Therapeutic Role of Coenzyme Q10 or/and α-lipoic acid on Cardiac Functions in Obese/Hypertensive Rats

Shawky, M.F.;* Wahba, S.R. *and Heibashy, M.I.**

*Zoology Department, Faculty of Women for Arts, Science and Education, Ain Shams University.

**Biological Applications Department, Radioisotopes Applications Division, Nuclear Research Center, Atomic Energy Authority, Egypt.

Abstract

This study focuses on the relationship between obesity and hypertension and the possible amelioration effects of co-enzyme Q10 (CoQ10) or/and α-lipoic acid (ALA) and their mixture on histological and physiological changes in rat heart.

To achieve this purpose, a comparison took place between normal control rats group (20 rats) and obese/hypertensive rats group (24 rats). The obese/hypertensive rats were injected (i.v) with Poloxamer-407(P-407) as a single dose (1g/kg b.wt dissolved in 1ml cold saline) to induce obesity and with the aid of oro-gastric tube 1g sodium chloride salt/kg b.wt/day for 30 days for induction of hypertension. Control rats group (20 rats) were divided into 5 animals (normal control rats subgroup), 5 animals treated with 200mg CoQ10/kg b.wt /day (Normal + CoQ10 rats), 5 rats treated with 100mg ALA/kg b.wt /day (Normal + ALA rats) and the last 5 animals treated with both antioxidants as the above subgroups (Normal + CoQ10 + ALA) by oro-gastric tube. The 24 obese/hypertensive rats were divided to four subgroups, the first subgroup (6 obese/hypertensive rats), the second subgroup (6 rats) was treated with 200mg CoQ10/kg/b.wt/day (obese/hypertensive rats + CoQ10 rats), the third (6 rats) was treated with 100mg ALA/kg b.wt/day (obese/hypertensive rats + ALA rats) and the last 6 animals were treated with both antioxidants as above described (obese/hypertensive rats + CoQ10 + ALA). All rats were dissected after 4 week experimental duration.

Histological alterations in cardiac tissue of obese/hypertensive rats included lack of striation of myocytes with pyknotic nuclei; interstitial edema; congested blood vessels and mononuclear cellular infiltration in expanded intracellular spaces. After the induction of obesity and hypertension in rats and in comparison to normal control animals, the results showed significant ($P<0.05$) increase in serum concentrations of cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol. Also, remarkable increments in the serum heart enzymes activities of creatine kinase (CK), creatine kinase -MB (CK-MB), lactate dehydrogenase (LDH) and aspartate aminotransferase (AST).

***Correspondent author:* monafathy.mona1993@gmail.com.**

The increment of serum levels of heart fatty acid binding protein (H-FABP) and endotheline-1 (ET-1) occurred. On the other hand, a significant ($P<0.05$) decrease in the level of serum total nitric oxide was recorded in obese/hypertensive rats compared with those corresponding normal control ones.

When obese/hypertensive rats subgroups were treated with CoQ10 or/and ALA, considerable ameliorative effects in all previous studied parameters were pronounced dependent on certain mechanisms discussed according to available recent researches. Moreover, histological studies of the heart also revealed a definite ameliorative effect of these antioxidants as regards tissue damage and structural integrity.

Keywords: Obesity/hypertension, Poloxamer 407, Sodium chloride salt, CoQ10, ALA, Rats.

INTRODUCTION

Obesity is a multi-factorial process with complex interactions among genetic, metabolic, hormonal, and psychological factors. Physiologically, obesity is an imbalance resulting from the failure of the coupling between intake and expenditure **(Krishnan *et al*., 2007 and WHO, 2017).** Obesity is characterized by hyperlepidemia, and resistance of hypothalamic satiety center to anorectic effect of adipose tissue hormone (**Heibashy *et al*., 2010 and Karri et al., 2019**).

Also, hypertension is a common problem facing man today. Because high blood pressure is one of the leading causes of stroke and a major risk factor for heart attack, one of the most important aspects of preventive cardiology should be to identify as many people who have the disease as possible and to take steps to lower the blood pressure before it causes damage to the blood vessels, heart, kidneys, eyes and other organs (**Samavat & Hojjatzade, 2012 and Mahmoud *et al*., 2016**). Fortunately, the last decades have seen enormous amount of scientific researches that dealt with supplementation of specific nutrients which showed remarkable advances in the treatment of high blood pressure. Hence, this study was focused on dietary approaches of hypertension induced artificially in animal models (**Heibashy & abdel Moniem, 2005; Kitada *et al.*, 2017 and Lanaspa *et al*., 2018).**

Co-enzyme Q10 (CO Q10) is a powerful antioxidant. It is a naturally occurring vitamin present in nearly all tissues **(Sander *et al*., 2006)**. Several studies have clearly shown the potential benefit of co-enzyme Q10 in treatment of hypertension and congestive heart failure (**Heibashy *et al*., 2014** and **Song *et al*., 2017**). Other authors found that coenzyme Q10 may also be effective in reducing total cholesterol (**Tsuneki *et al*., 2007**; **McMurray et al., 2010 and Sharma *et al*., 2016**). They indicated that CoQ10 can efficiently prevent high glucose induced endothelial cell apoptosis and adhesion to monocytes, which are relevant to the pathogenesis of atherosclerosis.

Moreover, it was found that CoQ10 levels of patients who have chronic cardiac failure are too low both in tissue and serum samples (**Venkat *et al.* 2009**). CoQ10 provides improvement in treatment of congestive cardiac failure, stroke and cardiac fraction (**Sander *et al*., 2006 and Song *et al*., 2017**).

CoQ10 also reduced elevated blood pressure, but did not affect body weight gain in cases of metabolic syndrome. In addition, CoQ10 improved endothelial dysfunction in the mesenteric arteries suggesting that the antioxidant properties of CoQ10 can be effective in ameliorating cardiovascular risk in metabolic syndrome (**Tiano *et al.*, 2007 and Bekir *et al.*, 2016**).

