Evaluation of food intake effect on liver stiffness values in patients with chronic viral hepatitis

Eman Ahmed Rewisha, Abdelaleem Khair Helal, Ashraf Eljaky, Mohamed Melegy Ahmed, Tary Abdel Hamid Salman

Department of Hepatology, National Liver Institute, Menoufia University, Shebeen El-Kom, Egypt.
ashrafeljaky@hotmail.com

Abstract: **Background:** Liver fibrosis is a wound healing response to various injuries to the liver. Liver biopsy is the gold standard for diagnosis and staging. Liver stiffness measurement (LSM) is a non-invasive physical approach for assessing liver fibrosis. **Aim**: impact of fasting and food intake on liver stiffness values measured by Fibroscan^{TM}. **Methods:** one hundred native patients with viral hepatitis (HCV=80, HBV=20) were enrolled. Liver functiontest, CBC, INR, HCV RNA, HBV DNA level and abdominal ultrasonography were done. Both APRI and FIB.4 formulae were calculated. LSM was done using Fibroscan^{TM} after 8 hours fasting and 90 minutes after eating diet (500 kcal, 55% carbohydrates, 25% fat and 20% protein). The patients were classified into F0-F1, F2-F3 and F4. **Results**: There was statistically significant difference (p=0.05) among the 3 groups regarding age, serum bilirubin, albumin, AST, ALT, INR, hemoglobin, platelets, APRI and FIB.4 score. In each group there was statistically significant (p=0.05) increase of LSM 90 minutes after meal compared to fasting status (F0-F1; 8.24 ±1.17 vs. 5.16 ±0.98 kPa), (F2-F3; 11.79 ±2.36 vs. 9.19 ±1.49 kPa), (F4; 22.41 ±7.17vs. 21.67 ±6.42) and total elastography value (13.65 ±10.15 vs. 11.57±8.62 kPa). The delta change (postprandial –fasting value) was more obvious with F4 fibrosis compared to F0-F1 (3.74 ±3.11 vs. 1.08 ±0.82 kPa) and F2-F3 (3.74 ±3.11 vs.1.6 ±1.97 kPa). The delta change was more noted in HCV patients than HBV patients (2.32 ±2.56 vs.1.09 ±1.05 kPa; p=0.009). **Conclusion:** Food intake increases the liver stiffness value measured by FibroScan^{TM} especially in HCV patients.

[Eman Ahmed Rewisha, Abdelaleem Khair Helal, Ashraf Eljaky, Mohamed Melegy Ahmed, Tary Abdel Hamid Salman. **Evaluation of food intake effect on liver stiffness values in patients with chronic viral hepatitis.** *J Am Sci* 2017;13(6):9-13]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 2. doi:10.7537/marsjas130617.02.

Keywords: Evaluation; food; intake; effect; liver; stiffness; value; patient; chronic viral hepatitis

1. Introduction

Liver fibrosis is the pathological yield of diseases that injure the liver like viral, autoimmune, metabolic, drug induced and congenital liver diseases. It is a wound healing process aiming at maintaining the integrity of the liver. Actually it is not a simple process but complicated signaling pathways process that ultimately activated the hepatic stellate cells with disturbances in the extracellular matrix with laydown of collagen [1]. By the time without elimination of the injurious agent the liver fibrosis progresses to cirrhosis. The advent of cirrhosis is usually associated with clinical sequlae especially when the patient is not compensated like ascites, portal hypertension, esophageal varices, encephalopathy and ultimately hepatocellular carcinoma[2].

Liver biopsy is the gold standard of liver fibrosis diagnosis and staging but it is associated with various drawbacks e.g. invasive, sampling errors as the pathology distribution is not homogenous, inter-observer variation and may be associated with fatal complication like bleeding [3]. As a result the non-invasive liver fibrosis diagnosis and staging was needed. This can be accomplished by physical methods by measuring the liver stiffness or laboratory methods and models e.g. FIB.4, APRI, FibroTest, etc.[4].

FibroScanTM is a physical diagnosis of liver fibrosis that has many advantages as being noninvasive, bedside, reproducible, painless, rapid and measures larger liver volume [5, 6].

The aim of the study was study the impact of fasting and food intake on liver stiffness values measured by Fibroscan^{TM}.

2. Patients and Methods

This study was conducted in National Liver Institute hospitals, Menoufia University, Egypt. Prior local ethical committee approval was obtained. Informed consent was obtained from all patients.

