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Original Article

Synergistic antihyperlipidemic effect of alpha lipoic acid with rosuvastatin in high-fat diet-induced hyperlipidemic rats

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Abstract

The main objective of this study was to assess alpha lipoic acid supplementation with rosuvastatin (lipid-lowering agent) for reducing serum total lipid levels in high-fat diet-hyperlipidemia in rats. For this purpose, twenty- five rats were randomly divided into five groups of normal control (n=5), hyperlipidemic (n=20) groups submitted to the following treatments: A: normal rats; B: hyperlipidemic rats; C: hyperlipidemic rats with rosuvastatin (0.2 mg/kg); D: hyperlipidemic rats with alpha lipoic acid (10 mg/kg); E: hyperlipidemic rats with a combination of rosuvastatin (0.2 mg/kg) plus alpha lipoic acid (10 mg/kg). The lipid profile of these animals was measured at the end of the study (one month). Using alpha lipoic acid alone significantly decreased the lipid profile ($p<0.05$). The combination of alpha lipoic acid with rosuvastatin is the most effective for reducing serum lipid levels in animals with hyperlipidemia. As a result, alpha lipoic acid supplementation improved the lipid-lowering effect of rosuvastatin.

Keywords: antihyperlipidemic, rosuvastatin, alpha lipoic acid, high-fat diet.

Introduction

Dyslipidemia is a term referring to a clinical condition in which there is an increase in plasma lipids (one or more), including cholesterol, triglyceride, cholesterol esters, and phospholipids. It may involve plasma lipoproteins (increased low-density lipoprotein, very low-density lipoprotein, and decrease in high-density lipoproteins) levels [1, 2].

About 100 million in the U.S. have elevated LDL-C levels, and about 31 million have more than 240 mg/dL cholesterol levels. Dyslipidemia usually doubles the risk of cardiovascular disease compared to people with normal cholesterol levels [3].

Dyslipidemia is classified as primary (familiar) due to a genetic defect and secondary (acquired) as a consequence of several chronic diseases, including chronic kidney disease, diabetes mellitus, and hypothyroidism, in addition to alcohol consumption and some medication like β –blockers, corticosteroid, oral contraceptive [4].

High-fat diet, smoking, obesity, and lack of exercise consider an s changeable risk factors for dyslipidemia. In contrast, others like diabetes mellitus, hypothyroidism, hypertension, and chronic kidney disease are secondary risk factors for developing dyslipidemia [3].

Since dyslipidemia has no clinical symptoms, this reason called a silent killer, so the main successful diagnosis is lipid profile screening (LDL, HDL, TG, VLDL, T- cholesterol) for males aged more than 35 years, females aged 45 years without a history of CVD and male aged more than 25 years, female aged 35 years if they have risk factors [5, 6].

Lifestyle modification, diet change, weight control, regular exercise, and cessation of smoking and alcohol successfully decrease serum cholesterol, LDL, and TGs by 30–40% in most patients [7].

The HMG-CoA reductase inhibitors (statins) consider the drug of choice in the reduction of low-density lipoprotein -cholesterol (the target of LDL-C is 100 mg/dl) (Syad *et al.* 1998). Statins are the most potent,

effective, safest, well tolerability and the lowest profound adverse effect; however, hepatotoxicity and myopathy are the worried complications of statins observed in clinical studies in patients who received a placebo the cause is still unclear; overdose of statins or multi drugs use, the renal and hepatic defect may explain this toxicity [8].

Rosuvastatin is a new generation of HMG-CoA reductase inhibitors with the most significant effect on LDL–cholesterol; it has low extrahepatic penetration, low cyto3A4 interaction, and low lipophilicity due to the presence of sulfonamide group, which increase ionic interaction with HMG-Co A enzyme and improved its efficacy [9].

The efficiency and safety of rosuvastatin *versus* atorvastatin in type 2 diabetic patients show that rosuvastatin significantly reduces LDL-C, Apo B, and total cholesterol. The favorable effect of rosuvastatin compared with atorvastatin in reducing LDL-C was demonstrated in (use of rosuvastatin *versus* atorvastatin in type 2 diabetes melitus) study [6, 9].

