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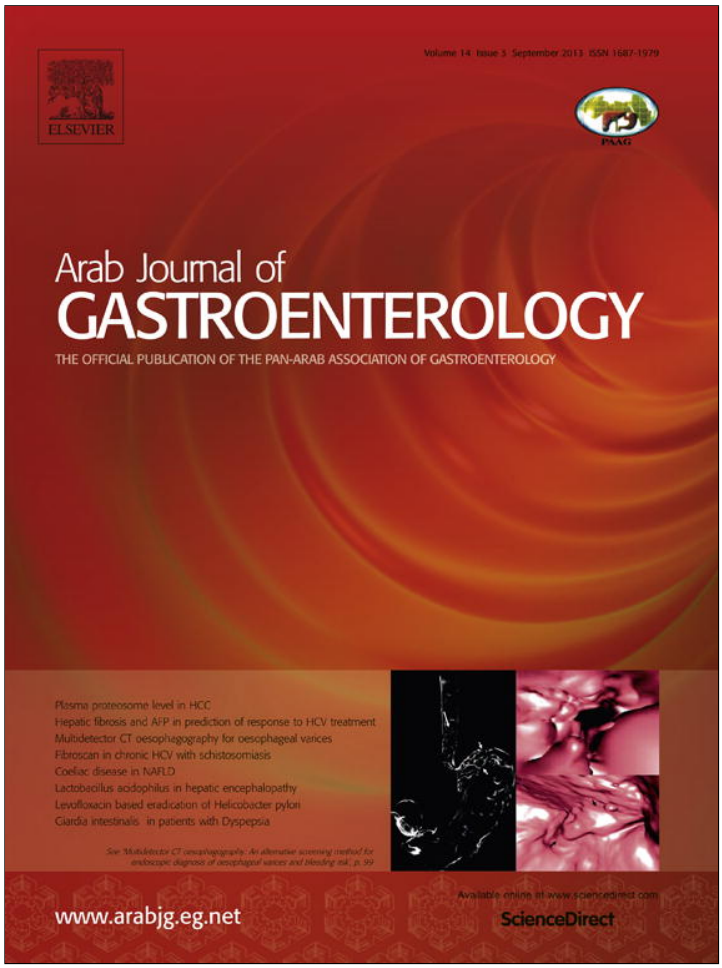

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Original Article

Fibroscan of chronic HCV patients coinfected with schistosomiasis

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ABSTRACT

Background and study aims: Both hepatitis C virus (HCV) and schistosomiasis are highly endemic in Egypt and coinfection is frequently encountered. Such coinfection is responsible for leading to a more severe liver disease. Hence, the aim of the study was to assess the fibroscan in chronic HCV patients coinfected with *Schistosoma*.

Patients and methods: This study included 231 chronic HCV patients. Routine pre-treatment work-up was done including anti-schistosomal antibodies. Liver stiffness measurements using fibroscan and reference needle-liver biopsy were done. Patients were categorised into two groups: HCV patients with positive schistosomal serology and HCV patients with negative schistosomal serology.

Results: Anti-schistosomal antibody was positive in 29% of the studied population. Positive schistosomal serology status was significantly associated with the disagreement between the results of liver biopsy (Metavir) and the fibroscan results (p value = 0.02), which was more obvious in F2 and F3 fibrosis stages. The sensitivity of fibroscan for the detection of the F2 stage decreased from 64% among negative schistosomal serology patients to 30.8% among positive schistosomal serology patients, and for the F3 stage it decreased from 43.8% to 21.4%, respectively. Multivariate logistic regression showed that fibrosis stages (F0–F1 and F4) were the most independent factors that were associated with the agreement between fibroscan and liver biopsy (odds ratio (OR) 3.4, 7.12 and p value <0.001, <0.001, respectively).

Conclusion: Although the sensitivity of fibroscan for the detection of fibrosis stages (F2 and F3) was impaired in patients with positive schistosomal serology, fibrosis stages (F0–F1 and F4) were the most independent factors associated with the agreement between fibroscan and liver biopsy.

