



Effect of L-Carnitine and/or Sitagliptin on Serum Lipids Profile of H₂O₂ Treated Rats (Part-1)

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Abstract | This study was designed to evaluate the ameliorative role of L-carnitine and/or sitagliptin on dyslipidemia induced by oral administration of 0.75% hydrogen peroxide in male rats. Thirty five (35) adult male rats were randomly and equally divided into five groups (C, T1, T2, T3 and T4) and were treated for 60 days as following: Group C (Control group), rats in all treated groups from T1 to T4 were given 0.75% H₂O₂ in drinking water. In addition to H₂O₂, 100mg/kg B.W of L-carnitine and 1.5mg/kg. B.W of sitagliptin were administered orally to rats in groups T2 and T3 respectively, while rats in group (T4) were administered orally. Combination of sitagliptin (0.75 mg/kg. B.W) plus L-carnitine (50mg/kg B.W.) Fasting (8-12 hrs.) blood samples were collected by Retro-orbital sinus technique at different times 0, 30 and 60 days of the experiment and serum were collected for measuring the following parameters: serum lipid profile including: total cholesterol (TC), triacylglycerol (TAG), cholesterol in High density Lipoprotein (HDL-c), Low density lipoprotein (LDL-c) and very low density lipoprotein (VLDL-c) concentrations. The results showed a case of dyslipidemia in rats exposed to H₂O₂ manifested by significant (p<0.05) increase in serum TC, TAG, LDL-C and VLDL-C with significant (p<0.05) decrease in serum HDL-C concentrations comparing to other treated groups. The protective (hypolipidemic) role of L-carnitine and sitagliptin was clarified in groups (T2, T3) manifested by hypocholesterolemia. It exhibited significant (p<0.05) decrease in serum, TAG, LDL-c, and VLDL-c concentration with significant (P<0.05) elevation in serum HDL-c concentration.

Keywords | L-Carnitine, Sitagliptine, Hydrogen peroxide, Lipid profile, Male rats

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INTRODUCTION

Reactive oxygen species (ROS) are normal by-products of cellular metabolism (Brawek et al., 2010). They are unstable and aggressive molecules, which have the tendency to give their unpaired electron to other cellular molecules or snatch electrons from other molecules to attain stability (Singh et al., 2009). The production of reactive oxygen species may produce oxidative stress and various degenerative diseases such as cancer, neurologic disorder, atherosclerosis and diabetes (Birben et al., 2012; Khan et al., 2015). Reactive oxygen species can be important mediators of damage to cell structures such as lipids, membranes, proteins and DNA (El-Gendy et al., 2010; Tanas et al., 2010). H₂O₂ is a type of ROS produced in many physiological and ab-

normal chemical reactions both intracellular and extracellular. Due to its small size and relatively benign reactivity, compared to the rest of the ROS, H₂O₂ can diffuse freely across several cell radii; therefore, it is able to mediate toxic effects far from the site of ROS production, especially if it becomes converted to the highly reactive OH[•] (Weslar and Bast, 2010; Noori, 2012). The overproduction of reactive oxygen species (ROS) via oxidative phosphorylation, induces an oxidative stress and ultimately an endothelial dysfunction (Msolly et al., 2013). Antioxidants may guard against ROS toxicities by the prevention of ROS construction, by disruption of ROS attack, scavenging reactive metabolites and converting them to less reactive molecules or by enhancing the resistance of sensitive biological target to ROS attack (Siddique et al., 2010) and oxidative stress

accompanied many diseased condition (Oviasogie et al., 2009; Raja, 2010).