Alpha lipoic acid is a potent natural antioxidant synthesized in the mitochondria of all cells in the body and can be obtained from animal and plant sources [10].

Alpha lipoic acid (ALA), or thioctic acid as a trading name, is chemically found as R and S enantiomers. Only the R form is biologically active [11]. The lipid-lowering effect of alpha lipoic acid was studied on various animal models, and some of these studies show the efficacy of ALA in reducing total LDL cholesterol and TGs and raising HDL cholesterol in both normal and high-fat diet rat models [12].

Rosuvastatin–Alpha lipoic acid combination has improved the serum lipid profile near the normal range compared to rosuvastatin alone; also, alpha lipoic acid reduced the adverse effects of statins on liver function [13].

Thus, this work aimed to study alpha lipoic acid's potential role in enhancing the efficacy of rosuvastatin (lipid-lowering agent).

Material and methods

Chemicals and reagents

Cholesterol was supplied by Sigma-Aldrich Co., St. Louis, CA, USA; rosuvastatin was supplied by AstraZeneca, U.K; alpha lipoic acid was supplied by Evapharma, Egypt and coconut oil was supplied by ABC, Spain.

Animals

This study was conducted from March 2022 to April 2022 at the University of Basrah, College of Pharmacy's animal house. Twenty-five Swiss adult male rats, around 175–200 gm, had been brought from the animal house at the University of Basrah College of veterinary medicine. Rats were divided into five groups (n=5). Rats were preserved in isolated plastic cages in the animal room for a week under measured circumstances of 22±4°C, 30% humidity and a twelve-hour dark/twelve-hour light cycle. The animals had unlimited access to standard chow and water until a high-fat diet was supplied throughout the study. The animal ethics committee at the University of Basrah, Iraq (No. 2013/32) authorized all animal handling measures reported in this work.

Methods

Induction of hyperlipidemia in rats

The high-fat diet (HFD) was prepared by mixing 2 g cholesterol as a dry powder with 16 g coconut oil and two egg mixed and completed to 100 g with chow, then put in the oven for 10 min. This diet was routinely used for feeding the rat for one month with minor modifications [14–16].

Study design

The experimental rats in this study were separated into five groups (n=5); one included healthy rats and served as the normal control group, while the rest were high-fat diet-induced hyperlipidemic rats models. This study lasted for four weeks, in which rats received daily oral treatments of distilled water, rosuvastatin alone, or with the alpha lipoic acid combination. These groups of rats were divided as follows:

Group A: normal control (water) + normal chow, Group B: negative control (water) +HFD, Group C: alpha lipoic acid 10 mg/kg +HFD, Group D: rosuvastatin 0.2 mg/kg +HFD, group E: rosuvastatin and alpha lipoic acid combination +HFD. Rosuvastatin and alpha lipoic acid were dissolved in the water and administered to rats via a stomach gavage tube. Lipid profile and liver function test were determined after four weeks.

Blood samples collection

At the end of the study, all experimental animals were fasted overnight and inhaled with chloroform as an anesthetic agent. The collection of blood samples

Table 1: Serum lipid levels in normal, negative, treated groups.

Group	Cholesterol	Triglycerides	HDL-Cholesterol	VLDL-Cholesterol	LDL-Cholesterol
A	78.31±7.40	72.05±5.24	30.16±4.27	14.40±2.25	33.82±4.24
B	138.72±14.83†††	122.26±13.31†††	15.61±2.68†††	24.42±4.21†††	98.7±6.25†††
C	128.08±11.50*	113.60±8.51*	26.36±3.26**	22.63±3.11*	79.12±7.51**
D	86.26±8.23***	87.53±6.32***	41.12±5.41***	17.41±3.25***	27.73±3.26***
E	72.30±5.31***	82.40±4.89***	44.05±4.62***	16.40±2.52***	11.93±2.04***

Note: Data expressed as means±SD. † – p<0.05; ††† – p<0.01; ††† – p<0.001 compared to normal control; * – p<0.05; ** – p<0.01; *** – p<0.001 compared to negative control.

was done by cardiac puncture. The blood was saved in gel tubes to collect serum after centrifugation for 15 min at 4000 rpm. Then serum samples were frozen till biochemical assays were determined.