One hundred treatment naïve patients with chronic viral hepatitis either HCV (n=80) or HBV (n=20) were included. They were either non-cirrhotic or cirrhotic but Child Pugh B (CTP) A or B. We choose two ages for inclusion to avoid bias; 35 and 55 years old.

Patients with the following criteria were excluded; Body mass index (BMI) <18kg/m^2, BMI >30 kg/m^2, other etiologies of liver disease e.g. autoimmune, acute hepatitis, CTP C and

hepatocellular carcinoma.

All patients underwent full history taking and clinical examination. The following labs were done serum bilirubin, albumin, AST, ALT, CBC, INR, HCV antibody, HBs Ag, HCV RNA and HBV DNA level. Body mass index =weight (kg)/height $(m)^2$. Liver cirrhosis diagnosis relied on clinical, laboratory, and abdominal ultrasonography findings [7].

The following formulae were used to indirectly assess fibrosis; APRI score [8] = (AST/upper limit normal)/Platelets 10^9L ×100 and FIB.4 [9,10]= [age (years) × AST (U/L)] /[Platelets (10^9L) × √ALT (U/L)].

Liver stiffness measurement was done using FibroScan™ (Echosens, Paris, France) after 8 hours fasting and 90 minutes after eating diet. This diet was egg, cheese, butter and juice with approximately 500 kcal, 55% carbohydrates, 25% fat and 20% protein) over a maximum period of 20 min.

The patients were in the supine position with maximally abducted right arm during measurement using the M probe. The results were expressed as a median value of the total measurements in kilo-Pascal (kPa). The examinations were considered reliable if >10 validated measurements were obtained from each patient with a success rate >60% and if the interquartile range (IQR) of all validated measurements was < 30% of the median value. The elastography value was correlated with fibrosis stage value [5, 6].

Statistical Analysis

Data was statistically analyzed using IBM® SPSS® Statistics® version21 for Windows. Data are expressed as mean ±standard deviation. All p- values are 2 tailed, with values <0.05 considered statistically significant.

Comparisons of the variables change in the same group were performed using Wilcoxon test for nonparametric data. Comparisons between multiple groups were performed by usage of ANOVA test for parametric variables and Kruskal Wallis Test for nonparametric variables.

3. Results

Firstly as shown in **Table 1**, there was statistically significant difference regarding age among the different groups were patients with F4 fibrosis were mainly elder (81.2 vs. 18.8%) in contrast to F0-F1 group (27.5 vs. 72.5%) and F2-F3 group (46.4 vs. 53.6%).

There was statistically significant difference ($p<0.05$) among the different groups as regards serum bilirubin (1.0 ±0.39, 0.82 ±0.20 vs. 0.74±0.26 mg/dL), serum albumin (4.19 ±0.47, 4.21 ±0.55 vs. 4.89 ±6.23 g/dL), AST (58.7 ±22.89, 57.42 ±32.24 vs. 35.71 ±12.57 IU/L) and ALT (57.28±29.53, 58.66 ±42.08 vs. 38.58 ±20.03 IU/L). The same was for the INR (1.20±0.20, 1.06 ±0.07 vs. 1.07 ±0.09).

Meanwhile non-statistically significant difference was found concerning WBCs and platelets count in contrast to hemoglobin (13.68±1.54, 13.88±1.46 vs12.93 ±1.70 g/dL) and platelets (262.40 ±86.8, 216.50 ±57.08 vs.146.34 ±49.15 10^9/L).

There was a statistically significant difference concerning both FIB.4 and APRI score. The percentage of FIB.4 score coinciding with fibrosis stage measured by Fibroscan™ was as following; F0-F1 (85.5%), F2-F3 (39.3%) and F4 (90.6%). The percentage of APRI score coinciding with fibrosis stage measured by Fibroscan™ was as following; F0-F1 (92.5%), F2-F3 (28.6%) and F4 (93.8%).

Table 2 showed the effect of fasting and meal intake on liver stiffness values. In each stage of measurement there is statistically significant (p=0.001) increase of the liver stiffness 90 minutes after meal compared to fasting status (F0-F1; 8.24 ±1.17 vs. 5.16 ±0.98 kPa), (F2-F3; 11.79 ±2.36 v.9.19 ±1.49 kPa), (F4; 22.41 ±7.17 vs. 21.67 ±6.42) and total elastography value (13.65 ±10.15 vs. 11.57±8.62 kPa).

