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ORIGINAL ARTICLE

INFLUENCE OF COENZYME Q10 ON HYPERLIPIDEMIA INDUCED IN MICE

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Summary

Background and objectives: hyperlipidemia is the hallmark of cardiovascular diseases, namely hypertension, ischemic heart diseases, and strokes. Treatment should be satisfactory to tackle the lipid disorder and maintain the circulatory normal lipid profile. Many factors/cofactors coordinate to maintain lipid levels within normal to avoid subsequent hazards associated with hyperlipidemia. Coenzyme Q10 is a ubiquitous endogenous biomolecule that plays an important biological role in the lipid catabolic pathway. The goal of the study is to define the role of Coenzyme Q10 in hyperlipidemic mice model induced manually.

Methods: to do so, a diet based hyperlipidemia state was induced in mice and they were distributed into different groups to conform with our study objectives. A Coenzyme Q10 treated group was compared to the negative control group and the positive control group was used as well.

Results: The biochemical and histological outcomes declared that Coenzyme Q10 has important lipid-reducing effects which are parallel or even superior to lipid reducing drugs (e.g. Rosuvastatin). Conclusion of the present study addressed the lipid-lowering properties of Coenzyme Q10 in a newly induced hyperlipidemia mouse model bestowing the use of Coenzyme Q10 as add-on adjuvant therapy in a high-risk group or as a monotherapy in a prophylactic group.

Key words: Coenzyme Q10; Rosuvastatin; Hyperlipidemia; Oxidative stress

Introduction

The progression of atherosclerosis is traditionally believed to be due to dyslipidemia. Major causes of cardiovascular disease (CVD) are myocardial infarction, stroke (related complications) and atherosclerosis, an inflammatory disease of the vascular system, since the incidence of risk factors is increasing in developing countries, such as obesity and diabetes (1). The global incidence of CVD is expected to increase and put a higher economic burden on health care systems around the world. Therefore, CVD causes around one-third of the world's estimated annual global deaths (2).

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Coenzyme Q10 (CoQ10) is a fat-soluble product primarily produced by heart, liver, kidney, pancreatic and muscle mitochondria, in which utilized for the production of large amounts of ATP (3). Dyslipidemia, particularly hypercholesterolemia and low HDL-cholesterol levels, impair mitochondrial activity (4) result in an enhancing the production of reactive oxygen species and free radicals that lead to chronic inflammation and endothelial dysfunction (5). Also, Q10 has many extra mitochondrial functions, including anti-inflammatory properties, gene expression modulation, and lipid bilayer membrane stabilization explain its role in aging and age-related disorders such cardiovascular disease, renal failure, and neurological diseases (6, 7). Consequently, CoQ10 can boost endothelial dysfunction and exert a positive inotropic effect on the myocardium, improve cardiac ATP production and cardiac output. Additionally, CoQ10 can also have a decreasing impact on blood pressure (8).

Owing to its involvement in many cellular functions, CoQ10, which is known as ubiquinone, is a multifunctional chemical (9). CoQ10 has been advocated as a complementary/alternative treatment for CVD in general, and atherosclerosis in special (10). The objective of this research is a focus on the potential function of coenzyme Q10 in reducing elevated blood lipids and ameliorating their adverse effect on the body, especially the liver and kidney histology in comparison with stander statin drug (Rosuvastatin) on albino Swiss mice.

Materials and methods

Laboratory animals

The study is carried out on 20 female and male albino Swiss moues weighing between 25- 35 g. They were bought from the Laboratory Animal House of Veterinary Medicine College / Mosul University. The animals were placed in individual animal house plastic cages with wood chips; natural light, ambient temperature, and automated ventilation are all factors to consider in a controlled animal laboratory at the University of Mosul's College of Dentistry. Before any trial, the animals were allowed to acclimate for a week.

