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Synergistic Effect of Schistosomiasis on Hepatitis C Virus (HCV) of Human Liver Indicated by Antioxidant Biomarkers among Egyptian Population

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Abstract

The present study aimed to investigate changes of some oxidative stress biomarkers in Egyptian patients infected with schistosoma or/and hepatitis C virus (HCV). Regarding to oxidative stress markers, catalase was significantly higher in HCV- patients group and HCV & *Schistosoma* infected group compared to *Schistosoma* infected group. Glutathione peroxidase was significantly higher in all patient groups. Superoxide dismutase was significantly higher in HCV group, as well as HCV & *Schistosoma* infected patients. Non-significant changes were observed with superoxide dismutase in *Schistosoma* infected group. Nitric oxide was significantly higher in all patient groups. Catalase, glutathione peroxidase , nitric oxide, and superoxide dismutase levels might be used as monitoring markers for oxidative stress in *Schistosoma* infection or/and HCV carrier cases.

Key words: schistosoma, hepatitis C virus, catalase, glutathione peroxidase, nitric oxide, superoxide dismutase

Introduction

Schistosomiasis is a common parasitic disease affecting millions of people, mostly in tropical and developing countries [1]. More than 207 million people are infected worldwide – most live in poor communities without access to safe drinking water and adequate sanitation [2]. Egypt represents one of the most highly infected population with *schistosoma* in the world, it was traditionally the most important public health problem [3]. Egypt has one of the highest prevalence rates of hepatitis C virus (HCV) infection in the world. HCV infection leads to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) [4]. In Egypt, HCV together with schistosomal parasite infection is the biggest risk factor for chronic liver disease [5]. Cross-comparison of these 2 diseases in different patient groups may help to identify factors independent of the infecting agents that contribute to morbidity.

The aim of the present study was designed to illustrate the correlation between liver disease resulting from *schistosoma* infection or/and HCV carriers. It can be suggested that *schistosoma* infection has a synergistic effect

on HCV based on the induced changes of antioxidant biomarkers.

Materials and methods

Study Area

Kafr El-Ghab, Kafr Saad, Damietta, Egypt.

Patients

Between the beginning of February 2012 and the end of January 2013, all prospective or consecutive patients with chronic liver diseases tested positive anti-HCV antibody (HCV carriers) and some of them have *schistosoma* were admitted to Medical lab., Kafr El-Ghab, Markaz Kafr Sad, Damietta, Egypt, included in this study.

Patient groups

All selected patients were 48 based on the presence of schistosoma and HCV.

Patients were allocated into 4 groups .

Group 1 included 12 patients with schistosoma

Group 2 included 12 patients with HCV

Group 3 included 12 patients with schistosoma & HCV

Normal subjects

A group of 12 normal healthy adults were carefully selected as non infected cases. They were negative for anti-HCV antibodies and without *schistosoma*

Epidemiology

All patients and normal cases were reviewed for epidemiological data, including age, sex, occupation, medical diseases and others.

Physiological assessments

Serum samples and whole blood with anticoagulant were collected from all patients and normal cases. Each studied person was subjected to the following:

a. Detection of schistosomal or bilharizial antibodies in serum [6]
b. Detection of HCV- RNA quantitative PCR [7]
c. Determination of HCV antibodies [8]
d. Antioxidant determination (oxidative stress biomarkers)
    Catalase enzyme
    Glutathione peroxidase
    Superoxide dismutase
e. Nitric oxide

Chemicals

Kits for determination of HCV were purchased from PRECHEK BIO., INC, CA92806, USA. AccuPower® HCV Quantitative RT-PCR Kit. Kits for different biochemical investigation were purchased from ABC Diagnostics, and BIO-DIAGNOSTIC. Kits purchased from El-Ashraf trading company - 6 Ali Mubarak Street in Mansoura.

Statistical analysis

Statistical analysis was carried out for all patient groups against normal cases using t-test. Data also were processed using SPSS, version 18 (ANOVA one way analysis). The frequency of patients having abnormal values than the normal range was calculated to each patient group for every parameter and histographically represented in percentage. Data were listed as mean ± SD, median and range.

