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Research Article

Lipoic Acid and Coenzyme Q10 Protect Against Lead-induced Toxicity in Rats with Metabolic Syndrome

^{1,2}Hany A. Omar, ³Waleed H. Almalki, ³Hanan Shamardl, ³Abeer Y. Mahdy and ⁴Hekma A. Abd El-Latif

¹Department of Pharmacology and Toxicology, Faculty of Pharmacy, Beni-Suef University, Beni-Suef 62514, Egypt

²Sharjah Institute for Medical Research, College of Pharmacy, Department of Pharmacology, University of Sharjah, Sharjah 27272, UAE

³Department of Pharmacology, College of Pharmacy, Umm Al-Qura University, Makkah, Saudi Arabia

⁴Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt

Abstract

Obesity may lead to Metabolic Syndrome (MS). The MS is often characterized by oxidative stress which contributes to cellular damage and dysfunction. Lead toxicity is a major health problem especially in obese individuals. Therefore the aim of the current study was to investigate the biochemical and cardiovascular effects caused by lead exposure in rats with metabolic syndrome and suggesting possible protective measures. The MS was induced by feeding rats with high fat diet and fructose in drinking water for 90 days. Matched normal group was used as a control. Rats with metabolic syndrome were allowed to drink water containing lead acetate for 30 days either alone, with alpha-Lipoic Acid (LA) or coenzyme Q10 (CoQ10). At the end of experiment, body weight, systolic blood pressure and heart rate were assessed. Creatinine and uric acid were also determined. Lipid profile, oxidative stress biomarkers, nitric oxide, TNF α , calcium, insulin and glucose were determined. The exposure to lead worsens kidney function, oxidative stress and metabolic effects caused by metabolic syndrome. The use of LA or CoQ10 could ameliorate these harmful effects of lead. In conclusion, lead worsens the MS cases due to its ability to induce oxidative stress in rat tissues. The LA and CoQ10 beneficial effects could be attributed to their antioxidant capacity.

Key words: Lipoic acid, coenzyme Q10, lead, kidney function, oxidative stress, metabolic syndrome

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Corresponding Author: H.A. Abd El-Latif, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt
Tel: +2021212272734

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Metabolic Syndrome (MS) is a cluster of biochemical and vascular problems such as hypertension, abdominal obesity, impaired glucose tolerance, increased blood lipids and oxidative stress (Hsu *et al.*, 2010; Li *et al.*, 2015). Oxidative damage is one of the proposed mechanisms of lead toxicity, specially affecting the liver and kidney (Ponce-Canchihuaman *et al.*, 2010). In addition, lead causes many changes in lipid metabolism on both acute and chronic exposure (Ademuyiwa *et al.*, 2009). The exposure to lead hinders many of the antioxidant enzyme systems which increases lipid peroxidation and causes extensive degenerative cellular damage (Bolin *et al.*, 2006; Rahman and Sultana, 2006). However, many of these harmful effects of lead could be ameliorated by the use of many antioxidants (Newairy and Abdou, 2009).

In this study, coenzyme Q10 (CoQ10) and alpha-lipoic acid (LA) were selected to test their ability to ameliorate lead-induced oxidative stress in rats with metabolic syndrome. The CoQ10 is an oil-soluble, vitamin-like antioxidant synthesized by the body. It is an essential component of the Electron Transport Chain (ETC) which is required for aerobic respiration. The CoQ10 attenuates the generation of reactive oxygen species and improves the cellular antioxidant capacity via different mechanisms (Tsai *et al.*, 2012).

The LA is an indispensable cofactor for many mitochondrial enzymes that are needed for proper metabolic pathways (Reed, 1957). It has potent antioxidant activity which acts as a redox couple with its reduced form to generate natural antioxidants such as glutathione (GSH), vitamin C and coenzyme CoQ10 (Biewenga *et al.*, 1997). It also has the ability to directly scavenge free radicals (Wada *et al.*, 1997).

Thus, the current study investigated the possible beneficial roles of CoQ10 or LA supplementation in ameliorating lead-induced oxidative stress in rats with metabolic syndrome.

MATERIALS AND METHODS

Ethics statement: The experimental protocol of the current study was approved by the Ethics Committee on Animal Research of Umm Al-Qurah University. All the guidelines for the care and use of Laboratory Animals published by the US National Institute of Health (NIH publication No. 85-23, revised 1996) were followed in all the experimental procedures.

Animals: Adult female wistar rats weighing 160-200 g were obtained from the animal house of King Abdulaziz University, Jeddah, Saudi Arabia. The animals were maintained at

controlled laboratory conditions (temperature $22 \pm 1^\circ\text{C}$, humidity $60 \pm 5\%$) and a 12/12 h light/dark cycle).