Biochemical parameters assays

An automatic biochemical analyzer measured serum (TC, TGs, HDL-C, LDL-C, LDL-C, VLDL-C, LDL/HDL) (Cobas c 111, Roche). The liver function tests, which include ALT (alanine transaminase) and AST (aspartate transaminase), were measured in serum by standard diagnostic kits utilizing enzymatic colorimetric approaches (Bio Lab; France). The serum levels of (glutathione, catalase, and superoxide dismutase) were estimated using ELISA kits (Bioassay Technology Laboratory, China).

Statistical analysis

The results of all trials in this study are stated as Mean±SD. Statistical analysis was carried out by one-way ANOVA pursued by Dunnett's t-test. The probability (P) values less than 0.05 were considered statistically significant.

Results

Serum total cholesterol

Table 1 and Figure 1 show serum cholesterol levels among different experimental groups after one-month treatment. The result was a significant reduction (p<0.05) in serum cholesterol of group C (alpha lipoic

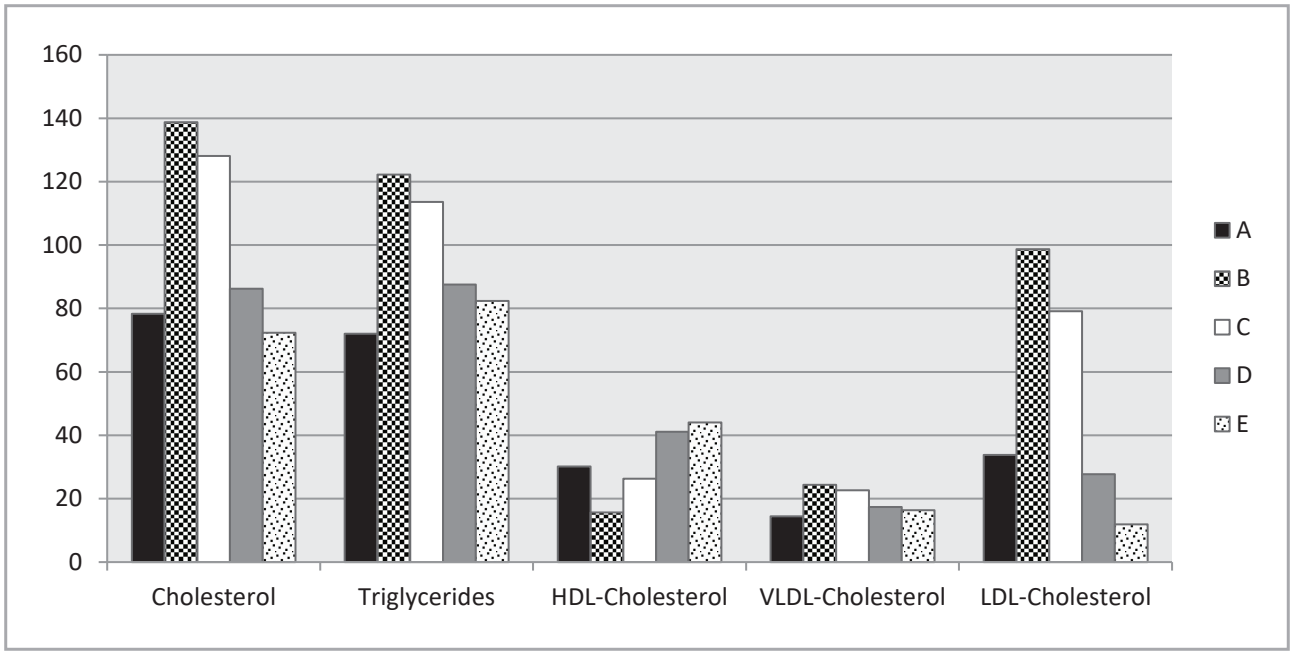

Figure 1: Serum lipid level of normal, negative, treated groups.