α-lipoic acid (ALA) acts by multiple mechanisms both physiologically and pharmacologically. Its pharmacological role is to improve glycemic control and prevent polyneuropathy. Physiologically, it acts as an antioxidant by directly terminating free radicals (**Zhang *et al.*, 2007 and Guofu *et al.*, 2014**). So, several studies have documented its positive therapeutic effect, particularly in diseases such as diabetes, atherosclerosis and neurodegenerative diseases (**Papanas & Ziegler, 2014 and Ambrosi *et al.*, 2018**).

The current investigation was undertaken to validate the possible effectiveness of the abovementioned nutrients (Coenzyme Q10 and α-lipoic acid) to adjust the disturbances in certain blood biochemical components and changes in histological heart studies reflecting some aspects of obesity and heart troubles associated with high blood pressure.

MATERIAL AND METHODS

Forty-four adult male albino rats (Rattus rattus) approximately of the same age (10±1 week old) and weight (130±10g) were obtained from the Breeding unit, Serum and Antigen Laboratories at Helwan and employed in this investigation. They were caged and provided with diet and tap water *ad libitum* for one week prior to the experiment for adaptation.

Experimental protocols followed the Guidelines for the Care and Use of Laboratory Animals approved by the Institutional Ethics Committee of Ain Shams University. The obese/hypertensive rats were injected (i.v) with Poloxamer-407 (P-407) as a single dose (1g/kg b.wt dissolved in 1ml cold saline) according to **Chaudhary & Brocks (2013)** to induce obesity and with the aid of oro-gastric tube 1g sodium chloride salt/kg b.wt/day for 30 days according to **Kitada *et al.* (2017)** for induction of hypertension. The control rats group (20 rats) were divided into 5 animals (normal control rats subgroup), 5 animals treated by oro-gastric tube with 200mg CoQ10/kg b.wt /day (**Khatta *et al.*, 2000**) (Normal + CoQ10 rats), 5 rats treated by oro-gastric tube with 100mg ALA/kg b.wt /day **(Goraca *et al.*, 2011)** (Normal + ALA rats) and the last 5 animals treated with both antioxidants as above subgroups (Normal + CoQ10 + ALA). The 24 obese/hypertensive rats were divided to four subgroups, the first subgroup (6 rats obese/hypertensive rats), the second subgroup of obese/hypertensive rats (6 rats) was treated with 200mg CoQ10/kg/b.wt/day (obese/hypertensive rats + CoQ10 rats), the third subgroup of obese/hypertensive rats (6 rats) treated with 100mg ALA/kg b.wt/day (obese/hypertensive rats + ALA rats) and the last 6 animals treated with both antioxidants as above described (obese/hypertensive rats + CoQ10 + ALA). All rats were dissected after 4 week experimental duration.

At the end of experimental period, rats were slightly anaesthetized by diethyl ether and sacrificed. Blood samples were immediately collected from the heart in clean dry test tubes and centrifuged at 10,000 rpm for 20 minutes. Sera were separated and kept at -20°C for the

biochemical parameters. Hearts were carefully removed aseptically, washed with cooling saline solution (0.9% NaCl) and placed in neutral buffer formalin for histopathological studies using the routine staining (haematoxylin and eosin).

Biochemical parameters included lipids profile: Serum total cholesterol (T-CH) **Allain *et al*. (1974)**, triglycerides (TG) **Fossati *et al*. (1982)** and HDL-cholesterol (HDL-C) estimated enzymatically **Grove (1979)**. LDL-cholesterol was calculated as peaccording to Assman's equation (**Assman *et al*., 1984**).

LDL = Total serum cholesterol – [serum triglyceride/5 –serum HDL- cholesterol].

Heart enzymes activities: Serum creatine kinase (CK) **Fisher *et al.* (1983)**, creatine kinase -MB ($CK\text{-}_{MB}$) **Griffiths *et al.*, (1977)**, lactate dehydrogenase (LDH) **Buhl & Jackson (1978)** and aspartate aminotransferase (AST) **IFCC (1978)** activities were esssatimated kinetically.

Cardiac profile**:** serum heart fatty acid binding protein (H-FABP) **Pagani *et al*. (2002)** and endotheline-1 (ET-1) **Wakisaka *et al*. (1996)** levels were assayed using commercial ELISA (Sandwich Immunoassay Technique) specific kit for rats (Kamiya Biomedical Company, USA). Serum total nitric oxide (TNO) **Griess *et al.* (1982)** level was assayed using commercial ELISA technique kit form Cayman Chemical Company (USA).

Data were statistically analyzed using Two Way Analysis of Variance (ANOVA) by the aid of SPSS (version 20.0) program. Values were considered statistically significant when $p \leq 0.05$.

RESULTS

Histological studies:

Cardiac sections taken from control rats manifested normal histological architecture of the myocardium (Fig. 1 a) with longitudinally striated branching and anastomosing muscle fibers with centrally located oval vesicular nuclei (Fig 1 b). Sections obtained from hyperlipidemic/hypertensive rats designated eosinophilic cardiac muscle fibres with lack of striation and pyknotic nuclei (Fig. 1 c). Also present in the interstitial tissue was nuclear fragments where necrotic muscle fibres were replaced by fibrous tissue. Mostly evident was lysis of groups of muscle fibres; interstitial edema; increased intracellular spaces between myocardial fibers invaded by nuclear fragments (Fig. 1 d). Congested blood vessels were prominent with attenuated elastic fibres replaced by reticular architecture and reduced tunica media layers (Fig. 1 e). Mononuclear cellular infiltration in-between muscle fiber was also a prominent feature .

Following treatment of hyperlipidemic/hypertensive rats with either CoQ10 or ALA cardiac sections manifested regenerative profiles (Fig 2 a) with lesser appearance of degenerative necrotic cardiac cells (Fig. 2 b). With the double treatment with CoQ10 and ALA necrotic remnants in interstitial tissue was minimal with oppressed interstitial edema (Fig. 2 c & d). Blood vessels partially regained normal appearance (Fig 2 e).