As shown in **Figure 1**, there was statistically significant difference (p=0.001) regarding the delta change of liver stiffness (postprandial –fasting value) between the three groups. The delta change was more obvious with F4 fibrosis compared to F0-F1 (3.74 ±3.11 vs. 1.08 ±0.82kPa) and F2-F3 (3.74±3.11 vs.1.6 ±1.97 kPa). The delta change in F0-F1 and F2-F3 was comparable. The overall delta change was 2.07±2.39 kPa. The delta change was more obvious in HCV patients than HBV patients (2.32 ±2.56 vs. 1.09±1.05 kPa; p=0.009) as shown in **Figure 2**.

4 Discussion

Liver fibrosis is a reversible wound-healing response that develops after either acute or chronic cellular injury [11]. Advanced stages of liver fibrosis are associated with increased morbidity and mortality [12]. Liver biopsy is the gold standard for liver fibrosis [13, 14] but nowadays noninvasive methods are currently used.

FibroScan™ is noninvasive physical diagnosis of liver fibrosis. One of its advantages that it examines a volume of the liver that is 100 times bigger than a biopsy sample and is therefore far more representative of the hepatic parenchyma [13, 15,16].

Traditionally the patient was fasting before measuring the liver stiffness by FibroScan™. But what is the effect of food intake. A pilot study found that food intake may increase the liver stiffness value that was confirmed in other recent studies.

The earlier study of ***Mederacke et al.,*** revealed that the liver stiffness increased after meal or food consumption in HCV patients and the control. It

increased immediately with food up to 60 minutes and normalized 180m post- prandial [17]. ***Arena et al.,*** conducted another study on HCV patients. They measured the liver stiffness after fasting and 15, 30, 45, 60, and 120 minutes post prandial. The liver stiffness increased after meal up to 45 minutes and normalized within 120 minutes. This phenomenon was more marked with advanced fibrosis stages especially those with cirrhosis [18].

In small number study by ***Berzigotti et al.,*** conducted in patients with cirrhosis and portal hypertension [19]. The liver stiffness, portal blood flow and hepatic artery blood flow ±HVPG were measured at fasting and 30 minutes postprandial. The liver stiffness increased postprandial and was correlated to increased hepatic artery blood flow unlike portal blood flow. ***Tangpradabkiet et al.,*** studied this topic in chronic HBV patients compared to HCV patients [20]. Both groups were the same for the postprandial increase in the liver stiffness.

In low number study conducted by ***Alvarez et al.,*** both the liver stiffness and the portal blood flow were measured after fasting and 30 minutes post meal. Both variables increased postprandial. This effect was the same in patients with <F1 and >F1 [21]. ***Barone et al.,*** ***measured*** the liver stiffness and portal blood flow after fasting and 60 min post prandial [22]. Both increased after meal consumption. Totally liver stiffness and all its subgroup stages increased postprandial. It is more obvious with advanced fibrosis. The liver stiffness correlated with portal blood flow changes in non-F4 patients only [22].

The explanation for this phenomenon is that there is increased blood flow to the liver after meals that increased the liver stiffness value. This effect is clear in patients with advanced fibrosis or cirrhosis [23-26].

Some studies found correlation between the liver stiffness increase and portal vein flow increase [22] and other found with only hepatic artery flow increase [19].

In our study the liver stiffness increased after food intake in accord with other previous studies [17-22]. This change was more obvious in F4 patients in accord with [18, 22] and in contrast to [21]. Patients with HCV had more delta change than HBV patients that is not in accord with [20].

In conclusion; Food intake increases the liver stiffness value measured by FibroScan™ especially in HCV patients.

Table 1. Comparison of the baseline parameters among the different groups.