L-Carnitine is a vitamins like substance found in different food items and it is derived from lysine and methionine, is a substance essential for the oxidation of long-chain fatty acids in the mitochondria and protection of cell membranes from damage caused by free oxygen radicals (Peivandi et al., 2010). Antioxidant properties have also been documented for L-Carnitine such as prevention of lipid, protein, and DNA damage, as well as increase of non-enzymatic and enzymatic antioxidant levels (Derin et al., 2004; Ribas et al., 2010), in addition, L-Carnitine is able to act as a metal chelator, scavenger of oxygen reactive species (Solarska et al., 2010; Ribas et al., 2012). L-carnitine has a cardio protective effect which is attributed to stimulating the antioxidant capacity of cardiac tissues (Mansour, 2013). L-Carnitine is impertuned in modulating systemic inflammation and lower circulating c-reactive protein (CRP) (Amirhossein, 2015), the most potent factor in developing Cardio Muscular Disease (CVD) (Popvic et al., 2014). Sitagliptin an oral antihyperglycemic drug (antidiabetic drug) of the DPP -4 inhibitor class (Kim et al., 2005; Herman et al., 2007), has been improved to possess antioxidant activity (Glorie et al., 2012). This study was aimed of studying the protective effect of L-Carnitine and/or Sitagliptine on hyperlipidaemia, the risk biomarkers of cardio vascular disease in H₂O₂ exposed rats.

MATERIAL AND METHODS

ANIMAL PREPARATION AND EXPERIMENTAL DESIGN

Thirty five male Albino Wister rats (200-270 g) were used in this investigation. Their age ranged between (2.5-3) months. Animals in all stages of the experiment were housed in plastic cages in conditioned room (22-25°C) for the period from September 2013 to October 2013 providing daily light of twelve hours (7.00 to 19.00) and twelve hours night cycle. They were left for ten days for adaptation with the experimental conditions. Animals had free access to water and standard pellet diet throughout the experiment.

Thirty five adult male rats were randomly and equally divided into five following groups (7 rat/group) and treated daily for two months as below: Group 1: Animal in this group were received ordinary distal water served as control group, group 2: rats were subjected to 0.75% hydrogen peroxide (H₂O₂) in drinking water, group 3: rats were given orally (using gavages needle) L-carnitine 100mg/kgB.W with 0.75% H₂O₂ in drinking water, group 4: rats were given orally sitagliptin (1.5 mg/kgB.W) (Gupta et al., 2009)+ 0.75% H₂O₂ in drinking water and group 5: rats were given orally sitagliptin (0.75 mg/kgB.W) + L-Carnitine (50 mg/kgB.W) with 0.75% H₂O₂ in drinking water. Blood samples were collected at 0, 30, 60 days of the

experiment. Blood was drawn by retro-orbital sinus technique from rats anesthetized by intra muscular injection of Ketamin-HCL 90mg/Kg B.W. and Xylazine 40mg/kg B.W., blood sample were kept in tube not more than 4 hours followed by centrifugation for 15 minutes at 3000 rpm. Serum were isolated and frozen at -20°C until analysis for measuring the following parameters. Determination of (a) serum total cholesterol (TC) concentration using total cholesterol kit (Linear chemicals S.L, Spain), (b) serum triacylglycerol (TAG) concentration using triacylglycerol kit (Linear chemicals S.L, Spain), (c) serum high density lipoprotein (HDL-c) concentration using HDL - cholesterol kit (Linear chemicals S.L, Spain), (d) serum very low density lipoprotein (VLDL-c) concentration and (e) serum low density lipoprotein (LDL-c) concentration according to (Friedewald et al., 1972). Statistical analysis of data was performed on the basis of two-way analysis of variance (ANOVA) using a significance level of (P<0.05). Specific group differences were determined using least significant differences (LSD) as described by Snedecor and Cochran (1973).

RESULTS AND DISCUSSION

SERUM TOTAL CHOLESTEROL (TC) CONCENTRATION

Table 1 pointed to time dependent significant (P<0.05) increase in the mean values of serum cholesterol concentration was observed in T1 at day 30 (105.45±0.749) and 60 (137.02±0.763) of the experiment comparing to the value in the pretreated period (8.34± 1.331). Besides, serum TC showed significant (P<0.05) decrease in its value after oral administration of L-carnitine, Sitagliptin or combination of both for 30 and 60 days of the experiment comparing to H₂O₂ (T1) treated group. Oral administration of sitagliptin or L-carnitine concurrently with H₂O₂ caused a significant (P<0.05) decrease in serum cholesterol concentration at the end of experiment with mean values of 89.21±0.536 and 88.84±0.628 for groups T3 and T4, respectively. The values in these groups tend to normalized that of control (88.94 ± 1.083).