Biochemical parameters:

1- Lipids profile:

According to the obtained data in Table (1), there was a significant ($p<0.05$) elevation in the levels of serum lipid profile (cholesterol, triglyceride, HDL and LDL) in obese/hypertensive rats group compared to their corresponding normal control. A remarkable correction occurred in the previous parameters after obese/hypertensive rats were treated with Co Q10 or ALA after 4 weeks treatment. The best corrections were reported in serum levels of T-Ch, TG, HDL-C and LDLC of obese/hypertensive rats group treated with both antioxidants (Co Q10 and ALA) compared to their corresponding normal control rats group (Table 1).

2- Heart enzymes activities:

Induction of obesity/hypertension in rats led to a significant ($p<0.05$) elevation in serum heart enzymes activities [creatine kinase (CK), creatine kinase -MB (CK-MB), lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) as shown in Table (2). Treated obese/hypertensive rats with 200mg CoQ10/kg/b.wt/day or 100mg ALA/kg b.wt/day led to considerable amelioration effects on prementioned enzymes activities. Best amelioration effects were reported after obese/hypertensive rats were treated with both antioxidants (Co Q10 and ALA) compared to their corresponding normal control 4 weeks interval (Table 1).

3- Cardiac profile:

The obtained data in Table (3) clarified a significant ($P<0.05$) elevation in serum heart-type fatty acid binding protein (H-FABP) and endothelial-1 (Et-1) levels in obese/hypertensive rats However, the induction of obesity/hypertension in the animals caused a significant ($P<0.05$) decrease in serum total nitric oxide (TNO) level (Table 3).

Treated obese/hypertensive rats with 200mg CoQ10/kg/b.wt/day or 100mg ALA/kg b.wt/day led to considerable modulation effects on H-FABP, Et-1 and TNO levels (Table 3). Again maximum corrections were recorded as obese/hypertensive rats were treated with a mixture of Co Q10 and ALA compared to their corresponding normal control rats group as shown in Table (3).

DISCUSSION

Obesity is the most common nutritional disorder that is associated with increased mortality and morbidity of cardiovascular disease **(WHO, 2017).** On the other hand hyperlipidemia caused by elevation of cholesterol levels is a major risk factor in the incidence and pathogenesis of degeneration diseases including atherosclerosis and cardiovascular disease **(Karri *et al.*, 2019).** In rats, P-407 administration as a single or repeated dose causes significant elevation in serum total cholesterol and triglycerides thus inducing hyperlipidemia **(Korolenko, 2016).**

Hypertension remains a common and serious problem, contributing in a major way to the most common causes of morbidity and mortality worldwide **(Hulanicka *et al.*, 2007)** where high salt intake is one of the major risk factors for developing hypertension **(Youshionwa *et al.*,**

2004). Simonds *et al.* (2014) have proposed that leptin mediates the increase in blood pressure associated with obesity.

Presently, administration of both P-407 and NaCl to induce hyperlipidemia/hypertension in rats caused a marked increment in serum T Ch, TG, HDL-C and LDL-C concentrations as compared to their corresponding control. These results may be due to the increase in free radicals production which led to alteration in the mitochondrial function (decrease in number and size and shape deformation) associated with alteration in the function of smooth ER due to the disturbance in the lipid oxidation. It may also be due to the increment in the de novo lipogenesis, disturbance in the hypothalamus-pituitary-thyroid axis (HPTA), alteration in the neuropeptide hormones (neuropeptide-Y, orexin-A and orexin-B) levels or/and the decrease of β-oxidation of lipid in the matrix of mitochondria. These results are in agreement with the viewpoint that mitochondrial dysfunction in the pathogenesis of hyperlipidemia as well as hypertension at different degrees mainly include lipid oxidation impairment and the induction of peroxidative production **(Heibashy, 2005; Tanaka *et al.*, 2009; Heibashy *et al.*, 2013; Korolenko, 2016 and Rana *et al.*, 2017).**

Enzymes of significance for diagnosis of cardiac conditions i.e. cardiac enzymes include CK, LDH and AST. CK values rise 4 to 6 hours after cardiac infarction. They reach peak in 24 to 36 hours. AST values start rising at this time and reach peak values in 2 to 3 days. They stay elevated for about 14 days **(Choi *et al.*, 2016)**.

It was obvious in the present investigation that induced myocardial dysfunction as a result of pronounced hyperlipidemia/hypertension in rats led to a significant ($p<0.05$) elevation in the serum heart enzyme activities (CK, CK-MB, LDH and AST) as compared to their corresponding control rats group.

These results may be due to excessive myocardial infarction as a result of increased production of reactive oxygen intermediates, a resultant rise in lipid peroxidation, epigenetic gene alteration, inhibition in activity of total nitric synathase (NOs) enzyme, increase in the level of serum endothelin-1 accompanied with elevation in serum asymmetric dimethyl arginine (ADMA) level as well as appearance of hypertension and metabolic syndrome. These results are in parallel with those obtained by **Tanaka *et al.* (2009) and Korolenko *et al.* (2013 & 2016).** The authors attributed these disturbances to the loss of cardiac troponin from myocytes and myofibrillar lyses in the plasma membrane.

Due to cellular damage and cardiac infarction LDH leaks into the serum. As height and duration of the increased activity depends on the size of lesion therefore, LDH is used as an index of membrane damage. Also, **Lau, (2018)** found that when vascular endothelial cells were exposed to oxidized LDL, there was a significant increase of LDH release indicating cell membrane injury and disturbance in the lipid peroxidation of cardiac tissues **(Faulx *et al.*, 2005). Heibashy & Abdel-Moneim, (2005)** explained the increment of cardiac enzymes to the elevation of cardiac troponin level which mediates the calcium activation of contraction of cardiac muscle.