		Liver stiffness stage			*P*
		F0-F1	**F2-F3**	**F4**	
		N=40	**N=28**	**N=32**	
Age	*35 years*	29 (72.5%)	15 (53.6%)	6 (18.8%)	**0.001**
	55 years	11 (27.5%)	13 (46.4%)	26 (81.2%)	
Sex	*Male*	25 (62.5%)	20 (71.4%)	22 (68.8%)	0.719
	Female	15 (37.5%)	8 (28.6%)	10 (31.2%)	
Virology	*HCV*	32 (80%)	20 (71.4%)	28 (87.5%)	0.3
	HBV	8 (20%)	8 (28.6%)	4 (12.5%)	
Bilirubin *mg/dL*		1.00 ±0.39	0.82 ±0.20	0.74 ±0.26	**0.007#**
Albumin *g/dL*		4.19 ±0.47	4.21 ±0.55	4.89 ±6.23	**0.004#**
AST *IU/L*		58.7 ±22.89	57.42 ±32.24	35.71 ±12.57	**0.001#**
ALT *IU/L*		57.28 ±29.53	58.66 ±42.08	38.58 ±20.03	**0.002#**
INR		1.20 ±0.20	1.06 ±0.07	1.07 ±0.09	**0.003**
Hemoglobin *g/dL*		13.68 ±1.54	13.88 ±1.46	12.93 ±1.70	**0.05**
WBCs *109/L*		6.80 ±1.97	7.24 ±1.67	6.36 ±2.11	0.224
Platelets *109/L*		262.40 ±86.8	216.50 ±57.08	146.34 ±49.15	**0.001**
FIB.4	*Normal*	34 (85.5%)	14 (50%)	0 (0%)	**0.001**
	F2-F3	6 (15%)	11 (39.3%)	3 (9.4%)	
	Cirrhotic	0 (0%)	3 (10.7%)	29 (90.6%)	
APRI	*Normal*	37 (92.5%)	16 (57.1%)	0 (0%)	**0.001**
	F2-F3	3 (7.5%)	8 (28.6%)	2 (6.2%)	
	Cirrhotic	0 (0%)	4 (14.3%)	30 (93.8%)	
#Kruskal Wallis Test					

Table 2. Liver stiffness change with food intake

	Liver stiffness *(kPa)*		
	Fasting	**90m post-meal**	***P***
F0-F1	5.16 ±0.98	8.24 ±1.17	0.001#
F2-F3	9.19 ±1.49	11.79 ±2.36	0.001#
F4	21.67 ±6.42	22.41 ±7.17	0.001#
Total Stiffness	11.57±8.62	13.65 ±10.15	0.001#
#Wilcoxon test			

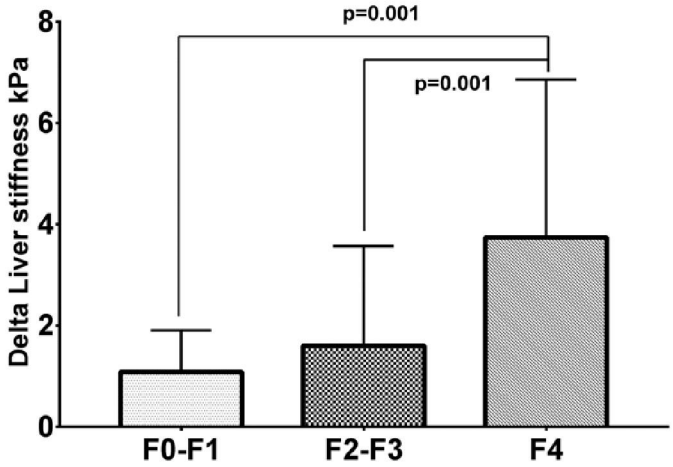

Figure 1. Delta change of the liver stiffness in the different groups

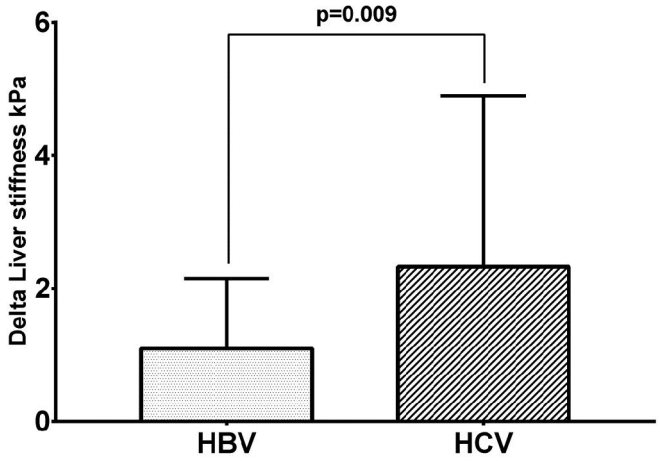

Figure 2. Delta change of the liver stiffness in HCV and HBV patients.