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acid alone) as compared with group B (negative control) (128.08±11.50 *vs*. 138.72±14.83), a very high significant reduction (p<0.001) in group D (rosuvastatin alone) and group E (combination of rosuvastatin and alpha lipoic acid) 86.26±8.23, 72.30±5.31) as compared with negative control (138.72±14.83).

Serum triglycerides

Serum triglyceride levels in all different groups are shown in Table 1 and Figure 1; the negative control (group B) exhibits a very highly significant increase in TGs (p<0.001) after four weeks compared with the healthy group (group A). However, the group of rats treated by alpha lipoic acid alone (group C) showed a significant reduction (p<0.05) in serum TGs (113.60± 8.51 mg/dL *vs*. 122.26±13.31 mg/dL) compared to negative control. In contrast, the combination of alpha lipoic acid plus rosuvastatin (group E) shows a very high significant reduction (p<0.001) in serum TGs (82.40±4.89 mg/dl *vs*. 122.26±13.31 mg/dl) compared to the negative control.

Serum HDL – Cholesterol

In Table 1 and Figure 1, we could notice a highly significant (p<0.01) elevation in serum HDL–C after 4-week treatment with alpha lipoic acid (group C) compared with negative control (group B) (26.36±3.26 *vs*. 15.61±2.68) and a very high significant (p<0.001) elevation with both groups D and E (rosuvastatin, rosuvastatin plus alpha lipoic acid respectively) (41.12±5.41, 44.05±4.62) compared with negative control (15.61±2.68).

Serum VLDL – Cholesterol

Table 1 and Figure 1 show a significant (p<0.05) reduction in serum VLDL-C when treated with alpha lipoic acid for four weeks compared with the hyperlipidemia group and a very high significant (p<0.001) reduction in serum VLDL-C of groups D (rosuvastatin alone) and group E (combination of rosuvastatin plus alpha lipoic acid) which show result near normal.

Serum LDL – Cholesterol

As clarified in Table 1, Figure 1, there was a highly significant (p<0.01) reduction in serum LDL-C after 4-week treatment with alpha lipoic acid and a very high significant (p<0.001) reduction in serum LDL-C in both group D and E (rosuvastatin, rosuvastatin plus alpha lipoic acid respectively) in comparison with hyperlipidemia group.

Serum AST (aspartate transaminase)

As shown in Table 2 and Figure 2, there was a highly significant (p<0.01) reduction in serum AST levels of group C (lipoic acid alone) and D (rosuvastatin alone). At the same time, there was a very high significant reduction in serum AST level in group E (alpha lipoic acid and rosuvastatin combination) compared with the B group (negative control).

Serum ALT (alanine transaminase)

Table 2 and Figure 2 show a very high significant (p<0.001) reduction in ALT serum levels of all treated groups (C, D, and E) compared to the negative group (B).

Serum GSH level

As clarified in Table 2 and Figure 3, there was a highly significant elevation (p<0.01) in the serum GSH level of both Groups C and D (alpha lipoic acid, rosuvastatin), respectively, and a very highly significant

Table 2: Liver enzymes, antioxidant enzymes status in normal, negative, treated groups.

Group	AST (U/L)	ALT (U/L)	GSH (unit/mg protein/min)	SOD (unit/mg protein/min)	CAT (unit/mg protein/min)
A	58.14±5.20	65.43±6.07	95.14±6.23	0.65±0.12	1.35±0.82
B	148.27±8.47†††	139.11±7.61†††	59.23±4.92†††	0.33±0.08†††	8.36±1.12†††
C	96.24±4.71**	105.12±6.48***	73.55±4.17**	0.53±0.11***	3.20±0.95***
D	95.85±6.91**	97.04±7.61***	68.04±5.76**	0.43±0.68**	5.23±1.08**
E	83.22±5.83***	85.71±4.41***	76.80±3.84***	0.54±0.11***	3.60±0.58***

Note: Data expressed as means±SD. † – p<0.05; †† – p<0.01; ††† – p<0.001 compared to normal control; * – p<0.05; ** – p<0.01; *** – p<0.001 compared to negative control.

