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Research Article

Evaluation of Ox-LDL and Extracellular Superoxide Dismutase in Hepatitis C Virus Patients Before and After Direct-Acting Antiviral Therapy

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ABSTRACT

Hepatitis C virus (HCV) lifecycle is closely connected to host cell lipid metabolism, from cell entry, through viral RNA replication to viral particle production and formation/assembly.

Objective: To determine the serum levels of ox-LDL, total antioxidant capability and superoxide dismutase, and estimate their role in HCV hepatitis patients. In addition, the effect of direct-acting antiviral therapy on their levels was evaluated.

Methods: This study included forty chronic hepatitis C (genotype 4) patients. Blood samples were taken from the patients before and after taking sofosbuvir (400 mg) and daclatsvir 60 mg; one time daily orally for 24 weeks. Forty volunteers were used as control group.

Results:

Total antioxidant capacity (TAC)

Serum TAC in chronic HCV hepatitis patients were significantly low 1.21 ± 0.28 mmol/liter before treatment as compared to the control group (1.61 ± 0.26 mmol/liter).

Ox-LDL

Serum levels of ox-LDL were significantly high in patients before (70.21 ± 10.59 µg/L) treatment and after treatment (68.48 ± 9.12 µg/L) as compared to control group (58.64 ± 6.44 µg/L). Antioxidants supplementations and direct antiviral drugs did not affect the levels of ox-LDL significantly.

Superoxide dismutase (SOD)

Serum levels of extracellular SOD were significantly higher in control group (15.03 ± 4.14U/ml), than levels in HCV patients before treatment (8.6 ± 1.1 U/ml) and after treatment (10.33 ± 1.6 U/ml). Treatment did not restore the levels of serum SOD in patients.

Quantitative HCV PCR

Direct-acting antiviral agents had a sustained virological response in the chosen group of patients.

Conclusion: Direct-acting antiviral agents did not normalize serum levels of ox-LDL and extracellular SOD. In addition, the currently used antioxidants did not decrease the oxidative changes in LDL. New antioxidants as well as inducers of SOD enzymes may be helpful in preventing the formation of ox-LDL (taken as early as possible) and may be helpful in the treatment of HCV hepatitis.

Keywords: Ox-LDL; Total antioxidant capacity; Superoxide dismutase; HCV hepatitis; Direct antiviral therapy; Sofosbuvir; Daclatsvir

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INTRODUCTION

Hepatitis C Virus (HCV) infection is the primary reason of liver diseases worldwide. Novel therapies have been developed and became available since 2014. These treatments are based on the so-called Direct Acting Antivirals (DAAs). DAAs target viral Nonstructural (NS) proteins, including NS3 protease, the NS5B polymerase, and the NS5A protein. Treatment with different DAAs in blend has been appeared to bring about high paces of continued virologic reaction, without the requirement for pegylated interferon, and a shorter span of treatment contrasted and interferon-based regimens [1].

DAAs can achieve sustained virological responses or cure in a high (>95%) proportion of patients and have few adverse events. Sustained virological response leads to substantial decreases in all-cause and liver-related mortality, liver transplantation, and hepatocellular carcinoma [2].

NS3 principally goes about as a protease that encourages preparing of the rest of the NS proteins (NS4A, NS4B, NS5A, NS5B). NS3 likewise has helicase movement that encourages replication and inactivates variables engaged with the host inborn insusceptible response. NS5A is a multifunctional phosphoprotein that has no enzymatic action, however is required for RNA replication, membranous web development, and viral molecule formation. NS5B is a RNA-subordinate RNA polymerase that duplicates the HCV genome [3].

HCV contamination regularly causes dynamic liver maladies that decay from ceaseless irritation to fibrosis, cirrhosis and even to hepatocellular carcinoma. A long haul, diligent and uncontrolled fiery reaction is a sign of these maladies and further prompts hepatic damage and increasingly serious sickness movement. The instruments of HCV-actuated irritation include great pathogen design acknowledgment, inflammasome enactment, intrahepatic incendiary course reaction, and oxidative and endoplasmic reticulum stress [4].