Grouping of experiments and induction of hyperlipidemia

The mice were split into 4 experimental groups (n=5) involving normal control groups and model (hyperlipidemic) groups. Group A: was fed a basal diet, including forage yellow corn 55%, soybean cake 20%, forage wheat, 14%, animal protein 10%, salt 0.5%, lime 0.5% and having unlimited access to water, ad libitum and acted as a (normal control group). Group B: In both sexes of albino Swiss mice, hyperlipidemia was created by giving them a high-fat diet comprising of: wheat flour, corn flour, barley flour, animal protein, fatty milk powder, salt (34%,25%,20%,10%,10% and 1%) respectively, for kneading, use vegetable oil and water, as well as potable water with 1% H2O2 (model control group) (11). The precision of hyperlipidemia in mice fed a high-fat diet was tested after three months of feeding to guarantee that the mice did not return to their original state. Group C: hyperlipidemic mice fed a diet rich in fat and treated with Q10 (Windmill, U.S.A.) each pill includes 400mg of CoQ10 for oral intake, (100mg/kg) for two weeks (12). Group D: hyperlipidemic mice fed a diet rich in fat and treated with Rosuvastatin (Al-TaqaddomL/ Pharmaceutical Industries/ Amman-Jordan) (7mg/kg) for 2 weeks.

Normal saline (NS) (Primeera Healthcare Private Limited/India) was used as a solvent for the preparation of Rosuvastatin suspensions (20mg of Rosuvastatin tablet dissolved in 10ml of NS) and olive oil (Turkey) was used as a solvent for the preparation of Q10 dosage (100mg of Q10 dissolved in 5ml of olive oil). After that, the mice were given 0.2 ml of Q10 and Rosuvastatin via intragastric gavage once a day for 15 days.

Plasma lipid composition analyses

A clinical biochemical analyzer was used to measure triglyceride (TG), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), and total cholesterol (TC) in plasma (Mindray, BS-120, Mindry Bio-Medical Electronics Co., Shenzhen, China). All the tests were done three times, blood samples were obtained from all animals at the baseline for the measurement of these parameters and after expiration of 3-months feeding with 10 h fasting and then at the end of the experiment for treated groups. The venous blood from the eye was obtained for lipid level testing.

Preparation of tissue for histopathological examination

Each mouse's liver and kidney were fixed in a 10% formalin solution before dehydrated with a gradual addition of alcohol solution for histological examination. Tissue samples were then cleaned before being placed in paraffin wax for sectioning. Then, the samples were sectioned and stained with hematoxylin and eosin to examine the histological alterations in comparison to the control group under a light microscope.

Statistical analysis

The study's mean and standard deviation (SD) were calculated statistically. For statistical comparisons, ANOVA and paired t-tests were used. The value of 0.05 was chosen as the level of statistical significance.

Results

The level of total cholesterol in the mice group-administered hydrogen peroxide (model control) was significantly more as well of (normal control animals). The treatment groups of animals with CoQ10 may significantly decrease TC enhancement (96.3 ± 3.2) in comparison with the model control animals (175.6± 10.5). The degree of triglyceride in the model untreated mice was greater significantly than that in normal control animals. Treated animals with CoQ10 significantly inhibit the increase of triglyceride (78.9±9.2) in comparison with the model control animals (194.0±88.0) (Table 1).

Table 1. Blood lipid parameters of the treated and control groups in mice.

		Parameters				
		Total Cholesterol mg/dl	**HDL-Cholesterol mg/dl**	**LDL-Cholesterol mg/dl**	**VLDL-Cholesterol mg/dl**	**Triglyceride mg/dl**
Groups	Normal Control	68.0 ± 6.2^{A}	70.0 ± 1.6^{A}	3.5 ± 0.5^{A}	12.5 ± 1.5^{A}	62.6 ± 7.0^{A}
	Model Control	175.6 ± 10.5^{B}	38 ± 2.6^{B}	31.7 ± 3.7^{B}	42 ± 2.9^{B}	194.0 ± 88.0^{B}
	Rusovatatin	80 ± 8.6^{A}	108.7 ± 4.9^{C}	15.6 ± 2.5^{C}	12.6 ± 1.5^{A}	69.0 ± 6.5^{A}
	Q10	96.3 ± 3.2^{C}	113.5 ± 8.8^{C}	5.1 ± 0.7^{A}	16.1 ± 2.5^{A}	78.9 ± 9.2^{A}

Different capital letters in the same column represent a significant difference with $p<0.05$.