Experimental design and treatment protocol: The animals were divided into 2 groups, according to their experimental treatment as follows: Normal (control) group rats (10 rats) received only 2% tween 80 once daily till end of experiment. Metabolic Syndrome (MS) group rats (40 rats) received 10% fructose for two months and then 20% in drinking water for another one months (modified ref.). In addition, rats were allowed to feed sheep fat 5% kg diet for 90 days. After induction of MS the rats were further subdivided into four groups: MS group, MS rats allowed to drink distilled water with 10% fructose and lead, 150 ppm, third and fourth groups given intraperitoneally lipoic acid (100 mg kg^{-1}) or CoQ10 (10 mg kg^{-1}) in addition to lead and fructose. The treatment was continued for one month. The selected doses were chosen according to those reported before (Vaziri, 2008; Sena *et al.*, 2009; Ozdogan *et al.*, 2012; Mansour *et al.*, 2013).

Tissue collection and preparation: At the end of experiment body weight and blood pressure were measured and fasted overnight and sacrificed under light ether anesthesia to collect blood and kidneys. Blood samples were allowed to stand for 30 min and then centrifuged at $1000 \times g$ for 15 min at 4°C to separate serum and stored at -70°C . The kidney tissues were quickly harvested and kept at -70°C for biochemical investigations.

Biochemical analysis: Blood glucose (mg dL^{-1}) and insulin ($\mu\text{IU mL}^{-1}$) levels were measured using a glucose test reagent kit (EMAPOL, Poland) and rat insulin immunoassay kit respectively (Laboratory Block, The University of Hong Kong, Hong Kong) as described before (Zhang *et al.*, 2002). The serum levels of total cholesterol, triglycerides (TG) and high density lipoprotein cholesterol (HDL) were quantified using Spinreact kits (Spain). For measuring low density lipoprotein cholesterol (LDL) level in serum, Friedewald equation [$\text{LDL} = \text{TC} (\text{HDL-c} + \text{TG}/5)$] was employed as mentioned before (Elhemely *et al.*, 2014). Plasma creatinine were estimated by Jaffe reaction using Creatinine Assay Kit from Sigma-Aldrich as mentioned before (Hervey, 1953; Ciddi and Dodda, 2014) and Blood Urea Nitrogen (BUN) was estimated using commercially available diagnostic kits (Transasia Bio Medicals Ltd., India). Total urine protein was quantified by Bradford method (Bradford, 1976).

Measurement of blood pressure and heart rate: Blood pressure and heart beat rate of rats were assessed by CODA™,

a computerized non-invasive blood pressure system (Kent Scientific, Torrington, CT, USA). The systolic and diastolic blood pressures were measured before and after drug administration. Blood pressure was measured 4 times and the mean value was used as the blood pressure measurement. To minimize stress induced variations in blood pressure, all measurements were taken by the same individual in the same peaceful environment at the same time of the day.

Oxidative stress biomarkers: Glutathione (GSH) levels in kidney tissues were determined using Glutathione Colorimetric Assay Kit (BioVision, Milpitas, CA, USA). The assay depends on the reaction of DTNB (5,5'-dithiobis 2-nitrobenzoic acid) and GSH to generate 2-nitro-5-thiobenzoic acid which has yellow color which is measured at 412 nm as previously described (Ellman, 1959). The determination of lipid peroxides, expressed as malondialdehyde (MDA), in kidney tissues was carried out as mentioned before (Buege and Aust, 1978). Superoxide Dismutase (SOD) activity in kidney tissues was measured using a SOD assay kit-WST (Dojindo Molecular Technologies, USA) as described previously (Ikegami *et al.*, 2002). Tissue homogenates were used to determine nitric oxide (NO) essentially as mentioned before using nitric oxide (NO₂/NO₃) Assay Kit (BioVision, Milpitas, CA, USA) following the manufacturer's instructions. The levels of NO were determined as total nitrate/nitrite using Greiss reagent.

Statistical analysis: Results were presented as the Mean $\pm$ S.D. and statistical comparisons were made using the Student's t-test or one way analysis of variance (ANOVA) followed by Tukey multiple comparisons test. Prism statistical package version 4.0 (GraphPad, San Diego, CA, USA) was used for statistical analyses. Differences were considered significant at $p < 0.05$.

RESULTS

Effects of LA and CoQ10 on body weight, blood glucose, insulin and lipid profile in rats with MS and treated by lead:

The high fructose/fat administration to rats for 90 days caused a significant increase in rats body weight which is a characteristic sign for MS (Table 1). The administration of lead to rats with MS caused a significant decrease in body weight compared to MS alone. Treatment of MS rats drinking lead with LA caused lesser reduction in body weight while CoQ10 showed higher one compared to MS drinking lead rats.

