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Impact of old Schistosomiasis infection on the use of transient elastography (Fibroscan) for staging of fibrosis in chronic HCV patients

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ABSTRACT

Background and aim: In tropical regions, Hepatitis C virus (HCV) − Schistosomiasis coinfection remains one of the health problems. With the new era of HCV treatment and the variety of methods of assessment of liver fibrosis so we aimed to evaluate the effectiveness of FibroScan for staging hepatic fibrosis in HCV-Schistosomiasis coinfected patients.

Methodology: Three groups of patients were enrolled. Group 1: chronic HCV with out antischistosomal antibody (122 patients), Group 2: chronic HCV with positive antischistosomal antibodies and without periportal tract thickening (122 patients), Group 3: chronic HCV with positive antischistosomal antibodies and ultrasonographic picture of periportal tract thickening (108 patients). Routine laboratory workup, serum Antischistosomal antibody, and Schistosomal antigen in serum were performed. Ultrasound guided liver biopsy with histopathological examination; abdominal ultrasound and fibroscan examination were done for all patients.

Results: The agreement between results of liver biopsy and results of fibroscan in the staging of fibrosis was the best in group 1 (55.7%), Although the agreement was higher among those with no periportal tract thickening (70.7%) and the disagreement was higher among those with positive schistosomal serology (66.5%), yet this relation was not statistically significant. Multivariate logistic regression analysis showed that disagreement is significantly associated with older age, higher BMI (≥30), and increase in anti Schistosomal antibody titer.

Conclusion: Fibroscan is a reliable, non-invasive tool for staging hepatic fibrosis among HCV-schistosomiasis co-infected patients with no effect of the induced periportal tract thickening on the readings. Only higher anti-schistosomal antibody titres may cause disagreement between liver biopsy and fibroscan.

1. Introduction

The hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease. (Ghany et al., 2009).

In Egypt about 13.3% of population are chronically infected with HCV and are at risk of liver complications. Individuals living in rural areas had significantly more anti-HCV seropositivity (36.1%) than those living in urban areas (24.7%) (Guerra et al., 2012; Mohamed, 2004). Egypt has the highest reported prevalence of hepatitis C virus (HCV) globally (Esmat et al., 2013a; Obach et al., 2015).

Liver fibrosis represents a major health problem worldwide (Friedman 2000).Assessment of liver fibrosis by Liver biopsy and histological analysis, was considered the gold standard technique. However, it is a painful and invasive procedure, prone to sampling errors and may have some life-threatening complications, (Strader et al., 2004).

A variety of methods including the measurement of liver stiffness, using transient elastography (TE), and serum markers especially FibroTest, and aspartate-to platelet ratio (APRI) are the most widely used and validated non-invasive methods for assessment of liver fibrosis (Castera 2012; Castera 2009)

Patients with hepatosplenic Schistosomiasis were found to be 7–10 times more susceptible to co-infection with hepatitis (Agha et al., 2006).The reasons for this interaction between Schistosomiasis and hepatitis viruses include the direct stimulation of viral replication by soluble egg antigen, defects in cell mediated immunity and the high

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exposure of Schistosomal patients to repeated specific parenteral therapy, blood transfusion and non specific therapy (El-Awady et al., 2006).

The impact of this schistosomiasis coinfection in our Egyptian population on the performance of fibroscan is not well studied so our aim was to evaluate the effectiveness of FibroScan for staging hepatic fibrosis in chronic HCV infected patients with or without schistosomiasis.

2. Subjects and methods

This study was conducted on 352 Egyptian patients with chronic hepatitis Patients were subjected to history taking, clinical examination and routine laboratory work up including Complete blood count (CBC), blood glucose, kidney functions tests and liver functions tests. Antischistosomal antibodies by the indirect haemagglutination test (IHAT) was done and considered positive if titre ≥1/160 with a sensitivity up to 95% and specificity up to 99%. (Sorgho et al., 2005; Kinkel et al., 2012), Schistosomal antigen in serum was done using the fast (ELISA) with a sensitivity 93%, specificity 89%, and efficiency 91%. (Attallah et al., 1999).