The degree of LDL in the model control mice was greater significantly than that in normal control animals. The handling of animals with CoQ10 significantly decrease of LDL (5.1 ±0.7) in comparison with the model untreated animals (31.7±3.7). The level of VLDL in the model control group was significantly more than that in normal control animals. The handling of animals with CoQ10 significantly inhibits the increase of VLDL in comparison with the untreated mice model animals. The untreated mice had a level of HDL was significantly lower than that in normal control animals. The treatment of an animal with CoQ10 and Rosuvastatin significantly increase HDL (113.5 ± 8.8) (108.7 ± 4.9) respectively in comparison with the untreated mice (38 ±2.6) at $P < 0.05$) (Table 1).

In the normal control group (without treatment), the histological section of liver shows a normal architecture of liver tissue characterized by normal hepatocytes and sinusoids. The section of the liver in model control, showed coagulative necrosis of hepatocytes, hydropic degeneration and infiltration of inflammatory cells as foci. In the Rosuvastatin treated group, the histological section showed coagulative necrosis of hepatocytes and infiltration of polymorph nuclear inflammatory cells as foci. While in mice treated with CoQ10, the histological section showing a normal architecture of liver tissue representing the central vein, hepatocytes, sinusoids, and the portal area (Figure 1).

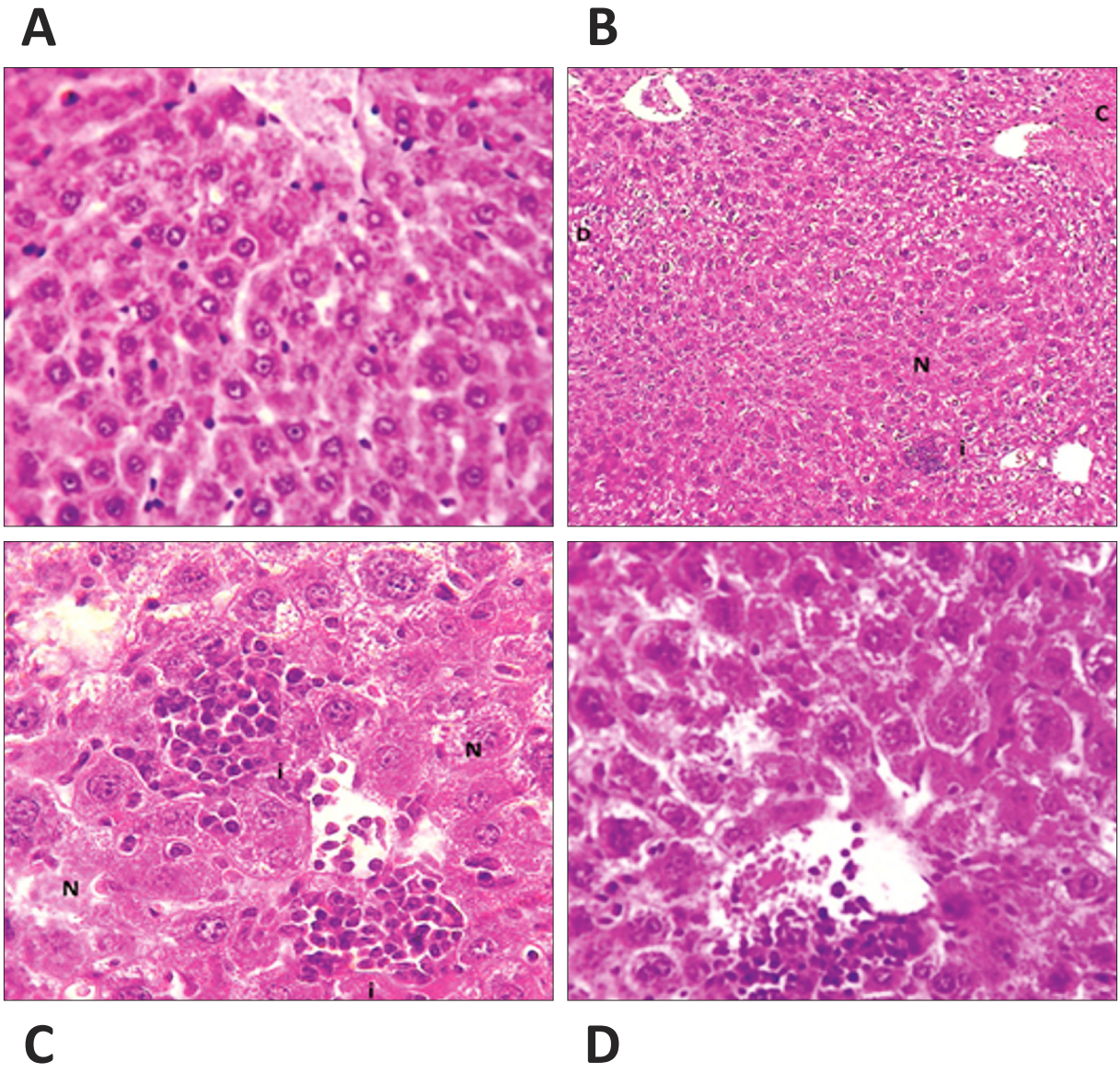