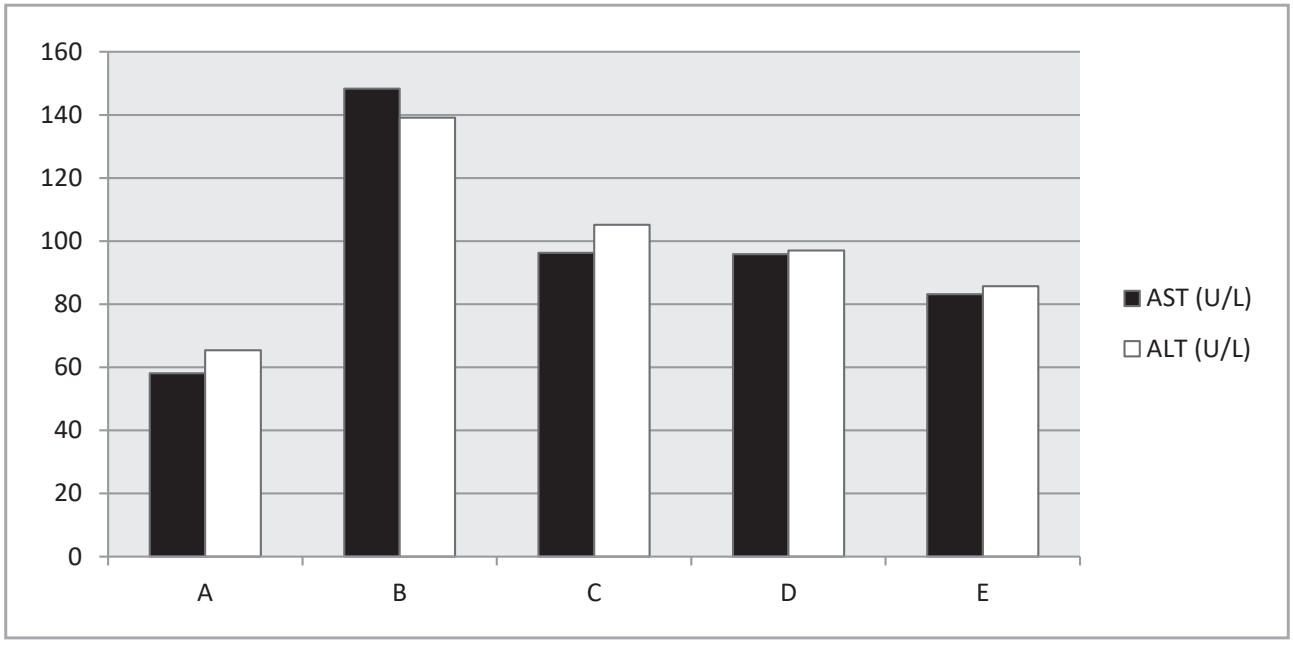

Figure 2: Liver enzymes status in normal, negative, treated groups.

elevation (p<0.001) in serum level of GSH in group E (combination of alpha lipoic acid and rosuvastatin) as compared to group B (negative group).

Serum SOD level

Table 2 and Figure 4 show there was a very high significant elevation (p<0.001) in the serum level of SOD when treated rats with alpha lipoic acid (group C) and a highly significant elevation of (p<0.01) in serum level SOD with rosuvastatin treatment (group D), a very high considerable elevation (p<0.001) in combination therapy (group E) when compared to hyperlipidemia group.

Serum CAT level

From the result of Table 2 and Figure 5, a very high significant reduction of (p<0.001) in the serum level of CAT in Group C, a highly significant decrease of (p<0.01) in the serum level of CAT in Group D, a very high significant reduction of (p<0.001) in the serum level of CAT in group E as compared with group B.