Results

Distribution of HCV by quantitative PCR and indirect haematoagglutination assay (IHA) for *Bilharizial* antibodies

Table 1 presents distribution of HCV by quantitative PCR, as well as, distribution of *schistosoma* or bilharizial antibodies. HCV showed non-significant changes in HCV-carrier patients compared to HCV & *Schistosoma*. HCV by PCR in HCV group was mean ± SD 980539± 1148570 IU ml^{-1} with median of 448500 IU ml^{-1} but it was 386053± 405985 in HCV & *Schistosoma* infected patients with median of 207000 IU ml^{-1} (Table 1).

According to the presence of bilharizial antibodies, *Schistosoma* , non-significant changes were observed *Schistosoma* group than that of HCV & *Schistosoma*, where mean ± SD was 1/640 ± 1/160 and 1/640 ± 1/160 respectively (Table 1).

Catalase

Table 2 and Fig. 1 present the results of catalase in control and other study subjects.

Significant changes (0.03) were observed in catalase activity in HCV-carrier patients compared to control group. Catalase in control group was 298.58 ± 84.18 U l^{-1} but it was 388.17± 111.21 U l^{-1} in HCV carrier patients (Table 2).

Catalase was significantly (<0.001) higher in HCV & *Schistosoma* infected patients compared to control, where mean ± SD was 543.42 ± 135.78 (Table 2).

According to the presence of *Schistosoma*, non-significant changes were observed at catalase activity in *Schistosoma* group compared to control.

Table 1 Distribution of HCV by quantitative PCR (IU ml^{-1}) and IHA for Bilharizial antibodies

	HCV-RNA (quantitative) by PCR		IHA for Bilharizial antibodies	
Factors	HCV	HCV & *Schistosoma*	*Schistosoma*	HCV & *Schistosoma*
Number	12	12	12	12
Mean	980539	386053	1/640	1/640
SD	1148570	405985	1/160	1/160
Median	448500	207000	1/640	1/640
Range	22000 -3462134	3644 – 1312000	1/320-1/1280	1/320-1/1280
t-test		0.11		0. 68

* Significant value at <0.05 t –test
** highly-significant at <0.01 t –test
*** extremely-significant at <0.001 t –test
[a] significant value at <0.05 based on one way ANOVA

Table 2 Plasma catalase (U l^{-1}) in different study subjects

Factors	control	HCV	*Schistosoma*	HCV & *Schistosoma*
Number	12	12	12	12
Mean	298.58	388.17	296.67	543.42
SD	84.18	111.21	95.87	135.78
SE	24.30	32.10	27.67	39.19
Median	303.5	350	275	514.5
Range	200-488	250-650	210-540	330-711
t-test	-	0.03*	0.95	<0.001***
ANOVA		<0.001 [a]		

* Significant value at <0.05 t –test
** highly-significant at <0.01 t –test
*** extremely-significant at <0.001 t –test
[a] significant value at <0.05 based on one way ANOVA

Glutathione Peroxidase

Table 3 and Fig. 2 present the results of glutathione peroxidase in control and other study subjects.

According to the presence of HCV, glutathione peroxidase was significantly (<0.001) higher in HCV-carrier patients compared to control group. Glutathione peroxidase in control group was 21.17 ± 2.21 mU ml^{-1} but it was 33.25 ± 5.21 mU ml^{-1} in HCV carrier patients.

Glutathione peroxidase was significantly (<0.001) higher in HCV & *Schistosoma* infected patients than that of control, where mean ± SD was 39.75 ± 3.55 (Table 3).

According to the presence of *Schistosoma*, Glutathione peroxidase was significantly (<0.001) higher in *Schistosoma* infected group compared to control, where mean ± SD was 25.75 ± 2.37 (Table 3).

Superoxide dismutase

Table 4 and Fig. 3 represent the results of

superoxide dismutase in control and other study subjects.