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Introduction

Hepatitis C virus (HCV) is a major public health problem and one of the leading causes of chronic liver disease. An estimated 180 million people are infected worldwide [1]. HCV represents one of the major causes of liver fibrosis worldwide [2].

Liver biopsy followed by histological analysis is considered the gold standard technique for the evaluation of liver fibrosis. However, it is a painful and invasive procedure, with rare but potentially life-threatening complications, and is prone to sampling errors. Thus, many patients with chronic viral hepatitis are reluctant to undergo liver biopsy and may be discouraged to start therapy for this reason [3].

These limitations have stimulated the search for new noninvasive approaches. A variety of methods including the measurement of liver stiffness, using transient elastography (TE), and serum markers, ranging from routine laboratory tests to more complex algorithms and statistical models, has been proposed for the noninvasive assessment of hepatic fibrosis [4].

Schistosomiasis is a chronic parasitic disease. The largest epidemiological survey in Egypt mentioned the prevalence of *Schistosoma heamatobium* in Upper Egypt (where it is endemic) to be around 7.8%, while the prevalence of *Schistosoma mansoni* in Lower Egypt (where it is endemic) was found to be around 36.4% [5].

Concurrent HCV-genotype 4 infection and schistosomiasis result in a much more severe liver disease than that observed with either disease alone [6].

The aim of this study was to assess the performance of fibroscan in fibrosis staging in Egyptian chronic HCV patients coinfected with schistosomiasis.

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Patients and methods

This study included 231 chronic HCV patients as diagnosed by seropositivity for HCV antibodies and HCV RNA by polymerase chain reaction (PCR). They were referred for assessment prior to interferon (IFN) therapy as a part of the national programme for combating viral hepatitis in Egypt.

The patients included were naive to antiviral therapy and their ages ranged from 18 to 60 years. Patients with other liver diseases, decompensated liver cirrhosis, hepatocellular carcinoma, liver biopsy contraindication, those who are not fit for combined IFN and ribavirin treatment due to persistent haematological abnormalities and those with body mass index (BMI) >30 kg/m^2 were excluded.

The patients were subjected to thorough history taking, clinical examination, routine pre-treatment laboratory work-up and anti-schistosomal antibodies by the indirect haemagglutination test (IHAT). Previous exposure to *Schistosoma* was identified by a history of previous contact with canal water and/or receiving anti-bilharzial treatment with a positive serology titre $\geqslant$1/160.

The study protocol was approved by the Institutional Review Board and written informed consent was given by each patient.

Liver stiffness was measured on the same day as liver biopsy using the ultrasound TE fibroscan device (Echosens, Paris, France), which consists of a 5-MHz ultrasound transducer probe mounted on the axis of a vibrator. TE measures liver stiffness in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 25 and 65 mm below the skin surface, and the technique was performed according to that described in previous studies [7].

The classification used for fibroscan stiffness was that described by Castera et al. [8]:

F0–F1 $\leqslant$ 7 kPa,
F2 = 7.1–9.4 kPa,
F3 = 9.5–12.4 kPa and
F4 $\geqslant$ 12.5 kPa

The liver biopsy was performed after fibroscan examination on the same day, using a semi-automatic true-cut needle (16 G). The biopsy specimen was fixed in formalin and embedded in paraffin and all biopsy specimens were analysed by an experienced pathologist blinded to the result of fibroscan. All biopsy specimens were at least 15 mm long and contained six portal tracts.

No bilharzial granuloma was detected. Liver fibrosis staging was evaluated according to the Metavir scoring system [9] and fibrosis was staged on a 0–4 scale as follows:

F0: No fibrosis.
F1: Portal fibrosis without septa.
F2: Portal fibrosis with rare septa.
F3: Numerous septa without cirrhosis.
F4: Cirrhosis.

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 agreement between fibroscan and liver biopsy was the dependent variable. In all tests, p value <0.05 was considered significant.

Results

The study was conducted on 231 Egyptian chronic HCV patients. According to the results of anti-schistosomal antibody serology, they were categorised into: group 1 comprising 67 (29%) patients with positive anti-schistosomal antibody and group 2 including 164 (71%) patients with negative anti-schistosomal antibody.