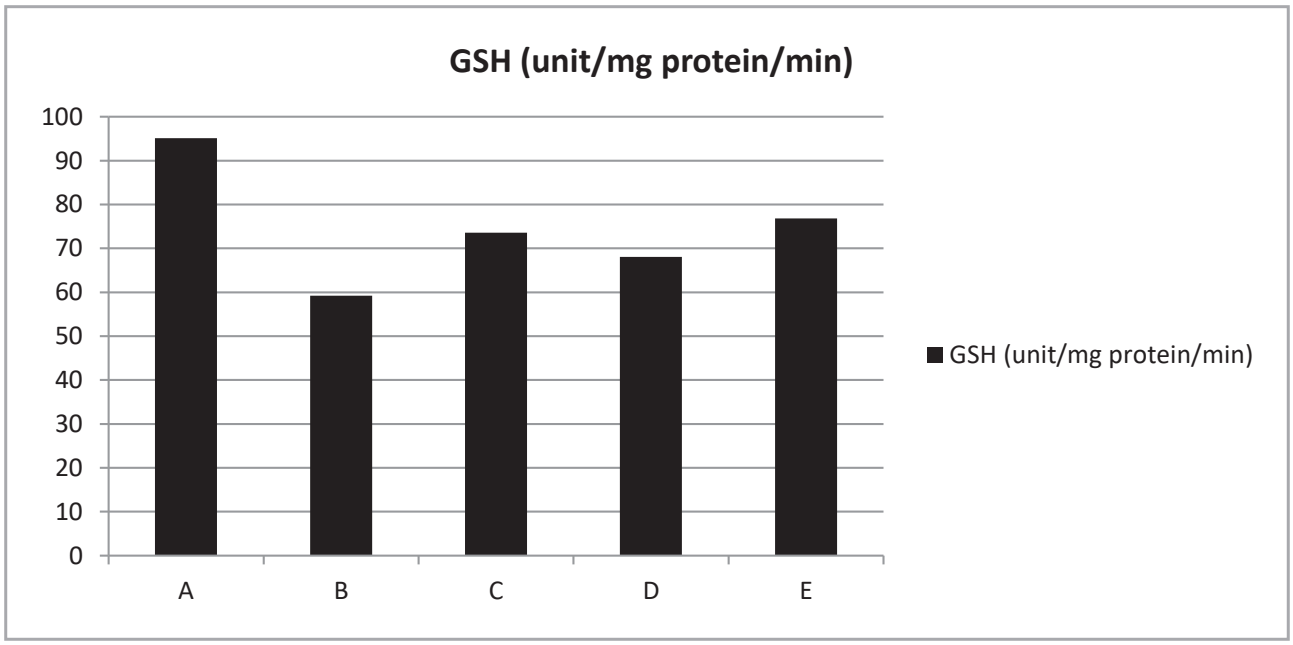

Figure 3: Glutathione reading in normal, negative, treated groups.

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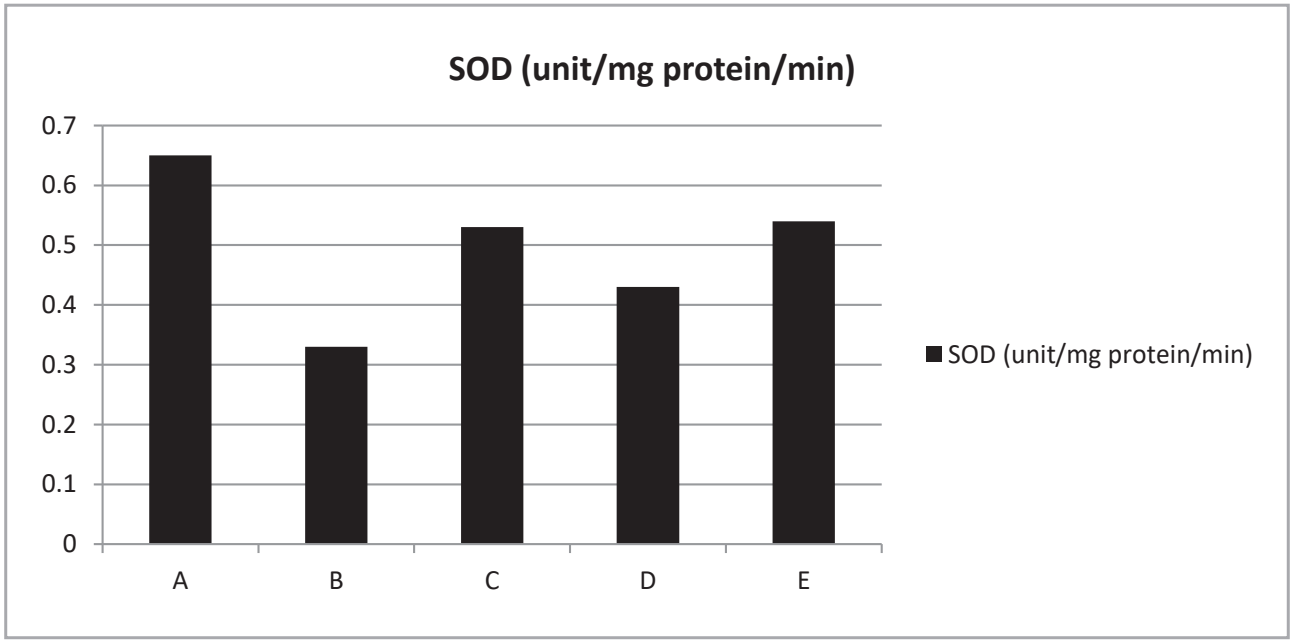