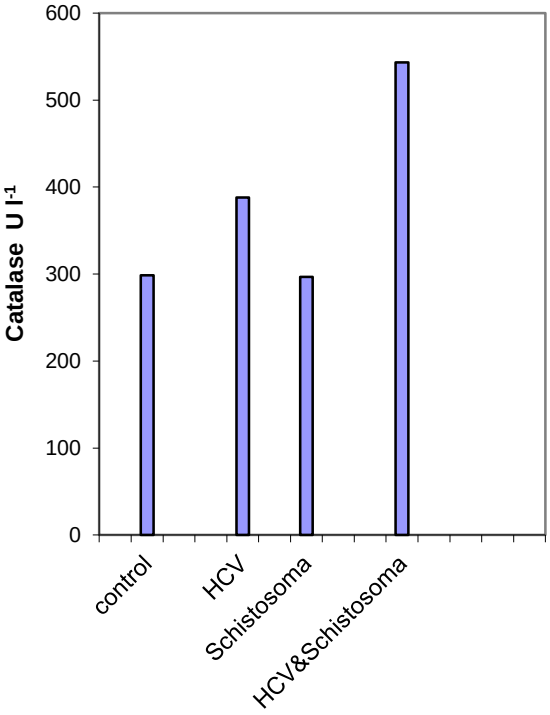

Fig. 1 Plasma catalase (U l^{-1}) activity

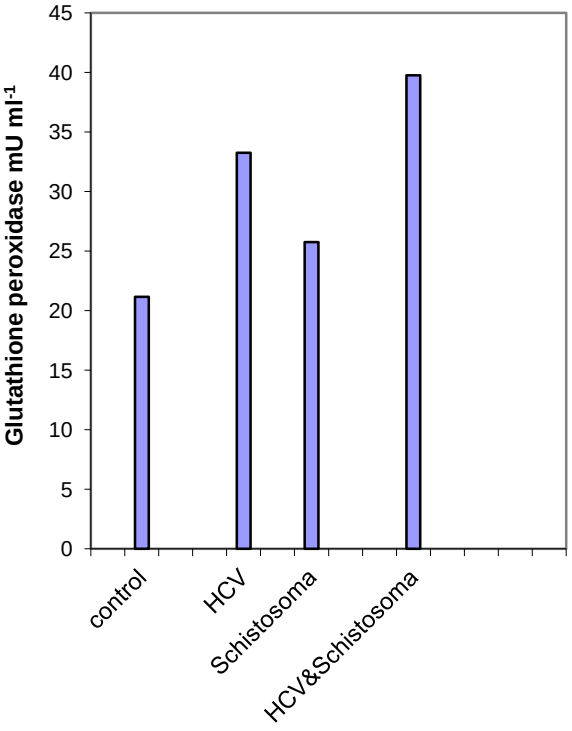

Fig. 2 Glutathione peroxidase (mU ml^{-1}) activity

According to the presence of HCV, superoxide dismutase was significantly (<0.001) higher in HCV-carrier patients compared to control group. Superoxide dismutase in control group was 23.92 ± 4.39 U ml^{-1} but it was 33.92± 4.93 U ml^{-1} in HCV carrier patients (Table 4).

Superoxide dismutase was significantly (<0.001) higher in HCV & *Schistosoma* infected patients compared to control, where mean ± SD was 38.67 ± 4.59 (Table 4).

According to the presence of *Schistosoma*, non-significant changes were observed at superoxide dismutase in *Schistosoma* group than control.