SERUM TRIACYLGLYCEROL (TAG) CONCENTRATION

The result in Table 2 Oral administration of L-carnitine (T2) group and sitagliptin (T3) group caused a significant (P<0.05) decrease in the TAG concentration after 30 day of the experiment with mean values of (70.50±1.190) and (74.12±1.224) respectively as compared to H₂O₂ (T1) group, where significant (P<0.05) elevation in this parameter was observed with mean values of (82.70±1.840). On the other hand, a significant (p<0.05) decrease in this parameter at day 60 was observed after combination of the two treatment in T4 group with mean value of (67.65±0.749) comparing with the values in T1, T2, T3 (102.82 ±1.647), (73.40 ± 0.822), (77.11 ± 1.002) respectively, indicating the synergistic and preventive effect of combination of

Table 1: Effect of L-carnitine or/and sitagliptin on serum total cholesterol (TC) concentration (mg/dl) in 0.75% H₂O₂ treated male rats

Days	Groups				
	C	T1	T2	T3	T4
Zero time	88.61±1.361 A a	89.34± 1.331 A c	88.18±1.744 A c	89.51±1.405 A b	87.92± 1.215 A b
30 days	88.55±1.274 D a	105.45±0.749 A b	98.30±1.074 B a	94.32±0.744 C a	92.02±0.386 C a
60days	88.94± 1.083 C a	137.02±0.763 A a	94.22±0.709 B b	89.21±0.536 C b	88.84±0.628 C b

LSD =2.59; Values are expressed as mean ± SE, n = 7 each group; **C:** Control group; **T1:** Animals received 0.75% H₂O₂ in drinking water for 60 days; **T2:** Animals received 0.75% H₂O₂ in drinking water and 100mg/kg. B.W of L-Carnitine orally for 60 days; **T3:** Animals received 0.75% H₂O₂ in drinking water and 1.5 mg/kg B.W of sitagliptin orally for 60 days; **T4:** Animals received 0.75% H₂O₂ in drinking water and 50 mg/ kg B.W of L-Carnitine and 0.75 mg/kg of sitagliptin orally for 60 days; Different small letters vertically represent significant difference within group (p<0.05) vs. zero time; Different capital letters horizontally represent significant difference between groups (p<0.05) vs. control.

Table 2: Effect of L-carnitine or/and sitagliptin on Serum triacylglycerol (TAG) concentration (mg/dl) in 0.75% H₂O₂ treated male rats

Days	Groups				
	C	T1	T2	T3	T4
Zero time	61.22±0.791 A a	60.90± 0.846 A c	62.18±0.953 A b	61.64±0.975 A b	60.22± 0.513 A b
30 days	62.58±1.544 C a	82.70±1.840 A b	70.50±1.190 B a	74.12±1.224 B a	70.48±1.000 B a
60 days	63.64±1.007 D a	102.82±1.647 A a	73.40±0.822 C a	77.11±1.002 B a	67.65±0.749 D a

LSD = 4.02; Values are expressed as mean ± SE, n = 7 each group; **C:** Control group; **T1:** Animals received 0.75% H₂O₂ in drinking water for 60 days; **T2:** Animals received 0.75% H₂O₂ in drinking water and 100mg/kg. B.W of L-Carnitine orally for 60 days; **T3:** Animals received 0.75% H₂O₂ in drinking water and 1.5 mg/kg B.W of sitagliptin orally for 60 days; **T4:** Animals received 0.75% H₂O₂ in drinking water and 50 mg/ kg B.W of L-Carnitine and 0.75 mg/kg of sitagliptin orally for 60 days; Different small letters vertically represent significant difference within group (p<0.05) vs. zero time; Different capital letters horizontally represent significant difference between groups (p<0.05) vs. control.