Conflict of interest: None

References

1 Lee UE, Friedman SL. Mechanisms of hepatic fibrogenesis. Best practice & research Clinical gastroenterology, 2011;25:195-206.
2 Saffioti F, Pinzani M. Development and Regression of Cirrhosis. Digestive diseases (Basel, Switzerland) 2016;34:374-81.
3 Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology (Baltimore, Md) 2009;49:1017-44.
4 Asrani SK. Incorporation of Noninvasive Measures of Liver Fibrosis Into Clinical Practice: Diagnosis and Prognosis. Clinical gastroenterology and hepatology: the official

clinical practice journal of the American Gastroenterological Association 2015;13:2190-204.
5 de Ledinghen V, Vergniol J. Transient elastography for the diagnosis of liver fibrosis. Expert review of medical devices 2010;7:811-23.
6 Castera L. Invasive and non-invasive methods for the assessment of fibrosis and disease progression inchronic liver disease. Best Pract Res Clin Gastroenterol 2011;25:291-303.
7 Schuppan D, Afdhal NH. Liver cirrhosis. Lancet 2008;371:838-51.
8 Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology (Baltimore, Md) 2011;53:726-36.
9 Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology (Baltimore, Md) 2006;43:1317- 25.
10 Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin- Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology (Baltimore, Md) 2007;46:32-6.
11 Lee UE, Friedman SL. Mechanisms of hepatic fibrogenesis. Best Practice & Research Clinical Gastroenterology 2011;25:195-206.
12 Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383:1749-61.
13 Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology 2012;142:1293-302.e4.
14 Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology (Baltimore, Md) 2009;49:1017-44.
15 de Ledinghen V, Vergniol J. Transient elastography (FibroScan). Gastroenterologieclinique et biologique 2008;32:58-67.
16 Wong VW, Chan HL. Transient elastography. Journal of gastroenterology and hepatology 2010;25:1726-31.
17 Mederacke I, Wursthorn K, Kirschner J, Rifai K, Manns MP, Wedemeyer H, *et al.* Food intake increases liver stiffness in patients with chronic or resolved hepatitis C virus infection. Liver international: official journal of the International Association for the Study of the Liver 2009;29:1500-6.
18 Arena U, Lupsor Platon M, Stasi C, Moscarella S, Assarat A, Bedogni G, et al. Liver stiffness is influenced by a standardized meal in patients with chronic hepatitis C virus at different stages of fibrotic evolution. Hepatology (Baltimore, Md) 2013;58:65-72.
19 Berzigotti A, De Gottardi A, Vukotic R, Siramolpiwat S, Abraldes JG, Garcia-Pagan JC, et al. Effect of meal ingestion on liver stiffness in patients with cirrhosis and portal hypertension. PloS one 2013;8:e58742.
20 Tangpradabkiet W, Praneenararat S, Chamroonkul N, Witeerungrot T, Piratvisuth T. Influence of meal intake on liver stiffness in patients with chronic hepatitis B and C. Journal of the Medical Association of Thailand = Chotmaihetthangphaet 2014;97:1033-9.
21 Alvarez D, Orozco F, Mella JM, Anders M, Antinucci F, Mastai R. Meal ingestion markedly increases liver stiffness suggesting the need for liver stiffness determination in fasting conditions. Gastroenterologia y hepatologia 2015;38:431-5.
22 Barone M, Iannone A, Brunetti ND, Sebastiani F, Cecere O, Berardi E, et al. Liver stiffness and portal blood flow modifications induced by a liquid meal consumption: pathogenetic mechanisms and clinical relevance. Scandinavian journal of gastroenterology 2015;50:560-6.
23 Szinnai C, Mottet C, Gutzwiller JP, Drewe J, Beglinger C, Sieber CC. Role of gender upon basal and postprandial systemic and splanchnic haemodynamics in humans. Scandinavian journal of gastroenterology 2001;36:540-4.
24 Dauzat M, Lafortune M, Patriquin H, Pomier-Layrargues G. Meal induced changes in hepatic and splanchnic circulation: a noninvasive Doppler study in normal humans. European journal of applied physiology and occupational physiology 1994;68:373-80.
25 Ludwig D, Schwarting K, Korbel CM, Bruning A, Schiefer B, Stange EF. The postprandial portal flow is related to the severity of portal hypertension and liver cirrhosis. Journal of hepatology 1998;28:631-8.
26 Bellis L, Berzigotti A, Abraldes JG, Moitinho E, Garcia-Pagan JC, Bosch J, *et al.* Low doses of isosorbidemononitrate attenuate the postprandialincrease in portal pressure in patients with cirrhosis. Hepatology (Baltimore, Md) 2003;37:378-84.