HCV relies on protein-lipid interactions at multiple steps of its life cycle to establish persistent infection, making use of hepatic lipid pathways. HCV requires elements of host lipid metabolism for every step in the viral life cycle. HCV replication in the membranous web and maturing of new virions from the Endoplasmic Reticulum (ER) happen in nearness to lipid beads and cell compartments associated with the combination of low thickness lipoprotein. This enables virions to connect with lipoprotein atoms to shape lipoviroparticles and be emitted by means of the host endogenous secretory pathway. In spite of the fact that reinfection can happen by means of an extracellular course, it is accepted that the significant course of transmission in vivo happens through cell-to-cell transmission, in this way dodging the impacts of killing antibodies [5].

HCV induces oxidative/nitrosative stress from multiple sources, including inducible nitric oxide synthase, the mitochondrial electron transport chain, hepatocyte NADPH oxidases, and inflammation, while decreasing glutathione. Oxidation reaction and Reactive Oxygen Species (ROS) induce chemical modification of the proteins and lipids in plasma LDL transforming it to the abnormal Oxidized-LDL (ox-LDL). Ox-LDL is not recognized by the liver LDL receptors but is taken up by lectin-like Ox-LDL Receptor-1 (LOX-1) present in macrophages, natural killer cells, and vascular endothelial cells. Its association with ox-LDL induces the activation of NF-kappa-B. Ox-LDL induces direct inflammatory response due to the activated respiratory burst and production of more ROS. LOX-1 is likewise associated with foundational leukocyte enactment in sepsis. Fundamental leukocyte initiation speaks to a vital factor in the weakness of the microcirculation of various tissues, causing different organ disappointment and hence demise [6].

HCV induces oxidative stress in infected cells. The mechanisms of oxidative stress induction include; alteration of functioning of the respiratory chain complex I, and induction of NADPH oxidases. NADPH oxidases contribute to production of H_2O_2 and O_2-H_2O_2 induces phosphorylation of eIF2α resulting in inhibition of global (including that of viral) protein synthesis and constitutes an important defense against virus infection [7].

Superoxide Dismutases (SODs) provide an important defense against oxidative/nitrosative stress. Three isozymes of SOD are expressed by cells. SOD1 copper and zinc ions and is principally confined to the cytoplasm. SOD2 is situated in the mitochondrial network where it speaks to the primary line of cell reinforcement protection against superoxide anions delivered as side-effects of oxidative phosphorylation [8].

SOD3 (Extracellular EC-CuZn SOD3) is emitted into the extracellular liquid, for example, plasma, lymph, and synovial liquid. It frames a glycosylated homotetramer that is tied down to the extracellular network and cell surfaces through an association with heparan sulfate and collagen. A small amount of the protein is separated close to the C-end before emission to create flowing tetramers. Extracellular superoxide dismutase (EC-SOD) is answerable for the dismutation of the superoxide radical delivered in the extracellular space communicated by incendiary cells, including macrophages and neutrophils [9]. Makino et al. demonstrated that ox-LDL decreases EC-SOD mRNA and protein levels by binding to lectin-like oxidized LDL receptor-1 (LOX-1) [10].

Overexpression of Cu, Zn-SOD (SOD1) and/or catalase attenuates the cell proliferation of human smooth muscle cells caused by ox-LDL stimulation [11].

The theme of this work was to decide the serum levels of ox-LDL, all out cell reinforcement limit and superoxide dismutase, and assess their job in HCV hepatitis patients. Also, the impact

of direct-acting antiviral treatment, Sofosbuvir (SOF) in blend with daclatsvir on their levels in serum was assessed.

SUBJECTS

This examination included 40 male patients with constant hepatitis C genotype 4 and 40 male controls. Patients were referred from Al-Hussain and Sayed Galal, Al Azhar University Hospitals, and Virology unit, Alharam Hospital, Ministry of Health; Egypt. The Ethical Committee of Al-Azhar University endorsed the convention of the work. The convention of the work was disclosed to all members and a composed medicinal assent was agreed upon.

Control group

Forty subjects showing negative HCV Ab, were selected and assigned as a control group.

