soft, New York City, New York, USA). Normality was assessed by the Shapiro-Wilk test and homogeneity of variance was evaluated according to normality results. 16 Normally distributed data were analyzed with a Student's t-test; otherwise, Mann-Whitney test was used. Statistical significance was attained at $p < 0.05$.When significance reached four decimal points, p value is reported as < 0.001, otherwise specific value is reported.

8 III.

9 Results

Significant ultrasound differences of the liver were noted between controls and diabetes mellitus type 2 patients (Table 1). Patients with DM2 showed larger (p=0.04) and stiffer livers (p=0.01) in comparison with controls patients. HbA1 c , ALT, AST and were also measured. As expected, HbA1 c levels confirmed diabetes status ($p< 0.001$).

With regard to liver function, alkalinephosphate (p=0.03) was significantly higher amongDM2 patients (Table 1).

A distinct patient distribution was detected when stratified by fibrosis category. Specifically, the distribution of control patients was as follows:F0 (n=6), F1 (n=19), F2 (n=3), F3 (n=1) and F4 (n=0), whereas the distribution of DM2 patients was as follows: F0 (n=4), F1 (n=18), F2 (n=4), F3 (n=7), F4 (n=1). Table 2 shows the HbA1c, liver enzymes and stiffness values when stratified by fibrosis category. It is of interest that a significant difference was noted between F1 groups for liver stiffness (p=0.006) and HbA1 c levels (p< 0.001). Regarding blood vessels hemodynamics, no statistical difference was found in main portal vein (MPV) velocity and hepatic artery velocity (HAV) between controls and DM2 patients (Table 3). In contrast, a significant difference was noted between MPV diameter (p=0.05), MPV pulsatility index (PI) (p=0.002) and hepatic artery resistive index (HARI; p=0.002).

10 IV.

11 Discussion

Diagnostic ultrasound with shear wave elastography of the liver shows some asymptomatic differences in DM2 patients. This study reported that the liver size was larger and liver stiffness was higher in DM2 groups when compared to controls. Although the largest number of patients in our cohort showed to be in an early stage category (F1), the diabetic group showed a greater proportion of patients in advanced stages (F2 to F4) of liver fibrosis. In agreement with previous studies, no significant differences in the levels of the liver enzymes AST or ALT was detected, which further supports the emergent opinion that liver enzymes may not always correlate with the severity of liver disease. 10 Hence, accurate and cost-effective diagnostic tools are needed for the long-term monitoring of liver health.

Among the hemodynamic parameters of interest, we found higher hepatic artery resistive index (HARI) in diabetic patients, which is consistent with the findings of greater liver stiffness among this group. This finding is similar to other studies that found a positive correlation between HARI and fibrosis degree. [17][18] Our study also found lower portal vein pulsatility index (PVPI) among DM2 patients. There is evidence of decreased venous pulsatility index in patients with NAFLD. [19][20] Taken together; these findings suggest a compensatory mechanismin vascular compliance that is secondary to fatty infiltration of the liver. This hypothesis warrants further research.

Over the last decade, NASH has become one of the main indicators for liver transplantation. [21][22] Our study detected significant changes in liver stiffness in diabetic patients at early stages (F1), where changes can be potentially reversible with early treatment to avoid further clinical complications. This is of great significance in preventive care as advanced stages of liver fibrosis had been associated with increased cardiovascular risk and mortality. 23 Whether the changes observed in hemodynamic parameters correlates with cardiovascular disease in our patient cohort warrants further evaluation.

There are a number of limitations of this study. First, this is a transversal study that did not control for the time with DM2 diagnosis. Therefore, it is of interest to conduct a longitudinal study where timing of the disease ought to be monitored. Second, this study did not include liver biopsy sampling, albeit this still remains as the gold standard confirmation of liver damage. Third, it could have been valuable to collect data on platelets and albumin levels as part of the blood panel to further asses long-term biochemical changes among DM2 patients.

This study supports the notion that hepatic ultrasound with shear wave elastography is a useful tool for the diagnosis and classification of liver fibrosis among DM2 patients. [12][13][14] A main advantage of this clinical approach is the ability to evaluate the elasticity of the tissue while obtaining a visual image of the area of interest in real time. In addition, it allows for the evaluation of different areas of the organ within a single imaging session. As a non-invasive procedure, it is clinically feasible to follow-up the patient over time to assess liver health and to implement early therapeutic intervention whenever necessary. Taken together, we believe that the use of shear wave elastography in low resource and fast-paced environments provides an insightful first-line clinical assessment of liver health among DM2 patients. [1]

1

	CONTROL	DM2	P value
STIFFNESS (kPa)	6.6 (1.5)	7.9 (2.1)	0.01
LIVER SIZE (cm)	14.3 (1.6)	15.5 (2.8)	0.04
HbA1c (%)	5.4 (0.3)	7.7 (1.7)	< 0.001
ALT (units/L)	25.7 (14.4)	34.2 (27.1)	0.12
AST (units/L)	21.8 (6.0)	25.5 (15.2)	0.21
ALK PHOSP (units/L)	71.8 (15.2)	82.7 (23.9)	0.03

DM2=diabetes mellitus type 2

Figure 1: Table 1 :

2

	C-F0	DM2-F0	P value	C-F1	DM2-F1	P value	C-F2	DM2-F2	P value
STIFFNESS (kPa)	5.1 (0.6)	4.4 (1.1)	0.28	6.6 (0.7)	7.2 (0.6)	0.006	8.9 (0.4)	8.8 (0.4)	0.83
LIVER SIZE (cm)	14.2 (1.7)	14.8 (1.8)	0.57	14.2 (1.7)	15.8 (3.1)	0.13	14.6 (0.7)	13.7 (1.0)	0.24
HbA1c (%)	5.4 (0.4)	7.7 (2.0)	0.01	5.4 (0.3)	7.6 (1.9)	< 0.001	5.3 (0.3)	7.8 (2.4)	0.06
ALT (units/L)	22.1 (11.0)	27.3 (12.3)	0.56	25.5 (16.2)	37.6 (31.3)	0.11	37.0 (7.5)	28.0 (12.4)	0.32
AST (units/L)	21.3 (6.2)	23.0 (6.8)	0.66	21.3 (6.0)	27.3 (16.6)	0.20	27.7 (3.8)	22.0 (5.3)	0.18
ALK PHOSP (units/L)	68.6 (17.3)	92.5 (12.4)	0.04	72.4 (14.0)	83.3 (28.0)	0.14	82.3 (17.1)	67.0 (18.8)	0.32

C= Control, DM2=diabetes mellitus type 2

Figure 2: Table 2 :

3

Control	DM2	P value

Figure 3: Table 3 :

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