The diagnosis of chronic hepatitis C (CHC) was established by the presence of HCV RNA using polymerase chain reaction assays. All patients underwent a pretreatment liver biopsy within 6 months prior to the initiation of therapy. All patients underwent a pretreatment abdominal ultrasound and fibroscan examination. Patients with HCV genotype other than genotype 4, chronic liver disease other than HCV, decompensated liver cirrhosis and hepatocellular carcinoma, were excluded from the study.

2.1. Patients were classified into three groups

Group 1: chronic HCV with negative antischistosomal antibody (122 patients).

Group 2: chronic HCV with positive antischistosomal antibodies and without periportal tract thickening (122 patients).

Group 3: chronic HCV with positive antischistosomal antibodies and ultrasonographic picture of periportal tract thickening fibrosis (108 patients).

Abdominal ultrasound was done to all patients to assess the degree of periportal tract thickening: grade I if thickness = 3–5 mm, grade II = greater than 5–7 mm, and grade III = greater than 7 mm. (Abdel-Wahab et al.1992; Frank et al., 2000)

Institutional Review Board (IRB) study approval was obtained prior to commencement of the study and signed informed consent was obtained from all study patients.

3. Histological classification

Histopathological examination of ultrasound-guided percutaneous liver biopsy using 16-G semi-automated biopsy needles. Liver specimens of a minimum of 15 mm in length with at least four portal tracts were fixed in 10% neutral formalin, processed then embedded in paraffin. Sections were stained with hematoxylin–eosin and Masson-trichrome for detection of fibrosis. Histopathological examination according to the METAVIR scoring system demonstrated different stages of fibrosis (F0–F4) and grades of necroinflammatory changes activity (A0–A3) (Bedossa and Poynard, 1996)The histopathological examination of all the liver biopsies was performed by a single expert pathologist.

4. Fibroscan (ultrasound transient elastography)

Liver stiffness measurements were done for all patients with FibroScan® (ECHOSENSE, FIBROSCAN 502, Paris, France) located in Kasr Alainy Viral Hepatitis Center, Cairo university. Ten valid measurements were performed, and median of liver stiffness expressed in kilopascals (kPa) was reported (Sandrin et al., 2003). Only examinations with success rate > 60% and interquartile range (IQR) < 30% were included in this study and were considered reliable. Cut offs used are those used by (De ledinghen and vergniol, 2008) as follows:

F0 < 5.5 kpa
F0-F1 = 5.5 till 5.9 kpa
F1 = 6 till 6.9 kpa
F1-F2 = 7 till 8.7 kpa
F2 = 8.8 till 9.4 kpa
F3 = 9.5 till 12.4 kpa
F3-F4 = 12.5 till 14.4 kpa
F4 ≥ 14.5 kpa

5. Statistical analysis

The quantitative data were described with mean and standard deviation (SD) and compared by the Student's *t*-test. Qualitative variables were described by number and percent. They were compared by the chi-squared or Fischer's exact test, when appropriate. Multivariate logistic regression was used in which the disagreement between fibroscan and liver biopsy was the dependent variable. In all tests, p value < 0.05 was considered significant.

6. Results

Our study included 352 Egyptian patients with chronic hepatitis C infection categorized in three groups. The demographic features of the studied patients are shown in Table 1.

Regarding the laboratory parameters Hb, WBCs, Bil T, and albumin, all showed statistically significant difference between groups as shown in Table 2. Serum schistosomal antigen (AG) was negative in (around 90%) of HCV-schistosomiasis, coinfected patients (group 2 + 3)

Portal tract thickening by abdominal ultrasound was found in 108 patients (group 3) (47% of HCV-schistosomiasis coinfected patients) mainly grade 1 in 101 patient of them.