L-carnitine and sitagliptin against H₂O₂. While, there were no significant differences in lipoprotein-cholesterol (VLDL-c) at zero time in all treated groups when compared to each other, at day 30 of the experiment there was a significant (P<0.05) decrease in the mean values of serum VLDL-C concentration in groups T2 (14.10±0.23) and T3 (14.82± 0.24) and T4 (14.09±0.20) comparing to the mean value of T1 (16.54±0.36) group (Table 3). Further significant (p<0.05) decrease in this parameter was observed in groups T2 and T3 at day 60 comparing to the values in H₂O₂ treated (T1) group which showed further significant (p<0.05) increase in VLDL-c concentration.

SERUM LOW DENSITY LIPOPROTEIN-CHOLESTEROL (HDL-C) CONCENTRATION

Table 4 pointed to Significant (P<0.05) decrease in serum LDL-c concentration was observed after 30 days of intubation of L-carnitine (56.04±1.267) or sitagliptin (51.91±0.921) or combination of both concurrently with H₂O₂ (49.26±0.443) comparing to H₂O₂ (T1) groups. Fur-

ther significant (P<0.05) decrease in this parameter was observed at the end of the experimental in T2,T3,and T4 groups with mean values of 47.20±0.414, 44.34±0.905, and 3.91±0.626, respectively as compared to T1 (93.92±0.737) treated group. The result also showed that combination of sitagliptin and L-carnitine caused significant (P<0.05) depression in this parameter comparing to L-carnitine alone and the value tend to normalize that of the control (44.89±1.389).

SERUM HIGH DENSITY LIPOPROTEIN-CHOLESTEROL (HDL-C) CONCENTRATION

Oral administration of L-carnitine or sitagliptin for 30 day caused significant (P<0.05) increase in this parameter in groups T2 (28.15±0.578), T3 (27.60±0.703) and T4 (28.67±0.401) comparing to the value of (25.21±0.897) in H₂O₂ (T1) treated group (Table 5) Correction of dyslipidemia (elevation in HDL-c concentration) was observed also at the end of experiment,where further significant (P<0.05) increase in this parameter was observed in

Table 3: Effect of L-carnitine or/and sitagliptin on serum very low density lipoprotein-cholesterol (VLDL-c) concentration (mg/dl) in 0.75% H₂O₂ treated male rats

Days	Groups				
	C	T1	T2	T3	T4
Zero time	12.24±0.158 A a	12.18±0.169 A c	12.43±0.190 A b	12.32±0.195 A b	12.04±0.102 A c
30 days	12.51±0.304 C a	16.54±0.368 A b	14.10±0.238 B a	14.82±0.244 B a	14.09±0.200 B a
60 days	12.72±0.201 E a	20.56±0.329 A a	14.68±0.164 C a	15.42±0.200 B a	13.53±0.149 D b

LSD = 0.801; Values are expressed as mean ± SE, n = 7 each group; **C:** Control group; **T1:** Animals received 0.75% H₂O₂ in drinking water for 60 days; **T2:** Animals received 0.75% H₂O₂ in drinking water and 100mg/kg. B.W of L-Carnitine orally for 60 days; **T3:** Animals received 0.75% H₂O₂ in drinking water and 1.5 mg/kg B.W of sitagliptin orally for 60 days; **T4:** Animals received 0.75% H₂O₂ in drinking water and 50 mg/ kg B.W of L-Carnitine and 0.75 mg/kg of sitagliptin orally for 60 days; Different small letters vertically represent significant difference within group (p<0.05) vs. zero time; Different capital letters horizontally represent significant difference between groups (p<0.05) vs. control.