Avoidance criteria

Subjects experiencing any fundamental ailment or immune system illness were barred from the investigation. Moreover, subjects with positive HBV or have taken HBV vaccine, smokers, drug addicts and subjects suffering from hepatocellular carcinoma or any other malignancies were excluded from the study. Only patients with HCV hepatitis diagnosed by quantitative PCR were included in this study.

Anthropometric body measurements, which include; weight, height, BMI, triceps skin fold, mid arm circumference and waist circumference were done to patients and control group and were matched. Obese subjects with BMI>30 kg/M² were excluded from the study.

All the patients were taking glutathione; 50 mg daily orally, zinc as zinc oxide (11 mg orally once daily), vitamin A as retinyl acetate; (700 micrograms orally once daily), vitamin C (0.5 g orally once daily), and vitamin E as α-tocopherol (15 milligrams daily orally), and selenium as sodium selenate; 100 µg daily orally.

Patients were dealt with orally with the blend of sofosbuvir (a nucleotide polymerase inhibitor), 400 mg one time every day, and daclatasvir, a first-in-class NS5A replication complex inhibitor, 60 mg, once day by day for 24 weeks [12].

Blood samples

Blood tests were gotten from patients and sound controls following 12 hours of fasting. 4 mL were added to polypropylene tubes with stopper, left to clot for 20 minutes at 37°C, centrifuged at 3000 xg for 10 minutes and serum was separated. Serum was used for estimation of liver function tests, total proteins, albumin, oxidized low-density lipoprotein, superoxide dismutase, total antioxidant capacity and quantitative PCR. PCR for HCV was done for all included subjects; control and patients before and after treatment.

METHODS

Total proteins, albumin, Alanine Transaminase (ALT), Aspartate Transaminase (AST) and Alkaline Phosphatase (AP) were performed on Roche/Hitachi 902 auto analyzer, Roche Diagnostic, Germany by using kits supplied by Roche Diagnostic, Germany.

Total antioxidative capacity was measured colorimetrically using a kit supplied from Biodiagnostic Research Agents, Cairo. Complete plasma antioxidative limit was controlled by the response of cell reinforcements in the example with a characterized measure of exogenously gave hydrogen peroxide (H_2O_2). The cancer prevention agents in the example dispense with a specific measure of H_2O_2, The residual H_2O_2 was resolved colorimetrically by an enzymatic response which includes the transformation of 3, 5, dichloro-2-hydroxy benzene sulphonate to a shaded item which was estimated at 505 nm [13].

Quantitative PCR

Technique which was used is real time PCR by applied biosystem 7500, kit is qiagen.

Determination of SOD

Superoxide dismutase levels in serum were determined by a kit supplied from Biodiagnostic Research Agents, Cairo. The examine depends on the capacity of the compound to repress the phenazinemethosulphate-interceded decrease of nitrobluetetrazolium color [14].

Determination of ox-LDL

Oxidized-LDL in serum was measured using WKEA human oxidized LDL ELISA kit supplied from WKEA MED SUPPLIES CORP, USA. Focused ELISA technique depends on the monoclonal immune response explicit to human ox-LDL. Oxidized LDL in the example contends with a fixed measure of oxidized LDL bound to the microtiter well for the authoritative of the biotin-marked explicit antibodies. After a washing step that evacuates lifeless example parts, the biotin-named counter acting agent bound to the well is recognized by HRP-conjugated streptavidin. Following a subsequent hatching and an extra washing venture, the bound conjugate is recognized by response with 3,3',5,5'-Tetramethylbenzidine (TMB). The response is halted by adding corrosive to give a colorimetric endpoint that is perused spectrophotometrically [15].

Statistical analysis

Results were stated as Mean ± standard deviation (SD). Comparison between groups was done using Student's t-test with significance defined as $p \leq 0.05$.

RESULTS

Anthropometric body measurements data

Age, weight, height, BMI, triceps skin fold, mid arm circumference and waist circumference of all subjects included in this study were matched. All subjects were not obese; their BMI was less than 30 (Table 1).

Table 1: Anthropometric body measurements in control group and HCV hepatitis patients before and after treatment.