There was significant association between positive schistosomal serology and the presence of liver fibrosis, especially stages $\geqslant$F2 (Metavir) (p value = 0.049) (Table 1).

No statistically significant difference in the laboratory tests (complete blood count (CBC), liver function tests and kidney function test) was observed between both groups.

For the whole studied population, there was a statistically significant concordance between fibroscan and histopathology results (p value = 0.000, kappa = 0.49). Moreover, there was a significant concordance between fibroscan and histopathology results between the individual groups (p value = 0.000, 0.000; and kappa = 0.47, 0.49, respectively) (Table 2).

The sensitivity of fibroscan for the detection of F2 and F3 stages in negative schistosomal serology patients was better than that in positive schistosomal serology patients (64% and 43.8%, vs. 30.8% and 21.4%, respectively) (Table 2).

In group 1 patients, the disagreement between the results of liver biopsy and fibroscan was obvious in F2 and F3 fibrosis stages (p value = 0.02) (Table 3).

Multivariate logistic regression, in which the agreement between fibroscan results and liver biopsy is the dependent variable, was performed. Among the independent factors (gender, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fibrosis stage and schistosomal serology status), only fibrosis stages (F0–F1 and F4) were associated with the agreement between fibroscan and liver biopsy (OR 3.4, 7.12; and p value <0.001, <0.001, respectively).

Positive schistosomal serology seems to be impairing that agreement, though insignificantly (p value = 0.29, OR 0.72) (Table 4).

Discussion

Histology of a liver biopsy specimen is necessary to establish the extent of liver fibrosis in liver diseases [10]. However, measurement of liver stiffness by TE (FibroScan) is widely used nowadays as a validated non-invasive method for the assessment of liver fibrosis [7].

Coinfections with *Schistosoma* caused more severe liver disease than infection with HCV alone with higher probability of HCV chronicity and more rapid progression of complications [11]. Further, as schistosomiasis is endemic in Egypt, we aimed to find the impact of previous exposure to schistosomiasis and positive schistosomal serology on the performance of fibroscan as a reliable non-invasive method for staging of fibrosis in chronic HCV patients.

This study could demonstrate that previous exposure to Schistosoma was assumed to impair the performance of fibroscan, especially in F2 and F3 fibrosis stages. There was a statistically significant association between positive schistosomal serology and the presence of significant liver fibrosis $\geqslant$F2 (Metavir) (p value = 0.049). These results are consistent with previous studies [12,13], which showed significant increase in the progression rates of fibrosis in chronic HCV patients coinfected with *Schistosoma* compared to the HCV monoinfection group. However, other studies [14–16] concluded that schistosomal hepatic affection does not alter or interfere with the assessment of fibrosis in mixed HCV-schistosomal liver affection. More importantly, they showed a lack of enhancement of this pathology in schistosomal patients. These differences may be attributed to several factors such as duration of schistosomal infection, frequency of exposure to schistosomal infection and whether the patient has received treatment.

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Table 1
Characteristics of both groups.

	Group 1 (*n*, %) Schistosomal serology +ve *n* = 67	Group 2 (*n*, %) Schistosomal serology –v1e *n* = 164	*p* Value
Sex			
Male (*n* = 162)	51 (76%)	111 (68%)	0.2 (NS)
Female (*n* = 69)	16 (24%)	53 (32%)	
Age (mean ± SD)	41 ± 8.8	40 ± 10.5	0.5 (NS)
Liver biopsy F0–F1	31 (46.3%)	105 (64%)	0.049 (S)
F2	13 (19.4%)	25 (15.2%)	
F3	14 (20.9%)	16 (9.8%)	
F4	9 (13.4%)	18 (11%)	

Table 2
Fibroscan results in relation to liver biopsy (Metavir) for both groups.