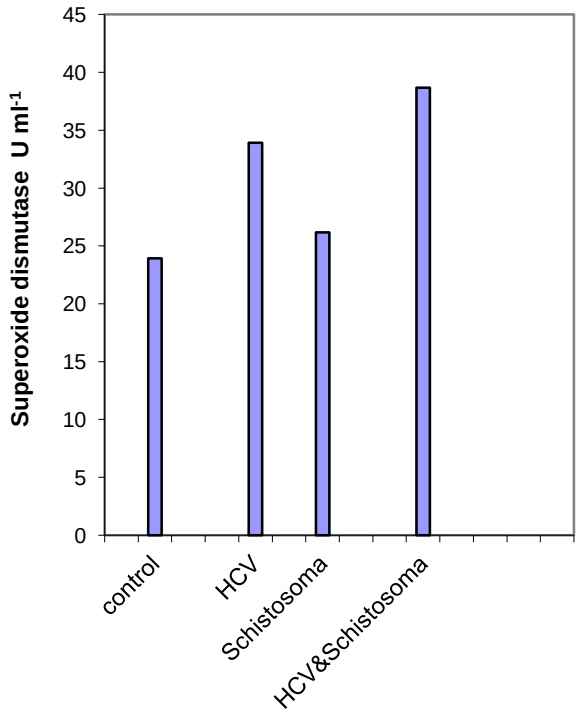

Fig. 3 Superoxide dismutase (U ml^{-1}) distribution

Nitric Oxide

Table 5 and Fig. 4 represent the results of urine nitric oxide in control and other study subjects.

According to the presence of HCV, nitric oxide was significantly (0.004) higher in HCV-carrier patients compared to control group. Nitric oxide in control group was 0.73 ± 0.53 µmol l^{-1} but it was 1.58 ± 0.76 µmol l^{-1} in HCV carrier patients (Table 5).

Nitric oxide was significantly (0.002) higher in HCV & *Schistosoma* infected patients compared to control, where mean ± SD was 3.41 ± 2.55 (Table 5).

According to the presence of *Schistosoma*, nitric oxide was significantly (0.004) higher in *Schistosoma* infected group compared to control, where mean ± SD was 1.54 ± 0.59 (Table 5).

Table 3 Glutathione peroxidase (mU ml^{-1}) in different study subjects

Factors	control	HCV	*Schistosoma*	HCV & *Schistosoma*
Number	12	12	12	12
Mean	21.17	33.25	25.75	39.75
SD	2.21	5.21	2.37	3.55
SE	0.64	1.50	0.69	1.02
Median	20.5	32.5	26.5	41
Range	18-26	22-39	22-29	32-43
t-test	-	<0.001***	<0.001***	<0.001***
ANOVA		<0.001 [a]		

* Significant value at <0.05 t –test
** highly-significant at <0.01 t –test
*** extremely-significant at <0.001 t –test
[a] significant value at <0.05 based on one way ANOVA.

Table 4 Superoxide dismutase (U ml^{-1}) in different study subjects

Factors	control	HCV	*Schistosoma*	HCV & *Schistosoma*
Number	12	12	12	12
Mean	23.92	33.92	26.17	38.67
SD	4.39	4.93	2.48	4.59
Median	23.5	35.5	27	39.5
Range	19-32	24-41	23-30	27-45
t-test	-	<.001***	0.14	<.001***
ANOVA		<0.001 [a]		

* Significant value at <0.05 t –test
** highly-significant at <0.01 t –test
*** extremely-significant at <0.001 t –test
[a] significant value at <0.05 based on one way ANOVA

Table 5 Urine nitric oxide (µmol l^{-1}) in different study subjects

Factors	control	HCV	Schistosoma	HCV & Schistosoma
Number	12	12	12	12
Mean	23.92	33.92	26.17	38.67
SD	4.39	4.93	2.48	4.59
SE	1.27	1.42	0.72	1.33
median	23.5	35.5	27	39.5
Range	19-32	24-41	23-30	27-45
t-test	-	<.001***	0.14	<.001***
ANOVA		<0.001 [a]		

* Significant value at <0.05 t –test
** highly-significant at <0.01 t –test
*** extremely-significant at <0.001 t –test
[a] significant value at <0.05 based on one way ANOVA.

Discussion

Over the last twenty years, considerable attention has focused on delineating some factors involved in the pathogenesis of liver injury. It appears that several forms of hepatic damage may be caused in part by oxidative stress, a condition caused by the formation of reactive oxygen species (ROS) [9]. Catalase is an antioxidant enzyme that, like superoxide dismutase (SOD) and glutathione peroxidase, is produced naturally within the body. Catalase is a common enzyme found in

nearly all living organisms exposed to oxygen [10]. Catalase helps the body to convert hydrogen peroxide into water and oxygen, thus preventing the formation of carbon dioxide bubbles in the blood.