Heart fatty acid binding protein (H-FABP) is an early and sensitive marker for myocardial infarction and myocardial injury **Heibashy *et al.*, 2013; Willemsen *et al.*, 2015 and Vupputuri et al. (2015).** Plasma level of endothelin-1 (ET-1) is elevated in obese or hypertensive patients. Nitric oxide (NO) is an important bioactive substance which plays an important role in the regulation of normal body function and disease occurrence **(Brealey *et al.*, 2004).**

Induced hyperlipidemia/hypertension in rats impair the integrity of the endothelial barrier resulting in endothelial cell injury, which contributes to greater permeability of endothelial cells and impaired homeostasis, and induces the release of cytokines and reactive oxygen species (ROS). Plasma level of endothelin-1 (ET-1) is elevated in obese or hypertensive patients associated with the severity of the illness **(Heibashy *et al.*, 2013; Willemsen *et al.*, 2015 and Vupputuri *et al.*, 2015).** Also, **Klotz et al. (2006)** noted that endothelin-1 (ET-1) is a potent endogenous vasoconstrictor, mainly produced by endothelial cells.

In the current work, it was shown that after cardiac injury from induced hyperlipidemia/hypertension in rats serum levels of H-FABP and ET-1 were increased significantly ($p<0.001$) as compared to their corresponding control. These data may be attributed to the inhibition of nucleic acids as well as protein synthesis; increment of free radical production and oxidative stress associated with release of vasoactive amines; changes in adrenergic functions; abnormalities in the mitochondria; lysosomal alterations; disturbance in sarcolemma and membrane bound enzymes activities; alteration in the myocardial electrolytes and occurrence of Ca^{2+} overload**; Kitada *et al.*, 2017 and Lanaspa *et al.*, 2018).**

Currently it was shown that induction of hyperlipidemia/hypertension in rats group led to a remarkable decrease in the serum level of total nitric oxide (TNO) compared to their corresponding control rats group. These data may be due to increment in the oxidative damage, inflammation and apoptosis appearance as well as alterations in endothelial scavenger receptor class-B member-1 (SR-B1), phosphoinosotide-3 kinase (PI3K), mitogen activated protein kinases (MAPK) and protein kinase-B activity (Akt) associated with mutation of HDL-cholesterol production. These results are in harmony with several recent investigations **(Heibashy & Abdel-Moneim, 2005; Ramanathan & Thekkumalai, 2014; Kitada *et al.*, 2017 and Vanhoutte, 2018).**

To study the effect of P-407 and NaCl salt on the structure of rat myocardium, sections were examined. Cardiac sections obtained from hyperlipidemic/hypertensive rats designated several pathological findings including eosinophilic cardiac muscle fibres with lack of striation and pyknotic nuclei; lysis of groups of muscle fibres; interstitial edema; increased intracellular spaces between myocardial fibers invaded by nuclear fragments; congested blood vessels with attenuated elastic fibres replaced by reticular architecture and karyolitic cardiac muscles. In addition, areas of pale homogeneous acidophilic cytoplasm were observed with either degenerative or deeply stained pyknotic nuclei. Mononuclear cellular infiltration in-between

muscle fiber was also a prominent feature. These data are in accordance with those obtained by **Brahmbhatt and Cowie, (2018); Saidu *et al.* (2018); Khallaf and El-Mansy, (2019).**

Obesity is usually associated with increased myocardial oxygen consumption, increased fatty acid metabolism and thus reduced myocardial efficiency. Increased oxygen consumption is also a normal sequel of hypertension. Present histological alterations may be primarily attributed to oxidative stress experienced by cardiac cells resulting in an imbalance in the production of ROS and intrinsic antioxidant defense. This may lead to inflammatory reactions and fibroblast activation. Cardiac fibroblasts on the other hand may change into myofibroblasts to secrete extracellular matrix components as collagen, fibronectin and laminin finally leading to fibrosis. In addition, degenerative necrotic changes alter the ejection of sufficient blood during systole leading to dilatation of the heart and stretching of the muscle fibres and fall of cardiac output.

Heart failure (HF) may cause severe damage to the heart muscle via myocardial fibrosis, ventricular remodeling, decreased contractility, and increased myocyte apoptosis **(Madamanchi & Runge, 2013).** Similar results were achieved in vitro **(Ziegler *et al.*, 2011 and Papanas & Ziegler, 2014).**

The current investigation was designed to evaluate the therapeutic role of coenzyme Q10 (CoQ10) or α-lipoic acid (ALA) as well as their mixture on hyperlipidemic/hypertensive rats and their modulation effects on the myocardial dysfunction.

Coenzyme Q10 (CoQ10) also known as ubiquinone is a fat-soluble molecule found primarily in the mitochondrial inner membrane, functions as a physiologically essential electron carrier in the electron transport chain bucket brigade. When electrons have been added to CoQ10, the molecule is known as "ubiquinol"; in this "reduced" form, CoQ10 can donate electrons to free radicals, quenching them. The oxidant scavenging activity of ubiquinol is versatile and important; in particular, ubiquinol can quench peroxynitrite-derived radicals, protecting the proteins of the electron transport chain from peroxynitrite-mediated damage. Ubiquinol also helps to prevent the peroxidation of fats in mitochondrial membranes. The high utility of CoQ10 as a mitochondrial antioxidant reflects the fact, that after it has donated an electron to quench a free radical, the electron transport chain "reloads" it with another electron, so that it is once again primed to scavenge oxidants **(Rodick *et al.*, 2018).**

Other researches indicated that CoQ10 may aid the protective function of the endothelial lining of arteries throughout reflecting a role for mitochondrial oxidant production in endothelial dysfunction **(Hodgson & Watts, 2003 and Tiano *et al.*, 2007).** In rodent studies, pre-administration of CoQ10 has a favorable impact on the damage to cardiac tissue evoked by a temporary cessation of blood flow and decreased the oxidative stress in ischemia-reperfusion damage **(Littarru *et al.*, 2007).**

In the current study, the supplementation of (COQ10) to hyperlipidemic/hypertensive rats caused marked amelioration effects in all studied including histological profile.