No statistically significant difference was observed in the mean liver stiffness among the three groups.

The agreement between results of liver biopsy and results of fibroscan in the staging of fibrosis was the best in group 1 (55.7%), however this relation was not statistically significant among groups.

Among those with positive antischistosomal antibody, titres were reported to be ≥1/160 in 58 patients (25% of group 2 + group3), ≥1/320 in 80 patients (35% of group 2 + group3), ≥1/640 in 51 patients (22% of group 2 + group3) and ≥1/1280 in 41 patient (18% of group 2 + group3)

Agreement between the reading of liver biopsy (METAVIR) and the results of fibroscan through the different stages of fibrosis are shown in Table 3.

The relations between agreement and different parameters of schistosomal infection are shown in Table 4.

Table 1
Demographic features of the studied groups.

	HCV	HCV + SCHISTO	HCV + SCHISTO + PPT	P value
	(group 1)(122)	(group 2) (122)	(group 3)(108)	
Age(Mean ± SD)	39.9 ± 10	43.9 ± 10	41.9 ± 11	0.015
SEX				
Female	53 (43.4%)	36 (29.5%)	18 (16.7%)	0.001
Male	69 (56.6%)	86 (70.5%)	90 (83.3%)	
BMI(Mean ± SD)	28.5 ± 3	26.8 ± 3	27 ± 3	0.376

BMI: body mass index.

Table 2
Laboratory and ultrasound findings for the studied groups.

Items	HCV (group 1)	HCV + SCHISTO	HCV + SCHISTO + PPT	P value
Mean + SD	(122)(n,%)	(group 2) (122)	(group 3)(108)	
Hb g/dl	13.6 ± 1.4	13.8 ± 1.3	14.3 ± 1.2	0.005
WBCs x10^3/ mm^3	5.9 ± 1.8	6.5 ± 2	5.8 ± 1.6	0.015
Plt x10^3/mm^3	220.2 ± 74.4	206.3 ± 72	199.9 ± 71.7	0.096
Bil T mg/dl	0.9 ± 0.2	1 ± 0.2	0.9 ± 0.2	0.011
AST U/L	46.5 ± 33.7	47 ± 30.3	42.1 ± 25.7	0.412
ALT U/L	51.9 ± 43.4	54.3 ± 38.8	49.2 ± 37.3	0.634
Albumin gm/dl	3.8 ± 0.5	3.6 ± 0.3	3.8 ± 0.4	0.009
Creatinine mg/dl	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.156
AFP IU/ml	5.3 ± 7.6	4.8 ± 8.2	3.7 ± 4.1	0.187
Schistosomal Ag				
Negative	107 (87.7%)	118 (96.7%)	90 (83.3%)	0.003
Positive	15 (12.3%)	4 (3.3%)	18 (16.7%)	
Spleen longest axis (cm)	12.5 ± 1.4	12.6 ± 1.3	13 ± 1.2	0.056
Stiffness(kpa)	10.7 ± 8.5	10.1 ± 8.2	10 ± 9.1	0.8
Agreement	68 (55.7%)	67 (54.9%)	56 (51.9%)	0.8

Hb: hemoglobin, WBC: white blood cells, Plt: platelets, Bil T: bilirubin total, AFP: alfa fetoprotein.

Table 3
Agreement between the biopsy and the fibroscan through the different stages of fibrosis.

Fibrosis (Metavir)	Agreement	HCV (group 1) (n,%)	HCV + SCHISTO (group 2) (n,%)	HCV + SCHISTO + PPT (group 3) (n,%)	P value
F0	Yes	1(33.3%)	1(50%)	1(100%)	0.5
	No	2(66.7%)	1(50%)	0	
F1	Yes	34(54.8%)	28(50%)	32(54.2%)	0.6
	No	28(45.2%)	28(50%)	27(45.8%)	
F2	Yes	13(48.1%)	16(55.2%)	7(41.2%)	0.6
	No	14(51.9%)	13(44.8%)	10(58.8%)	
F3	Yes	6(42.9%)	10(45.5%)	10(41.7%)	0.9
	No	8(57.1%)	12(54.5%)	14(58.3%)	
F4	Yes	14(87.5%)	12(92.3%)	6(85.7%)	0.8
	No	2(12.5%)	1(7.7%)	1(14.3%)	

Table 4
Agreement between liver biopsy and fibroscan in relation to different Schistosoma parameters.