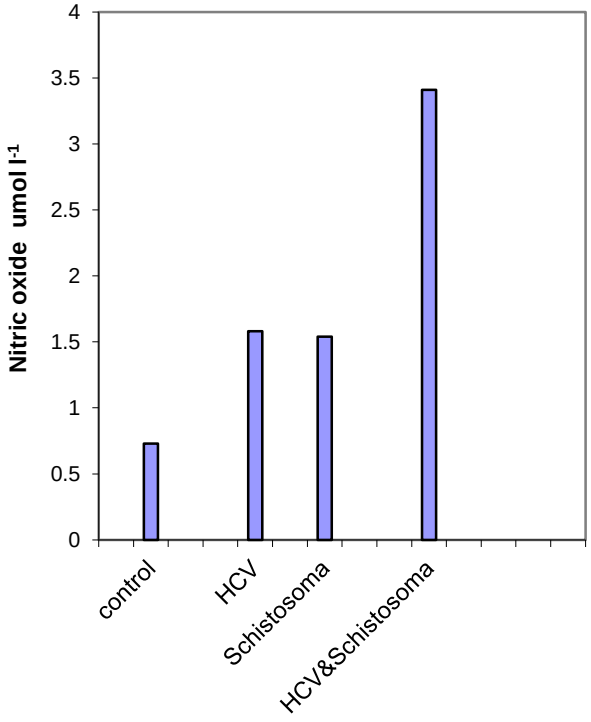

Fig. 4 Nitric oxide (µmol l^{-1}) levels

Catalase also uses hydrogen peroxide to break down potentially harmful toxins in the body, including alcohol, phenol, and formaldehyde [11].

In the present work, catalase was significantly higher in HCV-carrier patients compared to normal subjects. Catalase in normal subjects was 298.58 ± 84.18 U l^{-1}, while it was 388.17 ± 111.21 U l^{-1} in HCV carriers patients, in agreement with Li *et al*. [12]. This study revealed that catalase was significantly higher in HCV and *Schistosoma* carrier patients compared to control, where elevated mean values of catalase in HCV and *Schistosoma* groups [13].

Glutathione-peroxidase is part of the enzymatic antioxidant defenses; patients with mild to moderate liver damage, comparable to those in the present study, had increased glutathione-peroxidase levels in response to increased oxidative stress [14].

In the present work, glutathione peroxidase was significantly higher in HCV-carrier patients than that of normal subjects. Glutathione peroxidase in normal subjects was 21.17 ± 2.21 mU ml^{-1}, while it was 33.25 ± 5.21 mU ml^{-1} in HCV carriers patients, in agreement with Hsu *et al.* [15]. This study revealed that glutathione peroxidase was significantly higher in HCV and *Schistosoma* carrier patients compared to control, where elevated mean values of glutathione peroxidase in HCV and *Schistosoma* groups were 39.75 ± 3.55 mU ml^{-1} [16]. Although we did not observe a difference in glutathione-peroxidase levels between different study subjects, as the severity of liver disease increased, regardless of its etiology or HCV status, glutathione-peroxidase levels significantly increased.

Reactive nitrogen species (RNS) as nitric oxide (NO) can induce and inflect tissue injury [17]. The production of high levels of NO within the liver, via inducible NO synthase (iNOS), may promote damage via interference with mitochondrial respiration [18]. An increased serum nitrate level because of increased metabolites of NO was demonstrated in patients with chronic liver diseases [19].

In the present work, NO was significantly higher in HCV-carrier patients compared to normal subjects. NO in normal subjects was 0.73 ± 0.53 µmol l^{-1}, while it was 1.58 ± 0.76 µmol l^{-1} in HCV carriers patients, in agreement with Osman *et al.* [20]. This study revealed that NO was significantly higher in HCV and *Schistosoma* carrier patients than that for control , where elevated mean values of NO in HCV and *Schistosoma* groups were 3.41 ± 2.55 µmol l^{-1}, in agreement with Salim *et al.* [21].

Superoxide dismutase SOD levels are reported to be biomarker of oxidative stress in several diseases, including liver disease [22].