	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m²)	Skin fold (cm)	Mid arm circumference (cm)	Waist circumference (cm)
Control	49.9 ± 8.23	78.2 ± 6.81	170.65 ± 3.66	26.85 ± 2.03	1.18 ± 0.26	22.8 ± 1.63	92.5 ± 6.7
HCV patients before treatment	57.6 ± 7.44	68.55 ± 12.25	68.55 ± 12.25	24.31 ± 4.13	1.24 ± 0.52	21.4 ± 2.65	97.4 ± 14.22
HCV patients after treatment	57.6 ± 7.44	73.55 ± 9.26	168.1 ± 5.3	26.1 ± 2.63	1.26 ± 0.32	21.92 ± 1.94	97.7 ± 14.83

Serum total proteins

Serum total proteins levels were 7.12 ± 0.73 g/dl in the control group. Serum total proteins levels were 6.72 ± 0.58 and 6.55 ± 0.84 g/dl in HCV hepatitis patients before and after treatment respectively. Serum total proteins were not significantly lower in hepatitis patients.

Serum albumin

Serum albumin level was 5.76 ± 0.74 g/dl in the control group. Serum albumin levels were 4.01 ± 0.44 and 3.79 ± 0.26 g/dl in HCV hepatitis patients before and after treatment respectively. Serum albumin level was significantly lower in HCV patients.

Serum alanine aminotransferase

Serum alanine aminotransferase level was 23.7 ± 4.5 U/dl in the control group. Serum alanine aminotransferase levels were 84 ± 8.3 and 80.45 ± 14.9 U/dl in HCV hepatitis patients before and after treatment respectively. Serum alanine aminotransferase levels were significantly higher in HCV patients before and after treatment.

Serum aspartate aminotransferase

Serum aspartate aminotransferase level was 25.2 ± 3.1 U/dl in the control group. Serum alanine aminotransferase levels were 196 ± 10.8 and 89.8 ± 14.7 U/dl in HCV hepatitis patients before and after treatment respectively. Serum aspartate aminotransferase levels were significantly higher in HCV patients before and after treatment.

Serum alkaline phosphatase

Serum alkaline phosphatase level was 63.8 ± 16.3 U/L in the control group. Serum alkaline phosphatase levels were 196 ± 38 and 178 ± 43 U/L in HCV hepatitis patients before and after treatment respectively. Serum alkaline phosphatase level was significantly higher in HCV patients.

Serum PCR

Serum PCR in control group was<15 IU/ml and 399521 ± 215675 IU/ml in HCV hepatitis patients before treatment. Only patients who showed virological clearance were included in this study (<15 IU/ml) (Table 2).

Table 2: Serum total proteins, albumin, aminotransferases, alkaline phosphatase and PCR in control group and HCV hepatitis patients before and after treatment (mean ± SD).

	AST U/dl	ALT U/dl	ALP U/L	PCR IU/ml	Serum total proteins g/dl	Serum albumin g/dl
Control	25.2 ± 3.1	23.7 ± 4.5	63.8 ± 16.3	<15	7.12 ± 0.73	5.76 ± 0.74
HCV hepatitis patients before treatment	104 ± 10.8	84 ± 8.3	196 ± 38	399521 ± 215675	6.72 ± 0.58	4.01 ± 0.44
HCV hepatitis patients after treatment	89.8 ± 14.7	80.45 ± 14.9	178 ± 43	<15	6.55 ± 0.84	3.79 ± 0.26

Serum total antioxidant capacity

Total serum antioxidant capacity levels were 1.61 ± 0.26, 1.21 ± 0.28 and 2.2 ± 0.38 mmol/liter in the control group and HCV hepatitis patients before and after treatment respectively. Serum TAC levels in chronic HCV hepatitis patients were significantly low before treatment. While after treatment which included antioxidants were significantly high as compared to control group and before treatment (Table 3).

Table 3: Serum total anti-oxidant capacity (mmol/liter) in control group and HCV hepatitis patients before and after treatment

	Control	HCV hepatitis patients before treatment	HCV hepatitis patients after treatment
Mean± SD	1.61 ± 0.26	1.21 ± 0.28	2.2 ± 0.38
Control	t test p value	6.33<0.001	7.74<0.001
HCV before treatment	t test p value	---------	12.77<0.001

Serum ox-LDL

Serum levels of ox-LDL (µg/L) were 58.64 ± 6.44, 70.21 ± 10.59 and 68.48 ± 9.12 in the control group, and HCV hepatitis patients before and after treatment respectively. Serum levels of ox-LDL were significantly high in HCV hepatitis patients as compared to control group. Antioxidants supplementations and direct antiviral drugs did not affect the levels of ox-LDL significantly in HCV hepatitis patients (Table 4).