	Agreement			
	YES	NO	Total	P value
Schisto Ag				
Neg	168(88%)	147(91.3%)	315	0.3
Positive	23(12%)	14(8.7%)	37	
PPT				
NO	135(70.7%)	109 (67.7%)	244	0.5
YES	56 (29.3%)	52 (32.3%)	108	
Antischisto AB				
Neg	68(35.6%)	54(33.5%)	122	0.6
Positive	123(64.4%)	107(66.5%)	230	

PPT: periportal tract thickening.

Multivariate logistic regression analysis showed that disagreement is significantly associated with older age, higher body mass index BMI (≥30), and increase in anti Schistosomal antibody titer. Table 5.

It's worthwhile to mention that periportal tract thickening was significantly correlated with schistosomal antibody titre and splenic longest axis (r = 0.33, 0.14 and p = 0.000, 0.012 respectively),

7. Discusion

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease all over the world. The long-term impact of HCV infection is variable, ranging from minimal histological changes to advanced fibrosis with or without hepatocellular carcinoma (HCC) (Lavanchy, 2011).

The drivers of the HCV epidemic in Egypt are not well understood, but the mass parenteral antischistosomal therapy (PAT) campaigns in the second half of the 20th century with no infection control precautions followed are believed to be the determinant of the high prevalence (Cuadros et al., 2014)

Assessment of liver fibrosis is an important issue; even with the appearance of the new oral DAAs, we still need the staging of fibrosis to monitor the response to treatment whether progression or regression of liver fibrosis.

Using the noninvasive methods, especially Fibroscan for assessment of liver fibrosis goes hand in hand with this new era. Being easy, reliable and accurate, facilitate its wide use.

Many studies evaluate the role of fibroscan in the staging of liver fibrosis and reported its higher diagnostic accuracy in the prediction of significant fibrosis and cirrhosis especially in Egyptian patients. (Abd El Rihim et al., 2013; Bonnard et al., 2015; Alboraie et al., 2015; Yosry et al., 2016)

As we still have patients with HCV schistosomiasis co infection especially old age males, we aimed to assess the impact of old schistosomiasis and periportal tract thickening on the use of fibroscan for staging of fibrosis to be sure that fibroscan is suitable to use in all patients and determine the factors which may affect the agreement between the histopthological readings (Metavir) and the fibroscan reading in those patients.

Higher age and male predominance were reported among patients with HCV schistomiasis co infection (groups 2 and 3) and this goes with the fact that those males who were exposed to canal water in the past and received the tarter emetics injections are now suffering from this coinfection. This was similar to Abdel-Rahman et al., 2013 who showed a correlation of positive schistosomal serology in reference to sex, with the predominance involving males. HCV patients with positive schistosomal serology were also found to be older than those with negative serology. The use of schistosomal antigen in serum was not a good diagnostic tool to detect active schistosomiasis being positive in 12.3% in-group 1 and in 16.7% in-group 3. Also positive Schistosomal antigen didn't have any impact on the agreement between biopsy and fibroscan.

The agreement between the results of the histopathological readings (METAVIR) and the fibroscan reading was the best in group 1 patients (with no schistosomiasis infection) however; this relation was not statistically significant among the three groups.These results are consistent with a previous one (Esmat et al., 2013b) who stated that the agreement between the fibroscan and the liver biopsy was slightly better in patients with negative schistosomal serology than in those with positive schistosomal serology. Another study (Alboraie et al., 2015) confirmed that the disagreement between the results of liver biopsy and fibroscan was more obvious in those with positive Schistosomal serology

Through different fibrosis stages, agreement was the best among F4 patients whether they are co infected with schistosomiasis infection or not, and this confirms the great performance of fibroscan in the prediction of cirrhosis but this relation was not statistically significant among the three groups.