Figure 1. A: Photomicrograph of liver of the negative control group (without treatment) shows a normal architecture of liver tissue characterized by normal hepatocytes and sinusoids. HandE stain, 400X. B: The positive control group, histological section of the liver showed hydropic degeneration (D) and coagulative necrosis of hepatocytes (N), and infiltration of inflammatory cells as foci (i). HandE stain, 100X. C: Rosuvastatin treated group histological section of the liver showed coagulative necrosis of hepatocytes (N) and infiltration of polymorph nuclear inflammatory cells as a focus (i). HandE stain, 400X. D: Photomicrograph of the mice liver of CoQ10 treated group showed normal architecture of liver tissue representing by central vein (A), hepatocytes (B), sinusoids (C) and the portal area (D). HandE stain, 400X.

The histological section of the kidney of a negative control group (without treatment) shows a normal architecture of renal tissue characterized by glomeruli, proximal renal tubules and distal renal tubules. While in the positive control group, the histological section of the kidney showed interstitial nephritis represented by infiltration of polymorphonuclear inflammatory cells, the presence of poly cysts, atrophy of glomeruli, coagulative necrosis of epithelium of renal tubules and the presence of hyaline cast. In the Rosuvastatin group, the section of the kidney showed congestion of glomeruli with the normal architecture of the kidney. Also in CoQ10 group, it showed normal architecture of the kidney in the cortex area (Figure 2).