Table 4: Serum levels of ox-LDL (µg/L) in control group and HCV hepatitis patients before and after treatment

	Control	HCV hepatitis patients before treatment	HCV hepatitis patients after treatment
Mean ± SD	58.64 ± 6.44	70.21 ± 10.59	68.48 ± 9.12
Control	t test p value	5.97<0.001	5.57<0.001
HCV before treatment	t test p value	---------	0.79, 0.1

Serum levels of SOD

Serum levels of SOD (U/ml) were 15.03 ± 4.14, 8.6 ± 1.1 and 10.33 ± 1.6 in the control group, and HCV hepatitis patients before and after treatment respectively. Serum levels of extracellular SOD were significantly low in HCV hepatitis patients before and after treatment as compared to the control group (Table 5).

Table 5: Serum levels of SOD (U/ml) in control group and HCV hepatitis patients before and after treatment

	Control	HCV hepatitis patients before treatment.	HCV hepatitis patients after treatment.
Mean ± SD	15.03 ± 4.14	8.6 ± 1.1	10.33 ± 1.6
Control	t test p value	9.9<0.001	6.56<0.001
HCV before treatment	t test p value	----------	2.46, 0.02

DISCUSSION

Age, weight, height, BMI, triceps skin fold, mid arm circumference and waist circumference

Body measurement data (Anthropometric data) in adults are used to evaluate health and dietary status, disease risk, and body composition changes that occur over the adult lifespan. Anthropometric data of the patients were matching with the control group. In this study, the anthropometric data of all subjects were similar to the age group of American men [16]. Obese persons were excluded from the study. Obesity is linked with a state of increased oxidative stress. Obesity is a principal causative factor in the development of metabolic syndrome. It is associated with a high cardiovascular risk. Ox-LDL is strongly and independently associated with classical cardiovascular risk factors [17]. Changes in ox-LDL observed in this study were not due increased body weight.

Total anti-oxidant capacity

Examine of Total enemy of oxidant limit estimates a complex of non-enzymatic cell reinforcements present in blood, which incorporate exogenous cancer prevention agents, for example, ascorbic acid, α tocopherol, β carotene and polyphenols. Ascorbic acid restrains intracellular ROS age and lessens the ethanol-incited aggravation in hepatocytes [18].

Test of Total enemy of oxidant limit likewise measures the endogenous cell reinforcements, for example, decreased glutathione, uric acid, and bilirubin. All patients were taking cell reinforcements including glutathione and ascorbic acid, as normal since they were analyzed as HCV hepatitis patients. Taking cancer prevention agents may clarify the elevated level of blood complete cell reinforcements in HCV hepatitis patients when contrasted with the control group.

Serum ox-LDL

Serum levels of ox-LDL (µg/L) were 58.64 ± 6.44, 70.21 ± 10.59 and 68.48 ± 9.12 in the control group, and HCV hepatitis patients before and after treatment respectively. Serum levels of ox-LDL were significantly high in HCV hepatitis patients as compared to control group. Antioxidants supplementations and direct antiviral drugs did not affect the levels of ox-LDL in HCV hepatitis patients.

Ox-LDL was used as a marker of oxidative stress in this study. Ox-LDL is a stable marker molecule with longer half-live than free radicals as malondialdehyde. Ox-LDL can potentially contribute to the pathogenesis of liver diseases, kidney diseases, uremia, cardiovascular disease, and inflammation [19].

Hepatitis C virus is a lipid-wrapped virion molecule that makes contamination the liver, and as a major aspect of its life cycle, it upsets the host lipid metabolic hardware, especially the cholesterol amalgamation pathway. The existing straight-acting antiviral specialists have expanded the fix pace of HCV contamination. Viral the host hereditary foundations impact both the invulnerable reaction and lipid digestion. Cholesterol and its subsidiaries, for example, oxysterols may regulate and potentialize the hepatic inborn immune reaction created against HCV. The disability of the HCV life cycle balanced by serum cholesterol could be pertinent for the clinical administration of HCV-tainted patients when treatment [20].