The amelioration effects on current results may be due to the antioxidant action of CoQ10 which improves cardiac bioenergetics; has direct free radical scavenger and antioxidant effect; facilitate the synthesis of depleted glutathione; corrects coenzyme Q10 deficiency state; improves endothelial function and vasodilatory effect; increases the blood flow by increasing the soluble nitric oxide activity; has membrane-stabilizing activity due to phospholipid protein interactions; preserver of myocardial Na^+-K^+ ATPase activity; stabilizes the integrity of Ca^{2+} channels with correction mitochondrial leak of electrons during oxidative respiration and improves the immune response system. The current data are in harmony with those obtained by **Tsai *et al.* (2012); Yang *et al.* (2015); Acosta *et al.* (2016) and Song *et al.* (2017).**

α-lipoic acid (ALA), on the other hand, known as thioctic acid, is a naturally occurring compound that is synthesized by plants and animals, including humans **(Yi & Maeda, 2005).** It contains two sulfur molecules that can be oxidized or reduced. This feature allows ALA to function as a cofactor for several important enzymes as well as a potent antioxidant **(Özkan *et al.*, 2005).**

ALA exerts its effect mainly through its reduced form, dihydrolipoic acid (DHLA), a conversion to which is catalyzed by lipoamide dehydrogenase. This endogenous thiol antioxidant quenches reactive oxygen species (singlet oxygen, H_2O_2, hydroxyl radicals), regenerates reduced glutathione (GSH) and chelates metals such as iron, copper, mercury and cadmium, which are known to mediate free-radical production in biological systems. Both ALA and DHLA also protect the integrity of cell membranes by interacting with other antioxidants e.g; glutathione and vitamins E or C.

ALA being a very effective antioxidant is used in various diseases concerning age-dependent oxidative stress **(Rochette *et al.*, 2013).** Also, ALA acting as a cofactor for enzymatic reactions within the mitochondria can improve mitochondrial function by conserving cellular energy **(Packer & Cadenas, 2011).** Some studies on animal models have confirmed that ALA can prevent progressive remodeling and even improve cardiac function **(Papanas & Ziegler, 2014 Ambrosi *et al.*, 2018 and Genazzani *et al.*, 2018).** They suggested that the cardioprotective effects of ALA are obtained by immunoreactive insulin enzyme through a mechanism involving the activation of this enzyme.

In the concurrent investigation, the supplementation of ALA to hyperlipidemia/hypertensive rats caused considerable correction effects in all studied parameters. These data are confirmed but to lesser degree than hyperlipidemic/hypertensive rats treated with CoQ10. These effects may be attributed to reduction in oxidative stress induced by both P-407 and NaCl by alleviating lipid peroxidation through free radical scavenging or by enhancing the synthesis of antioxidants containing -SH groups and GSH which then detoxify free radicals. Current results are in agreement with several recent authors **(Rochette *et al.*, 2013; Papanas & Ziegler, 2014; Skibska & Goraca, 2015; Ambrosi *et al.*, 2018 and Genazzani *et al.*, 2018).** These authors attributed their results to the antioxidant effect of ALA which prevents the hyperlipidemia/hypertensive induced NO and prevents the elevation of serum cytokine.

Inhibition of an inflammatory mediator TNF-α as well as IL-1β points out an anti-inflammatory effect of ALA against hyperlipidemia/hypertensive induced heart failure. Also, these results are supported by the ability of ALA to prevent the hyperlipidemia/hypertensive necrotic damage in rat hearts and prevention of the increment in the activities of the cardiac enzymes marker CK, $CK\text{-}_{MB}$, LDH and AST.

On the basis of current data, the maximum corrections in all studied biochemical and histological parameters were recorded in hyperlipidemic/hypertensive rats group treated with a mixture of antioxidants CoQ10 and ALA probably due to the synergistic effects of their pharmadynamic and pharmakinetic properties.

From the above cited data, it could be concluded that treatment with CoQ10 or ALA and their mixture can prevent the hyperlipidemia/hypertensive induced oxidative heart damage as well as inflammatory stress in heart by alleviating lipid peroxidation through free radical scavenging or by enhancing the synthesis of antioxidants and improves glutathione redox system which then detoxify free radicals.