Fibroscan	Liver biopsy (*n*)			
	F0–F1	F2	F3	F4
Group 1*	(*n* = 31)	(*n* = 13)	(*n* = 14)	(*n* = 9)
F0–F1 (*n* = 29)	27	1	1	0
F2 (*n* = 7)	3	4	0	0
F3 (*n* = 9)	0	5	3	1
F4 (*n* = 22)	1	3	10	8
Group 2**	(*n* = 105)	(*n* = 25)	(*n* = 16)	(*n* = 18)
F0–F1(*n* = 90)	79	6	4	1
F2 (*n* = 36)	16	16	2	2
F3 (*n* = 14)	5	0	7	2
F4 (*n* = 24)	5	3	3	13

* *p* Value = 0.000, kappa = 0.47.
** *p* Value = 0.000, kappa = 0.49.

Table 3
The agreement between liver biopsy (Metavir) and the fibroscan in relation to schistosomal serology status.

Serology groups	Agreement		*p* Value
	No	Yes	
Group 1			
F0–F1 (*n* = 31)	4 (12.9%)	27 (87.1%)	0.02 (S)
F2 (*n* = 13)	9 (69.2%)	4 (30.8%)	
F3 (*n* = 14)	11 (78.6%)	3 (21.4%)	
F4 (*n* = 9)	1 (11.1%)	8 (88.9%)	
Group 2			
F0–F1 (*n* = 105)	26 (24.8%)	79 (75.2%)	0.37 (NS)
F2 (*n* = 25)	9 (36%)	16 (64%)	
F3 (*n* = 16)	9 (56.2%)	7 (43.8%)	
F4 (*n* = 18)	5 (27.8%)	13 (72.2%)	

Table 4
Multivariate logistic regression in which agreement of fibroscan and liver biopsy is the dependent variable.

Agreement	Odds ratio	*p* Value	95% Confidence interval	
Positive schistosomal serology	0.72	0.29	0.39	1.32
Liver biopsy (F0–F1)	3.9	0.00	1.87	8.11
Liver biopsy F4	7.12	0.00	2.37	21.39
Liver biopsy F2 and F3	2.25	0.073	0.92	5.48

The current study demonstrated that there was a statistically significant concordance between histopathology results (Metavir) and fibroscan results among the whole studied population. However, 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.

The sensitivity for the detection of F2, F3 and F4 stages among patients with negative schistosomal serology was 64%, 43.8% and 72.2%, respectively. These results were nearly similar to those reported by the study by Castera et al. [8] for the detection of F2 and F4; the sensitivity was 67%, and 87%, respectively, with some differences in the F3 group (sensitivity 73%) when using the same cut-off levels.

However, there was a statistically significant disagreement between the results of liver biopsy and fibroscan among patients with positive schistosomal serology, which was more obvious in the F2 and F3 fibrosis stages. However, this relation was not statistically significant among those with negative schistosomal serology.

Fibroscan was able to detect F2 and F3 stages with 64% (16/25) and 43.8% (7/16) sensitivity among negative schistosomal serology patients, while these values were reduced to 30.8% (4/13) and 21.4% (3/14), respectively, in positive schistosomal patients. Moreover, fibroscan tended to overestimate the stage of hepatic fibrosis among patients with positive schistosomal serology, especially for those with histopathology readings of F2 and F3.

The change in the sensitivity of fibroscan for F2 and F3 stages among both groups and the overestimation among patients with positive schistosomal serology may be attributed to the added effect of schistosomiasis on the rate of fibrosis progression among coinfected patients and the schistosomal periportal fibrosis, which affects the interpretation of the liver stiffness measurements by fibroscan.

Our results were further confirmed by multivariate logistic regression analysis, which revealed that fibrosis stages (F0–F1 and F4) were the most independent factors that were associated with that agreement and positive schistosomal serology seems to be impairing that agreement, though insignificantly (*p* value = 0.29, OR 0.72).

A major limitation of this study was the need to diagnose schistosomiasis in patients by using an anti-schistosomal serology approach with a commercially available IHAT rather than with a test that can differentiate between past and current infection.

We can conclude that although the sensitivity of fibroscan for the detection of fibrosis stages (F2 and F3) was impaired in patients with positive schistosomal serology, in the multivariate logistic regression in which the agreement between fibroscan and liver biopsy is the dependent variable, fibrosis stages (F0–F1 and F4) were the most independent factors that were associated with that agreement.

Conflict of interest

The authors declared that there is no conflict of interest.

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