Table 4: Effect of L-carnitine or/and sitagliptin on serum low density lipoprotein-cholesterol (LDL-c) concentration (mg/dl) in 0.75% H₂O₂ treated male rats

Days	Groups				
	C	T1	T2	T3	T4
Zero time	45.52±1.884 A a	46.46±1.336 A c	46.06±2.262 A b	47.28±1.047 A b	45.69±1.486 A b
30 days	44.83±1.633 D a	63.70±0.956 A b	56.04±1.267 B a	51.91±0.921 C a	49.26±0.443 C a
60 days	44.89±1.389 BC a	93.92±0.737 A a	47.20±0.414 B b	44.34±0.905 BC c	43.91±0.626 C b

LSD = 3.22; Values are expressed as mean ± SE, n = 7 each group; **C:** Control group; **T1:** Animals received 0.75% H₂O₂ in drinking water for 60 days; **T2:** Animals received 0.75% H₂O₂ in drinking water and 100mg/kg. B.W of L-Carnitine orally for 60 days; **T3:** Animals received 0.75% H₂O₂ in drinking water and 1.5 mg/kg B.W of sitagliptin orally for 60 days; **T4:** Animals received 0.75% H₂O₂ in drinking water and 50 mg/ kg B.W of L-Carnitine and 0.75 mg/kg of sitagliptin orally for 60 days; Different small letters vertically represent significant difference within group (p<0.05) vs. zero time; Different capital letters horizontally represent significant difference between groups (p<0.05) vs. control.

Table 5: Effect of L-carnitine or/and sitagliptin on Serum high density lipoprotein-cholesterol (HDL-c) concentration (mg/dl) in 0.75% H₂O₂ treated male rats

Days	Groups				
	C	T1	T2	T3	T4
Zero time	30.84±0.848 A a	30.70±0.601 A a	29.68±0.674 A b	29.90±0.760 A a	30.18± 0.599 A ab
30 days	31.21±1.189 A a	25.21±0.897 C b	28.15±0.578 B b	27.60±0.703 B a	28.67±0.401 B b
60 days	31.51± 0.392 A a	22.54±0.794 C c	32.34±0.287 A a	29.44±0.457 B a	31.40±0.201 A a

LSD = 2.31; Values are expressed as mean ± SE, n = 7 each group; **C:** Control group; **T1:** Animals received 0.75% H₂O₂ in drinking water for 60 days; **T2:** Animals received 0.75% H₂O₂ in drinking water and 100mg/kg. B.W of L-Carnitine orally for 60 days; **T3:** Animals received 0.75% H₂O₂ in drinking water and 1.5 mg/kg B.W of sitagliptin orally for 60 days; **T4:** Animals received 0.75% H₂O₂ in drinking water and 50 mg/ kg B.W of L-Carnitine and 0.75 mg/kg of sitagliptin orally for 60 days; Different small letters vertically represent significant difference within group (p<0.05) vs. zero time; Different capital letters horizontally represent significant difference between groups (p<0.05) vs. control.

groups T2, T3 and T4 with mean values of (32.34±0.287, 29.44±0.457 and 31.40±0.201) respectively, comparing to the mean value in T1 group (22.54±0.794). Synergistic effect of combination of L-carnitine and sitagliptin was clar-

ified at day 60 and the values in this group (T4) succeeded to restore HDL-c concentration value to the corresponding value in the control (31.51±0.392) at the end of the experiment.

diabetic rats (Tremblay et al., 2011; Saker, 2013) as well as in uncontrolled diabetes (Chawla et al., 2014).

Concerning lipid profile, the result of the present study documented the well-known fact that H_2O_2 is one of the reactive oxygen species which has a direct effect on the level of plasma TC, TAG and atherogenic lipoproteins. The results of this study are in accordance with the result of other workers (Khudaier, 2010; Al-Kennany and Khafaf, 2010; Zeklabi, 2011). The postulated oxidative change in the liver due to H_2O_2 exposure may result in alterations in sterol synthesis, leading to increased serum cholesterol levels with concurrent increases in serum phospholipids and changes in the ratios of their saturated to unsaturated fatty acids (Sadeek and Abd El-Razek, 2010).

Partial deficiency of lipoprotein lipase (the key enzyme determining the removal rate of TG from plasma), associated with increased output of lipoprotein from the liver may contribute to the elevation of serum TG level in H_2O_2 treated group (Fantiappie et al., 1989). Besides, increment of TAG level in animals received H_2O_2 in the present study may be due to an increase in serum VLDL-c level which acts as a carrier for the TAG in the plasma (Criqui and Golomb, 1998).