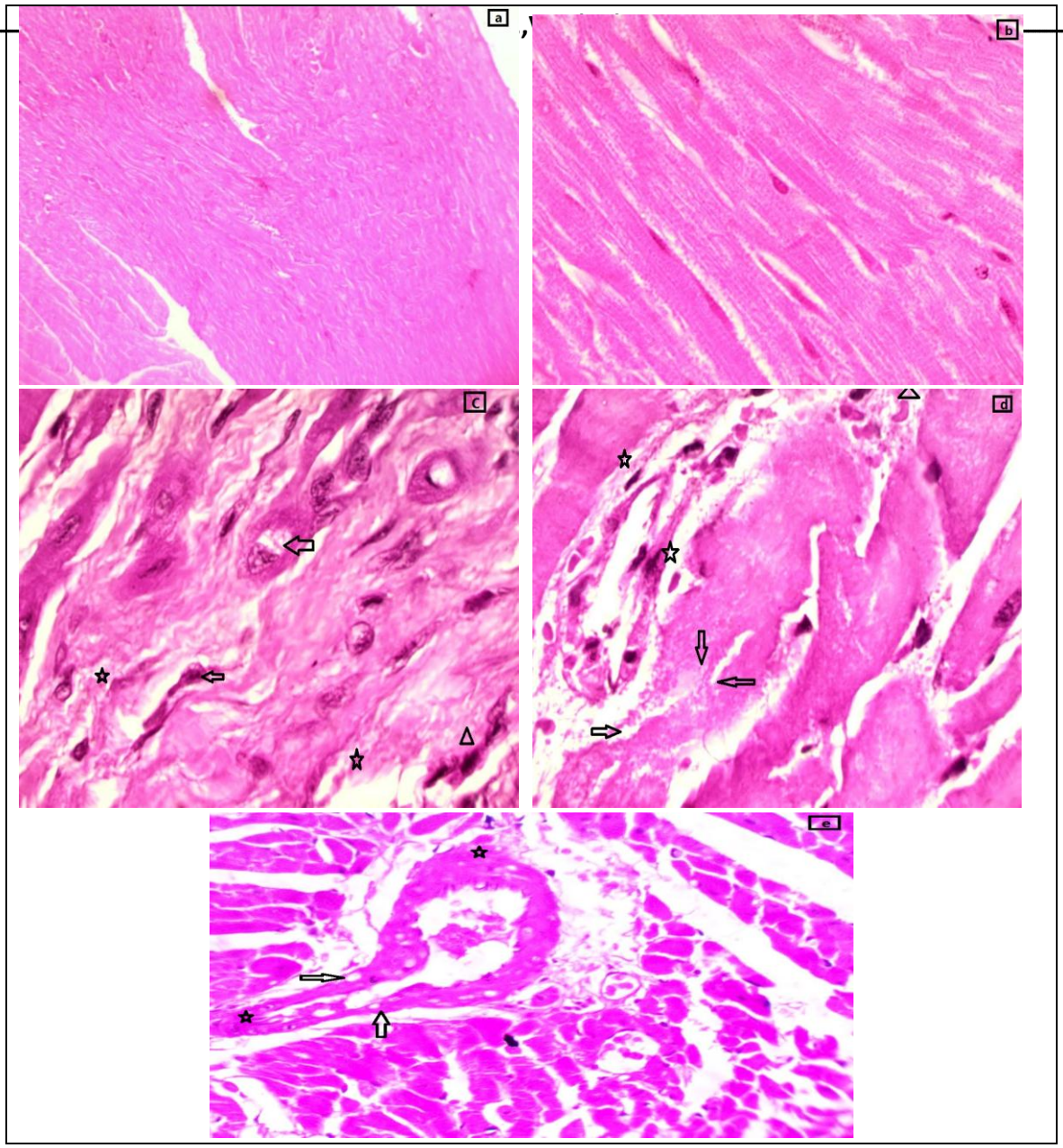

Figure 1: Photomicrographs of sections from control and obese/hypertensive rats (Hx&E.)

a- Heart section of normal control rat showing normal architecture of cardiac tissue (X 100)

b- Heart section of normal control rats at 4 weeks showing normal architecture of cardiac striations (X 1000).

c- Heart section of obese/hypertensive rats showing eosinophilic cardiac muscles; lack of striation [ ]; groups of muscle fibres [ ] and pyknotic nuclei [ ] (X 1000).

d- Heart section of obese/hypertensive rats showing loss of striation necrosis and lysis [ ]; interstitial edema [ ] and inflammatory cell infiltrate [ ] (X 1000).

e- Heart section of obese/hypertensive rats showing congested blood vessel infiltrated by fatty degenerative [ ] and reduced tunica media layer [ ] (X 400)