Figure 4: Superoxide dismutase reading in normal, negative, treated groups.

Discussion

Induction of dyslipidemia in experimental animals for research can be achieved by using rats more closely to the human model. A high-fat diet is a formula of oral feeding with high-fat content greater than 10% used for dyslipidemia induction. The main content is egg, coconut oil, pure crystalline cholesterol, and pellets; the formula is usually rich in fat and cholesterol more than protein and carbohydrate to achieve a better effect on lipid profile. This formula is widely used in America and Europe but still need more use in some area due to the high cost of cholesterol and its unavailability in the local market [17, 18].

The procedure of feeding rats with a high-fat diet has an important effect on the success of dyslipidemia induction; several studies using the oral gavage route resulted in unwanted side effects, such as allergies, which limit the uses of this route [19].

Our present study follows normal oral feeding by mixing the main content of a high-fat diet with chow, and the effect of this procedure was notified on lipid profile after four weeks; as illustrated in Table 1 and Figure 1, a significant elevation in (serum cholesterol,

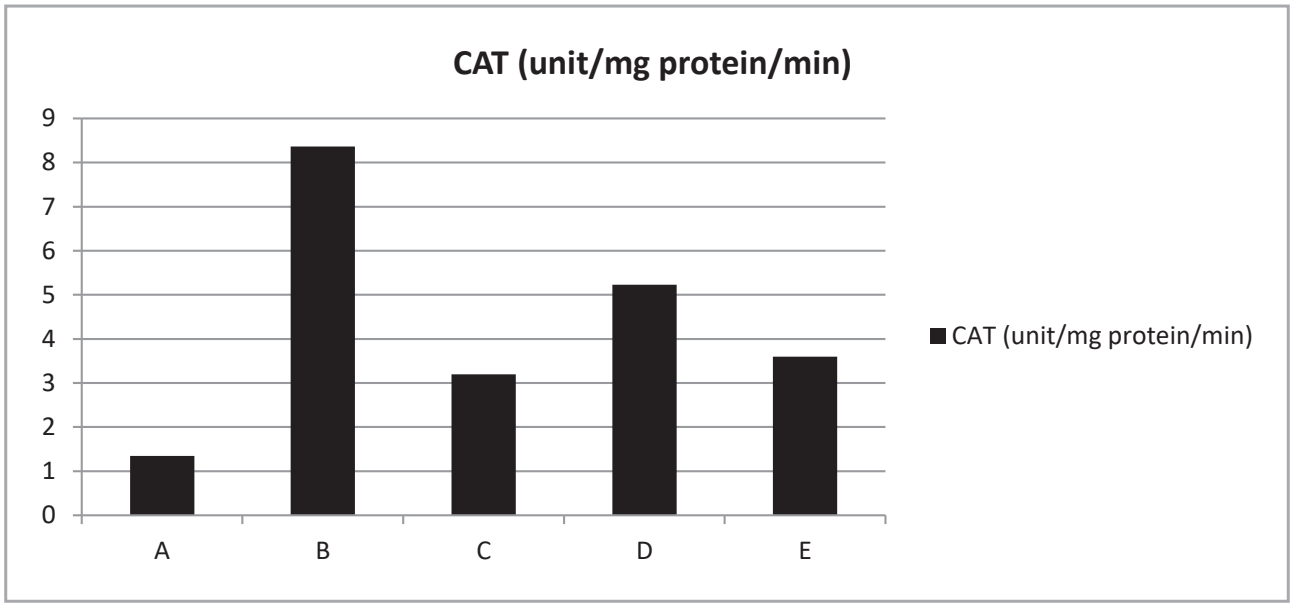

Figure 5: Catalase levels in normal, negative, treated groups.

triglycerides, LDL-C, VLDL-C) and a substantial reduction in HDL-C in the hyperlipidemic rats when compared with normal.

Oral treatment with 0.2 mg/kg of rosuvastatin daily for four weeks resulted in significant ($p<0.001$) reductions in serum cholesterol, triglycerides, LDL-C, VLDL-C, and a significant elevation in HDL-C.

However, dyslipidemia is usually associated with oxidative stress and ROS, leading to lipid peroxidation, oxidative cell injury, and decreased antioxidant enzyme activity in early dyslipidemia development [20].

Our findings agree with this theory as there was a significant reduction in both GSH and SOD and an elevation in CAT levels in dyslipidemic rats compared with normal. It is a logical point of view to add antioxidants to the treatment regime.

Alpha lipoic acid is an ideal supplement due to its anti-inflammatory and antioxidant properties. Oral treatment with alpha lipoic acid has been clinically assessed in diabetes mellitus, schizophrenia, Alzheimer's disease, and cancer. Alpha lipoic acid ameliorates oxidative stress in this clinical condition [21].