Serum HDL-c level was reported to be inversely correlated with serum VLDL-C, TG level, both in normolipidemic and hyperlipidemic subject (Gaziano et al., 1997). Results in group T2 explained that supplementation of L-carnitine had improvement effect on lipid profile (decrease in serum TC, LDL-c, TAG and VLDL-c concentrations and significant increase in HDL-c concentration) as compared with H_2O_2 (T1) group values. L-carnitine supplementation has been significantly reduced LDL-c, TAG and elevated HDL-c concentration by many investigation (Shojaei et al., 2011; Emami et al., 2012; Wasserstain, 2013; Eshghinia et al., 2014).

Interestingly, the reduction of total cholesterol contents in plasma of oxidative stressed rat supplemented with L-carnitine were attained mostly by a decrease of cholesteryl esters rather than by a decrease of free cholesterol (Tanaka et al., 2004). Also, L-carnitine may improve dyslipidemia through elevation in mitochondrial transport of FFA (carnitine shuttle) and reduction the FFA availability for TAG synthesis. This could decrease synthesis of triacylglycerol and VLDL-c cholesterol and likely increase mitochondrial β -oxidation of fatty acids (Hongu et al., 2003). Elevation in mRNA expression of acyl CoA synthase and Carnitinepalmitoyltransferase and depression in hepatic acyl CoA transferase mRNA expression in the liver could be the possible mechanism of hypolipidemic effect of L-carnitine (Mun et al., 2007). Sitagliptin significantly lowered the circulating cholesterol, triglycerides and LDL-cholesterol, with a significant increase in the HDL-cholesterol in

Beyond its glycemic control, DPP-4 inhibitors improve blood pressure, lipid profiles, and quality of life (QOL) in patients with T2DM (Kutoh and Yamashita, 2012; Sakamoto et al., 2013). Sitagliptin medication decreased serum levels of total cholesterol and triglyceride (Qin et al., 2005; Monami et al., 2012; Picatoste et al., 2013). A decrease in postprandial triglycerides with sitagliptin therapy was also reported by (Tremblay et al., 2011; Kubota et al., 2012). Multiple action mechanisms are assumed for the triglyceride-lowering effect of sitagliptin, including inhibited TAG absorption from the intestines, inhibited VLDL-c release from the liver, and decreased blood glucose levels and accompanying improvements in metabolic status (Monami et al., 2011; Cobble and Frederich, 2012). DPP-4 inhibitors treatment reduced the level of chylomicrones apo-B-48 and so it hinders intestinal TAG absorption. Besides, increased the level of norepinephrine and thereby increased in lipolysis of adipose tissue and fatty acid oxidation in the musculature are documented by DPP-4 inhibitors (Foley and Jordan, 2010).

Treatment with DPP-4 inhibitors increase the levels of Glucagon like peptide 1 (GLP-1), (Gutzwiller et al., 2004), such elevation in GLP-1 decreases the intestinal lymph flow and reduces triacylglycerol absorption and apo-B and apo-A IV production. Besides, DPP-4 inhibitors has been found to reduce hepatic expression of genes important for cholesterol synthesis (Flock et al., 2013). Sitagliptin reduced atherosclerosis progression in hyperlipidemic rabbits via its effect on lipid parameters and interfering with inflammatory and oxidative stress pathway (Zeng et al., 2014). However molecular and cellular mechanisms of how this drug lower lipid level (e.g. effects on synthesis secretion, absorption or clearance) will be an interesting research topic.

CONCLUSION

In conclusion, the results of this study documented the ameliorative role of L-carnitine or/and Sitagliptin against dislipidemia induced by H_2O_2 in male rats.

CONFLICT OF INTEREST

No conflict of interests are declared by authors for the contents in the manuscript.

AUTHORS CONTRIBUTION

Khalisa Khadim Khudair designed the experiment, gave technical support and interpreted the data. Ahmed Talib

Al –Doseri performed the experiments and wrote the paper.

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