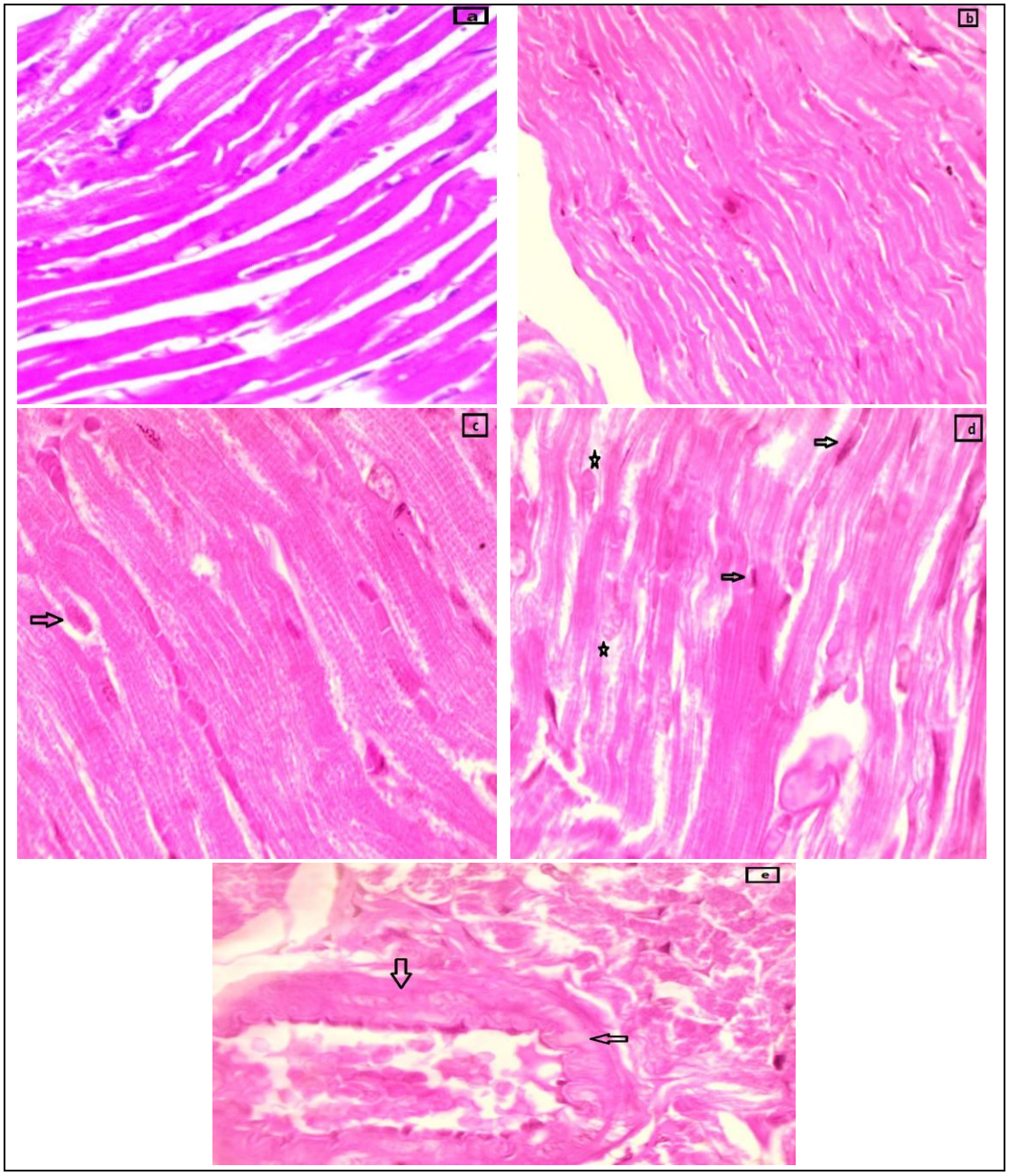

Figure 2: Photomicrographs of sections from obese/hypertensive rats treated with CoQ10 or/and ALA (Hx&E.)

a- Heart section of treated rats with CoQ10 showing regenerative profile with surviving muscle fibres (X 400)

b- Heart section of treated rats with ALA showing lesser appearance of degenerative necrotic cardiac cells. (X 400)

c- Heart section of treated rats with CoQ10 and ALA showing cardiac bands with very much attenuated degenerative muscle cells (X 1000)

d- Heart section of treated rats with CoQ10 and ALA showing lesser presence of cardiac necrotic remnants [⇧] and much oppressed interstitial edema [☆] (X 1000)

e- Heart section of treated rats with CoQ10 and ALA showing blood vessels regaining their near to normal appearance [⇧] (X 1000)

Table (1): The mean values of lipids profile (TC, TG, HDL and LDL) (mg/dl) concentrations in normal and obese/hypertensive rats treated with CoQ10 or ALA and their mixture at Four weeks.

Parameter	Control				Ob/Hyp			
	N	Q10	ALA	Mix	R	Q10	ALA	Mix
TCH	$55.35^{D}\pm0.453$	$55.40^{D}\pm0.429$	$54.71^{D}\pm0.221$	$55.00^{D}\pm0.464$	$83.84^{A}\pm0.464$	$61.27^{C}\pm0.750$	$70.46^{B}\pm0.635$	$53.21^{D}\pm0.319$
TG	$64.08^{E}\pm0.429$	$62.46^{E}\pm0.628$	$62.88^{E}\pm0.523$	$62.56^{E}\pm0.422$	$100.5^{A}\pm0.830$	$70.26^{C}\pm0.472$	$85.72^{B}\pm0.829$	$61.43^{D}\pm0.437$
HDL	$15.04^{C}\pm0.116$	$14.46^{C}\pm0.232$	$14.50^{C}\pm0.180$	$14.28^{C}\pm0.163$	$20.20^{A}\pm0.162$	$20.20^{A}\pm0.409$	$19.86^{A}\pm0.153$	$15.15^{B}\pm0.214$
LDL	$27.50^{E}\pm0.444$	$28.45^{E}\pm0.524$	$27.63^{E}\pm0.098$	$28.21^{E}\pm0.499$	$43.54^{A}\pm0.396$	$27.02^{C}\pm0.748$	$33.46^{B}\pm0.586$	$25.37^{D}\pm0.464$

-Data are expressed as mean±standard error (SE).

-$^{A, B, C, D, E}$ Means with a common superscript within a row are significantly different ($P<0.05$).

Table (2): The mean values of Heart enzymes activities (CK, CK_{MB}, LDH, and AST) (U/ml) activity in normal and obese/hypertensive rats treated with CoQ10 or ALA and their mixture at Four weeks.

Parameter	Control				Ob/Hyp			
	N	Q10	ALA	Mix	R	Q10	ALA	Mix
CK	$92.77^{E}\pm0.264$	$92.62^{E}\pm0.309$	$92.55^{E}\pm0.270$	$92.27^{E}\pm0.371$	$185.6^{A}\pm1.948$	$141.9^{C}\pm1.117$	$169.2^{B}\pm1.039$	$112.3^{D}\pm0.957$
CK_{MB}	$15.11^{D}\pm0.133$	$14.65^{D}\pm0.611$	$14.75^{D}\pm0.071$	$14.64^{D}\pm0.082$	$23.96^{A}\pm0.122$	$19.31^{C}\pm0.289$	$20.94^{B}\pm0.165$	$15.05^{D}\pm0.167$
LDH	$234.9^{E}\pm0.424$	$234.6^{E}\pm0.945$	$234.7^{E}\pm0.554$	$234.1^{E}\pm0.375$	$472.3^{A}\pm2.076$	$383.8^{C}\pm2.251$	$438.7^{B}\pm2.372$	$287.2^{D}\pm2.844$
AST	$121.5^{E}\pm0.449$	$121.9^{E}\pm0.311$	$122.1^{E}\pm0.242$	$121.8^{E}\pm0.450$	$212.6^{A}\pm3.446$	$160^{C}\pm0.905$	$184.6^{B}\pm2.061$	$124.2^{D}\pm0.687$

-Data are expressed as mean±standard error (SE).

-A, B, C, D, E Means with a common superscript within a row are significantly different ($P<0.05$).

Table (3): The mean values of Cardiac profile (H-FABP, Endo-1 and TNO) (μM) levels in normal and obese/hypertensive rats treated with CoQ10 or ALA and their mixture at Four weeks.