Alpha lipoic acid shows a significant effect on lipid profile and a very high significant effect on oxidative enzymes when used alone, so it has a curative and protective effect from dyslipidemia development and a beneficial effect in preventing metabolic disorders caused by high-fat diet [12].

Alpha lipoic acid supplementation reduces lipid peroxidation by improving the lipid profile (reducing TC, TGs, and LDL); Furthermore, lipid peroxidation considers the main source of ROS production; thus, alpha lipoic acid can scavenge and deal with it, also their ability to chelate with heavy metals such as copper, iron and other metals, which cause oxidation for many substances. Moreover, alpha lipoic acid is capable of preventing the oxidation of vitamin C catalyzed by copper and inhibiting lipid peroxidation by copper; in addition, alpha lipoic acid has been able to regenerate another antioxidant as vitamin C and E by their radical forms, and as we know that vitamin E is the primary antioxidant in the protection of cell membranes which is the target of lipid peroxidation caused by ROS [22, 23].

Our study shows a promising antioxidant effect of alpha lipoic acid by ameliorating the levels of (GSH, CAT, and SOD). This impact increased notably when combined with rosuvastatin as a result of our present study.

Both liver enzymes (ALT and AST) are augmented in the dyslipidemia group; the underlying mechanism of liver dysfunction in dyslipidemia is still unclear; the reason may be regarded as overcharged nutrient content [15]. Furthermore, the deposition of lipid particles on the liver cell may contribute to liver tissue inflammation and the release of free radicals, which lead to liver tissue cell injury and liver enzyme outside [24]. The last interpretation agrees more with our findings which revealed a significant reduction in the level of AST and ALT when dyslipidemic rats were treated with alpha lipoic acid alone; however, a greater effect was notified with the combination of alpha lipoid acid and rosuvastatin, as clarified in Table 2 and Figure 2.

Conclusion

This study concluded that supplementation of alpha lipoic acid has a considerable role as an antihyperlipidemic, antioxidant impacts and amelioration of liver function. Combining rosuvastatin with alpha lipoic acid reduces serum lipid in hyperlipidemic rats' models more efficiently, even in the shortest time, than treatment with individual compounds.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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