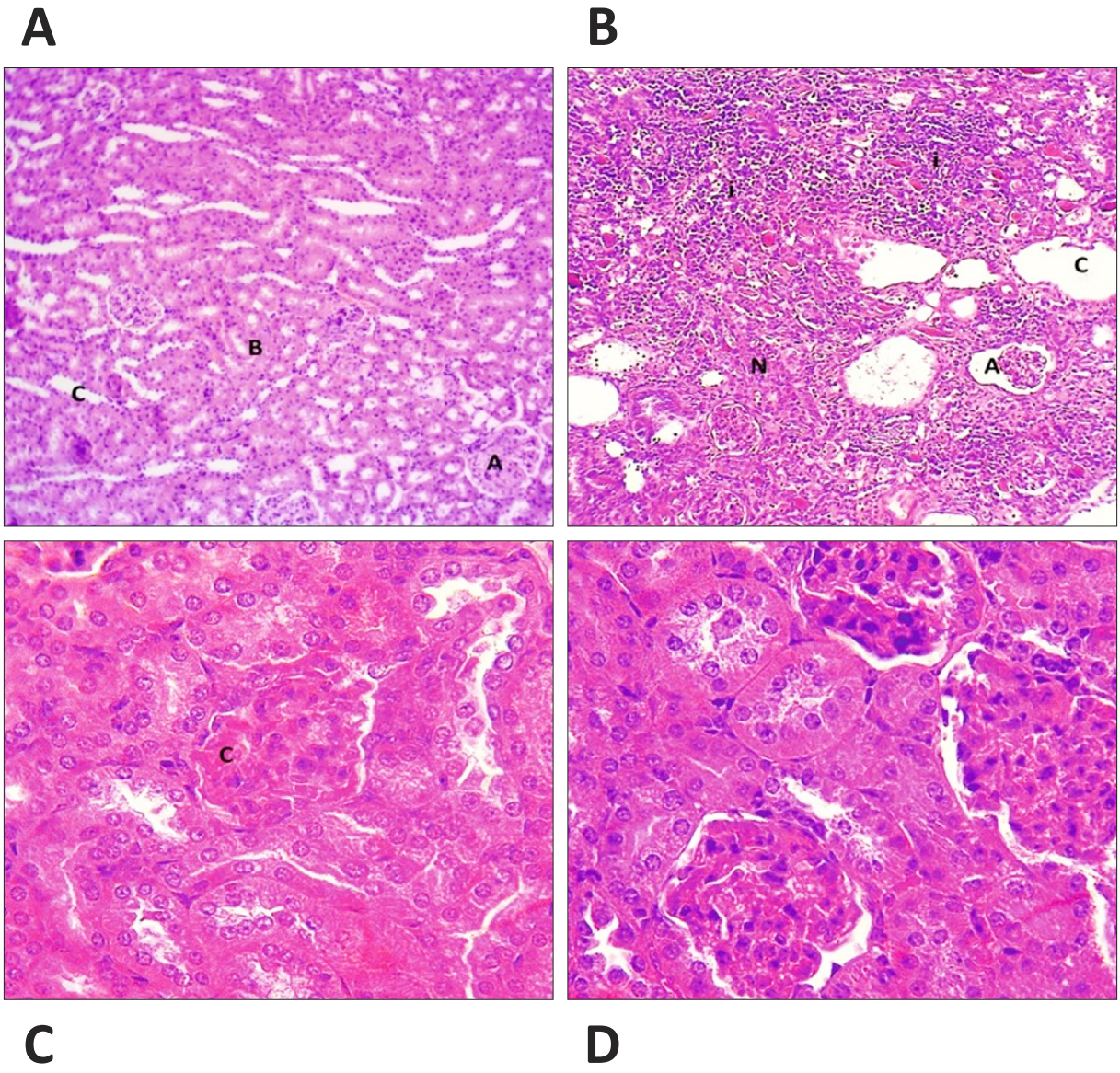

Figure 2. A: Photomicrograph of the kidney of the negative control group (without treatment) shows the normal architecture of renal tissue characterized by glomeruli (A), proximal renal tubules (B) and distal renal tubules (C). HandE stain, 100X. B: Positive control group, a histological section of the kidney showed interstitial nephritis represented by infiltration of polymorphonuclear inflammatory cells (i), the presence of poly cysts (C), atrophy of glomeruli (A), coagulative necrosis of epithelium of renal tubules (N) and the presence of hyaline cast (H). HandE stain, 100X. C: Rosuvastatin group, a histological section of the kidney showed congestion of glomeruli (C) with the normal architecture of the kidney. HandE stain, 100X. D: CoQ10 treated group, a histological section of the kidney showed normal architecture of the kidney in the cortex area. HandE stain, 400X.

Discussion

Diet-induced hyperlipidemia and hypercholesterolemia are the majority of important stimulus for the production of atherosclerotic lesions in people. They are always valuable for evaluating medicines that interfere with cholesterol degradation, absorption, and excretion with minimum impact on cholesterol biosynthesis. The concentration of cholesterol in the body comes from two places: gastrointestinal intake and endogenous de novo production.

The specific mechanism underpinning Coenzyme Q10's effects on cholesterol metabolism has to be clarified further. The current decrease in lipid profile levels could be attributable to hepatic cholesterol production suppression, the redistribution of cholesterol from plasma to the liver by the cholesterol metabolizing enzyme systems in the liver, and lipid consumption regulation (13).