Although the agreement was higher among those with no periportal tract thickening (70.7%) and the disagreement was higher among those with positive schistosomal serology (66.5%),yet this relation was not statistically significant.

As in previous studies (Abdel-Wahab et al., 1992), our study stated that Periportal tract thickening was correlated well with signs of portal

Table 5
The regression analysis in which disagreement between biopsy and fibroscan is the dependent variable.

	Univariate				Multivariate			
	OR	Lower CI	Upper CI	P value	OR	Lower CI	Upper CI	P value
gender	1.5	0.98	2.44	0.06				
Age	0.99	0.97	1.01	0.5	0.7	0.59	0.9	0.03
BMI	1.04	0.90	1.21	0.5	2.04	1.09	3.8	0.02
fibrosis	0.80	0.66	0.99	0.03	9.4	0.79	113.7	0.07
AST	1	1	1.01	0.3				
ALT	1	1	1.01	0.1	0.9	0.88	1.01	0.1
Albumin	0.63	0.37	1.07	0.08				
AFP	0.99	0.96	1.02	0.6				
Stiffness	0.98	0.95	1.00	0.1				
Schisto Ab. titer	1	0.87	1.14	0.9	6.5	1.02	42.1	0.04
PPT_groups	1.15	0.73	1.81	0.5				

BMI: body mass index, AFP: alfafetoprotein, PPT: periportal tract thickening.

hypertension as splenomegaly.

Multivariate logistic regression analysis showed that disagreement between the results of fibroscan and liver biopsy is significantly associated with older age, higher BMI (≥30) and increase in anti Schistosomal antibody titer.This was similar to Bonnard et al. (2015) who found that high BMI (> 30) was linked to high elastometry and that statistical linkage may be explained by a relation between BMI and fibrosis and steatosis in Egyptian population.

In our study, we tried to solve some limitations that were obvious in Esmat et al., 2013b study, they only use the antishistosomal antibody for the diagnosis of schistosomal infection and didn't take in consideration other parameters that may be present in patients with schistosomiasis infection such as serum schistosomal antigen and the periportal tract thickening.

Esmat et al., 2013b, confirmed by multivariate logistic regression that fibrosis stages (F0–F1 and F4) were the most independent factors that were associated with agreement and positive schistosomal serology seems to be impairing that agreement,though insignificantly (pvalue = 0.29, OR 0.72).

We concluded that Schistosomal antigen, Anti schistosomal antibody and periportal tract thickening did not have significant impact on the agreement between biopsy and fibroscan and that only higher antischistosomal antibody titres may impair this agreement. Fibroscan is a reliable method to use in different populations.

Author contributions

Aisha Elsharkawy: drafted the manuscript, collection of data, and assisted with data analysis; Iman Ramzy, Rabab Fouad, Maissa El Raziky and Gamal Esmat: participated in study design, conception and revision of the manuscript; Hanan Abdel Hafez and Mohammad El Sayed: participated in the data collection;Hany khattab: interpretation of results of liver biopsy; Mohamed Shehata and Marwa Elsharkawy: doing all patients labs and interpretation of results;,Wafaa El Akel and Amr Radwan:assisted in the data analysis and interpretation of results.

Institutional review board statement

The study was reviewed and approved by the institutional review board of faculty of medicine, cairo university, research ethics committee, number N-52-2012.

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Informed consent statement

All study participants, provided written consent prior to study enrollment.

Data sharing statement

There is no additional data available.

Conflict-of-interest statement

The authors of this manuscript having no conflicts of interest to disclose.

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