In the present work, superoxide dismutase was significantly higher in HCV-carrier patients compared to normal subjects. SOD in normal persons was 23.92 ± 4.39 ± 1.27 U ml^{-1}, while it was 33.92 ± 4.93 ± 1.42 U ml^{-1} in HCV carriers patients, in agreement with Clemente *et al.* [23]. This study revealed that SOD was significantly higher in HCV and *Schistosoma* carrier patients compared to control , where elevated mean values of SOD in HCV and *Schistosoma* groups were 38.67 ± 4.59 ± 1.33 U ml^{-1}, in agreement with, in agreement with Pinteaux *et al.* [24].

Conclusions

Based on the present data, the main biochemical responses in HCV carriers and patients infected with *Schistosoma* can be summarized as significant increase in oxidative stress biomarkers including catalase, glutathione peroxidase, nitric

oxide, and superoxide dismutase levels. It can be suggested that *schistosoma* infection has a synergistic effect on human hepatitis based on the induced changes of antioxidant biomarkers measured in the present work.

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الملخص العربى

التأثير المتداخل للإصابة بالبلهارسيا وفيروس الالتهاب الكبدي الوبائي سي على الكبد المستدل عليه من دلائل مضادات الأكسدة في بعض المرضى المصريين

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صمم هذا البحث لتقديم صورة عن مظاهر مرض الكبد الناتج عن طفيل البلهارسيا و فيروس سي . هذا بالإضافة إلى إبراز جهد الأكسدة ووطأة الأكسدة في أمراض الكبد الناجمة عن البلهارسيا وفيروس سي. واشتملت الدراسة الحالية علي اربعة مجموعات المجموعة الأولى وهي المجموعة الضابطة (هذه المجموعة التي لا تحتوي على البلهارسيا ولا فيروس سي). المجموعة الثانية هي المجموعة المصابة بالبلهارسيا، المجموعة الثالثة هي المصابة بفيروس سي الكبدي، المجموعة الرابعة هي المجموعة التي أصيبت بالبلهارسيا و فيروس سي. وأوضحت الدراسة مايلي:

- وجد ارتفاعا معنويا في Catalase في حاملي فيروس الالتهاب الكبدي "سي" و مرضى الكبد المصابيين بالبلهارسيا وحاملي فيروس الالتهاب الكبدي سي عن الأشخاص الطبيعيين. بينما لم يلاحظ تغيير معنوي في المجموعة المصابة بالبلهارسيا فقط.
- وجد ارتفاعا معنويا في Glutathione peroxidase في الثلاث مجموعات في حاملي فيروس الالتهاب الكبدي "سي" و مرضى الكبد المصابيين بالبلهارسيا وحاملي فيروس الالتهاب الكبدي سي عن الأشخاص الطبيعيين، وأيضا في المجموعة المصابة بالبلهارسيا فقط.
- وجد ارتفاعا معنويا في Superoxide Dismutase في حاملي فيروس الالتهاب الكبدي "سي" و مرضى الكبد المصابين بالبلهارسيا وحاملي فيروس الالتهاب الكبدي سي عن الأشخاص الطبيعيين. بينما لم يلاحظ تغيير معنوي في المجموعة المصابة بالبلهارسيا فقط.
- وجد ارتفاعا معنويا في Nitric oxide في الثلاث مجموعات (حاملي فيروس الالتهاب الكبدي "سي" ومرضى الكبد المصابين بالبلهارسيا وحاملي فيروس الالتهاب الكبدي سي) عن الأشخاص الطبيعيين، وأيضا في المجموعة المصابة بالبلهارسيا فقط.
- أن هناك ارتباط مابين أمراض الكبد الناتجة عن فيروس الالتهاب الكبدي الوبائي سي و طفيل البلهارسيا
- يمكن استخدام انزيمات catalase, glutathione peroxidase and superoxide dismutase بالإضافة إلى nitric oxide كدلائل كيميائية لتقييم جهد الأكسدة في أمراض الكبد الناتجة عن طفيل البلهارسيا وفيروس سي الكبدي .
- مما سبق فانه من الممكن استنتاج أن الإصابة بالبلهارسيا تزيد من وطأة الالتهاب الكبدي الوبائي بناء علي دراسة العلامات الحيوية المضادة للأكسدة في البحث الحالي.