Parameter	Control				Ob/Hyp			
	N	Q10	ALA	Mix	R	Q10	ALA	Mix
H-FABP	$15.10^{E}\pm0.166$	$15.21^{E}\pm0.240$	$15.06^{E}\pm0.737$	$15.27^{E}\pm0.202$	$33.26^{A}\pm0.394$	$21.95^{C}\pm0.424$	$27.35^{B}\pm0.270$	$16.46^{D}\pm0.204$
Endo-1	$0.387^{E}\pm0.003$	$0.386^{E}\pm0.002$	$0.385^{E}\pm0.002$	$0.386^{E}\pm0.002$	$0.759^{A}\pm0.003$	$0.506^{C}\pm0.007$	$0.687^{B}\pm0.005$	$0.407^{D}\pm0.007$
TNO	$53.24^{A}\pm0.366$	$54.98^{A}\pm0.255$	$55.12^{A}\pm0.148$	$54.81^{A}\pm0.356$	$35.57^{D}\pm0.244$	$48.37^{B}\pm0.300$	$39.91^{C}\pm0.445$	$53.07^{A}\pm0.411$

-Data are expressed as mean±standard error (SE).

-$^{A, B, C, D, E}$ Means with a common superscript within a row are significantly different ($P<0.05$).

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الملخص باللغة العربية

الدور العلاجى لأنزيم كيو- ١٠ أو/و حمض ألفا الليبوليك على وظائف القلب فى الجرذان البدينة ومرتفعة ضغط الدم.

منى فتحى شوقى نصر١، سناء محمد رفعت١، محمد اسلام حبيشى٢

١- قسم علم الحيوان/كلية البنات للأداب والعلوم والتربية/ جامعة عين شمس،
٢- مركز البحوث النووية/ هيئة الطاقة الذرية.

تركز هذه الدراسة علي العلاقة بين السمنة وارتفاع ضغط الدم والآثار المحتملةالمحسنة لانزيم Q10 المساعد (CoQ10) أو حمض α-ليبويك (ALA) وخليطهما علي الانسجه والتغيرات الفسيولوجية في قلب الجرذان.

ولتحقيق هذا الغرض، أجريت مقارنه بين مجموعه فئران المجموعة الضابطة (٢٠ جرذا) ومجموعه فئران السمنة/ارتفاع ضغط الدم (٢٤ جرذا). وقد تم حقن فئران السمنة/ارتفارع ضغط الدم ب P-407 بجرعة واحدة ١جم/كجم من وزن الجسم مذابة فى ١ مللى ملحول ملحى بالاضافةإلى ١ جم/كجم من وزن الجسم من ملح كلوريد الصوديوم لمدة ٣٠ يوما .وقد قسمت الجرذان إلى مجموعة ضابطة من (٢٠ الجرذان) وتنقسم إلى ٥ فئران (تحت مجموعة العادية) ، ٥ فئران عولجت من قبل أنبوب المعدة ب ٢٠٠ ملجم/كجم من وزن الجسم بانزيم كيو ١٠يوميا (الجرذان المجموعة العادية بانزيم كيو ١٠) ، 5 الجرذان التي تم علاجها بأنبوب المعدة بواسطة حمض الفا الليبوليك بجرعة ١٠٠ملجم/كجم من وزن الجسم يوميا(الجرذان العادية بحمض الفا الليبوليك) و المجموعة المختلطة التى تتكون من ٥ فئران تم علاجهما بكلا من انزيم كيو ١٠ و حمض الليبوليك، بالاضافة اللى المجموعة التى تم احداث مرض السمنة بها مع ارتفاع ضغط الدم وتتكون من ٢٤ جرذا و التى تنقسم كالاتى ٦ من الجرذان مصابة بمرض السمنة/ارتفاع ضغط الدم بدون معالجة و ٦ تم علاجها بانزيم كيو ١٠ بجرعة ٢٠٠ ملجم/كجم من وزن الجسم يوميا(المجموعة المرضية+ انزيم كيو ١٠) و ٦ من الجرذان المصابة بالسمنة مع ارتفاع ضغط الدم وتم علاجها بحمض الفا الليبوليك بجرعة ١٠٠ملجم/كجم من وزن الجسم يوميا (المجموعة المرضية+ حمض الفا الليبوليك) و ٦ من الجرذان من المجموعة المرضية المختلطة التى تم علاجها بكلا من انزيم كيو ١٠ و حمض الفا الليبوليك(المجموعة المرضية المختلطة+انزيم كيو ١٠+ حمض الفا الليبوليك). تم تشريح جميع الجرذان بعد ٤ أسابيع من مدة التجربة.

وشملت التغيرات النسيجية في انسجه القلب من الجرذان ذات السمنة مع/رتفاع ضغط الدم عدم وجود تخطيط فى الخلايا العضلية مع انوية محللة ؛ السوائل المحتبسة الداخلية؛ ضيق الاوعيه الدموية وتسلل الخلايا الاحاديه النواة في الخلايا الموسعة فى الفراغ الخلوى الداخلى بالمقارنة مع الجرذان الطبيعية الضابطة، أظهرت النتائج زيادة كبيرة ($P < 0.05$) في تركيزات المصل من الكوليسترول ، الدهون الثلاثية ، الكوليسترول الحميد والكوليسترول السيى منخفض الكثافة. وأيضا، زيادات ملحوظة في أنشطه انزيمات القلب فى المصل [(CK)، (CK-MB)،(LDH) و (AST)] وفي مستويات المصل من البروتين القلبى المرتبط بالحمض الدهنى (H-FABP) (ET-1) و من ناحية أخرى ، تم تسجيل انخفاض كبير ($P < 0.05$) في المص للمستوي الكلي لأكسيد النيتريك (TNO) في الجرذان ذات السمنة مع ارتفاع ضغط الدم مقارنه مع المجموعة الضابطة .

وعند معالجة مجموعة المرضية ذات السمنة مع ارتفاع ضغط الدم بانزيم كيو ١٠او/و حمض الفا الليبوليك، وجد تاثير تحسيني كبير في جميع الدراسات السابقة كانت واضحة معتمدا على علي بعض الأليات التي نوقشت وفقا للبحوث المتاحة مؤخرا. وعلاوة علي ذلك ، كشفت الدراسات النسيجية للقلب تاثيرا تحسينيا واضحا من هذه المضادات المؤكسده فيما يتعلق بتلف الانسجه والسلامة الهيكلية.