Oxidative stress is a condition in which the equilibrium between oxidative and antioxidative activities is disrupted, and it plays a crucial function in the progression of atherosclerosis (14). Cholesterol-wealthy nutrition cause lipid peroxidation by causing free radical production, which leads to increase cholesterol level, it has been linked to elevate in malondialdehyde tissue content and conjugated dienes (15). Gutierrez-Mariscal *et al.*, 2020 found that Coenzyme Q10 reduced lipid peroxidation, possibly due to a reduction in oxidative stress. In the liver homogenates of diabetic rats, CoQ10 therapy enhanced antioxidant indices such as glutathione, superoxide dismutase and catalase. In coronary artery disease patients, CoQ10 supplementation was linked to a considerable reduction in thiobarbituric acid reactive compounds, malondialdehyde, and diene conjugates, indicating a decrease in total oxidative stress. Another study, however, confirmed the association between oxidative stress and cholesterol levels (17).

Oxidative stress significantly increased serum LDL, VLDL, TG and TC concentrations in comparison with the control group. Treatment of hyperlipidemic animals with CoQ10 supplement decrease LDL, VLDL, TG and TC concentrations, also significantly increases the level of serum HDL in comparison with untreated animals (control positive). These results agree with a previous study that suggested that CoQ10 have hypolipidemic effects (18).

The mechanism of the hypolipidemic effect of antioxidants may be attributable to inhibition the absorption of lipids from diet in the gut or liver synthesis, or acceleration of biliary cholesterol secretion in the feces (19). CoQ10 is a lipid-soluble chemical found in adequate quantities in lipoprotein. Supplementation with coenzyme Q10 can reduce serum lipoprotein by inhibiting the expression of lipoprotein receptors(16). Natural antioxidants' hypolipidemic activity could also be attributed to the suppression of proteins, enzymes, and glycation lipoproteins involved in lipid and lipoprotein metabolism (20).

CoQ10 impacts cholesterol metabolism and reduces LDL-C peroxidation, which may play a crucial role in its anti-atherogenic actions and reduced heart damage, according to our findings. CoQ10 has been found to have antioxidant and anti-inflammatory properties, blocking protein oxidation and fat deposition. This shows that CoQ10 inhibited TNF- and IL-6 gene expression in mice fed a high-fat diet. Hyperlipidemia causes tissue damage, which is frequently accompanied by an increase in macrophage numbers. Foam cells made from macrophages secrete cytokines that recruit more macrophages to lesions and influence lipid foundation. This action suggests that CoQ10 reduced macrophage accumulation in mice fed a high-fat diet, as well as foam cell, development and lipid buildup (21).

The current study sowed that supplementing rats with Coenzyme Q10 for one month improved their serum lipid profile when compared to control levels in rats fed diet with high cholesterol. It also has the potential to reduce the risk of atherosclerosis, Furthermore, Fouad 2020 found that treating diabetic rats with Coenzyme Q10 resulted in significant reductions in blood VLDL-C, LDL-C, total cholesterol, triglycerides and index of atherogenicity, as well as enhanced HDL-C levels. The exact mechanism by which CoQ10 lowered blood triglycerides is uncertain, however, it could be linked to a decrease in VLDL-C synthesis, VLDL-C channeling to a mechanism other than LDL, or an increase in lipoprotein lipase activity (22).

Hypercholesterolemia produces structural changes in the liver and kidney of various groups in this study (HandE X400), so we were able to demonstrate that biochemical results were confirmed by histology investigations, demonstrating that CoQ10 can lower hyperlipidemia.

Hyperlipidemia is the causative agent for cardiovascular diseases (14, 23). Treatment based mainly on statins (25); however, other cofactors could have additional beneficial effects including vitamins (7, 19), Minerals (Hend *et al*, 2021) (26) and Coenzyme Q10 (6). The pharmacological medication might be as effective as CoQ10 with lower adverse effects.

Conclusion

Coenzyme Q10 administered to hyperlipidemia-induced mice reduced the lipid profile to a level parallel to Rosuvastatin, indicated by elevated HDL-C and reduced cholesterol, VLDL-C, LDL-C and triglycerides and correspondingly the index of atherogenicity were reduced.

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Adherence to Ethical Standards

The study was approved by an ethical committee in the university of Mosul. The study is registered by the scientific committee in the department of pharmacology and toxicology/College of Pharmacy in the University of Mosul (DPTCP07 on 10/04/2019).

Conflict of Interest

The authors have no conflicts of interest regarding the publication of this article.

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