LDL lipoperoxidation leads to modifications in apolipoprotein B-100 and lipids. Ganini and Mason reported the lack of protection of α-tocopherol on the Apo B-100 and lipid free radical formation by lipooxygenases. This may explain the failure of vitamin E as a cardiovascular protective agent for humans [21]. In addition, it may explain the high levels of ox-LDL in hepatitis patients although they are on vitamin E as a supplement

The significant high levels of ox-LDL reported in this study, may be a factor in the pathogenesis HCV hepatitis and HCV liver cirrhosis. Ox-LDL in serum of HCV patients may be a result of HCV induced oxidative stress in infected cells or it may be due to decreased endogenous production of antioxidants.

Oxidative stress results induces phosphorylation of eIF2α resulting in inhibition of global (including that of viral) protein synthesis and constitutes an important defense against virus infection. ROS; induced by HCV inhibit virus replication without affecting stability of its RNA genome. ROS can induce viral genome heterogeneity, which facilitates viral escape during treatment and probably escape from the immune system.

ROS induce fixed chemical modification of the proteins and lipids in plasma LDL transforming it to the abnormal ox-LDL. Oxidative alterations in amino acids just as proteolysis and cross-connections of apolipoprotein B happen that outcome in broad modification in the protein organization and structure forming carbonylated proteins. These protein oxidations ought to be treated before they are started at the primary stage of HCV disease [22].

Oxidized low-thickness lipoprotein is a main pathogenic element of vascular atherosclerosis. In addition, expanded levels of ox-LDL are related with hepatocellular damage in test cholestasis and fibrosis [23].

Ho et al. show that free cholesterol was restricted with ox-LDL in the wall of entryway vein, and was related with lumen narrowing, plaque arrangement, endothelium distortion, and gateway venous aggravation in exploratory rodents. The irritation was confirmed by the colocalization of Kupffer cells, IL-1β and the statement of LOX-1. Burst plaque was intently connected with entryway venous irritation. In addition, free cholesterol and ox-LDL gathering in periportal and sinusoidal fibrosis, which was related with provincial stellate cell initiation and chicken-wire fibrosis. Their discoveries uncover an immediate relationship between cholesterol collection, portal venous irritation and fibrosis in nonalcoholic greasy liver disease [24].

Superoxide dismutase

Serum levels of extracellular SOD were essentially low in HCV hepatitis patients when treatment when contrasted with the control group. Extracellular SOD is liable for the dismutation of the superoxide radical delivered in the extracellular space Extracellular superoxide SOD is expressed by provocative cells, including macrophages and neutrophils. Its gene is located on chromosome 4 (4p15.2).

The significant low levels of extracellular SOD observed in this study may be due to genetic predisposition of patients, or it may be due to permanent effects of HCV infection and not restored after virological clearance. Khedr et al. have revealed increment in the degrees of glutathione peroxidase and abatement in the levels of malondialdehyde in children with chronic hepatitis C after treatment with interferon [25].

New cell reinforcements just as inducers of cancer prevention agent proteins; Mn/superoxide dismutase and catalase, might be useful in counteractive action of arrangement of ox-LDL [26].

Superoxide dismutase (SOD)

Serum levels of extracellular SOD were significantly low (p value<0.001) in HCV hepatitis patients before and after treatment as compared to the control group. Treatment increased slightly the levels of serum SOD, but it did not restore the levels to those of the control group although of the sustained virological clearance.

CONCLUSION

Ox-LDL is a stable marker molecule of oxidative stress. ROS produce oxidative changes in proteins and lipids in LDL. There was a highly significant increase (p value<0.001) in serum ox-LDL levels in HCV hepatitis patients (70.21 ± 10.59 µg/L) as compared to the control group (58.64 ± 6.44 µg/L). Direct-acting antiviral agents did not normalize serum levels of ox-LDL. The level in HCV hepatitis patients after treatment was 68.48 ± 9.12 µg/L.

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