The high fructose/fat administration to rats for 90 days caused a significant increase in both blood glucose and insulin levels which are characteristic signs for MS (Fig. 1). Giving lead to MS rats caused further elevation of glucose level. Only CoQ10 significantly reduced serum glucose level in MS rats receiving lead in drinking water. The MS rats drinking lead showed lower serum insulin level than MS alone and treatment with LA caused similar action. While CoQ10 significantly elevated insulin level than MS rats drinking lead.

The high fructose/fat administration to rats for 90 days caused significant changes in serum lipid profile in MS rats like the increase in cholesterol, LDL and TG and concurrent decrease in HDL (Table 2). The administration of lead worsens the lipid profile while LA and CoQ10 could partially ameliorate the lipid profile.

Effects of LA and CoQ10 on the blood pressure and heart rate in rats with MS and treated by lead:

Rats with MS showed a significant increase in both systolic and diastolic blood pressure as well as heart rate. The MS rats drinking lead showed similar effect. The LA and CoQ10 nearly normalized blood pressure when administered to MS drinking lead. The MS rats drinking lead showed significant reduction of HR compared to MS alone. Treatments of MS rats drinking lead with LA or CoQ10 significantly elevated HR compared to MS and lead group (Fig. 2).

Table 1: Effects of LA and CoQ10 on body weight in rats with MS and treated by lead

Groups	Change in body weight (g)
After 3 months of high fructose/fat administration	
Control-I	60.5 $\pm$ 0.7
MS	105.5 $\pm$ 0.4 ^a
After 1 month more in presence of lead	
Control-II	9.1 $\pm$ 0.6
MS	72.8 $\pm$ 2.8 ^b
Lead	40.5 $\pm$ 0.7 ^{bc}
Lipoic acid	26.3 $\pm$ 0.4 ^{bc}
CoQ10	76.9 $\pm$ 0.6 ^b

Animals were either vehicle or 20% fructose in drinking water and high fat diet for 90 days. After induction of Metabolic Syndrome (MS) the rats were further subdivided into four groups to receive lead (150 ppm) plus lipoic acid (100 mg kg⁻¹) or coenzyme Q10 (10 mg kg⁻¹) for additional 30 days. Values are Mean $\pm$ SEM (n = 6), ^aSignificantly different from control-I group, ^bSignificantly different from control-II group, ^cSignificantly different from MS group

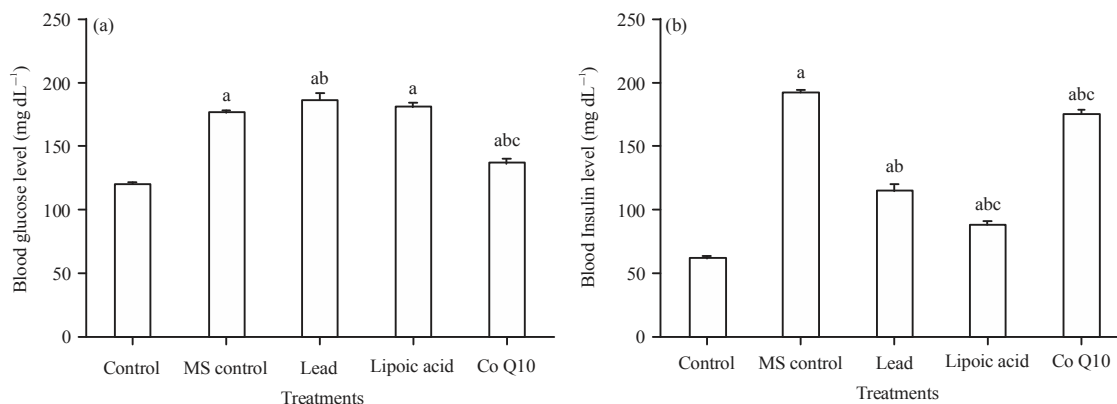


Fig. 1(a-b): Effects of LA and CoQ10 on (a) Blood glucose and (b) Insulin levels in rats with MS and treated by lead. The animals were either vehicle or 20% fructose in drinking water and high fat diet for 90 days. After induction of Metabolic Syndrome (MS) the rats were further subdivided into four groups to receive lead (150 ppm) plus lipoic acid (100 mg kg⁻¹) or coenzyme Q10 (10 mg kg⁻¹) for additional 30 days. Values are Mean $\pm$ SEM (n = 6), ^aSignificantly different from control group, ^bSignificantly different from MS group, ^cSignificantly different from lead group

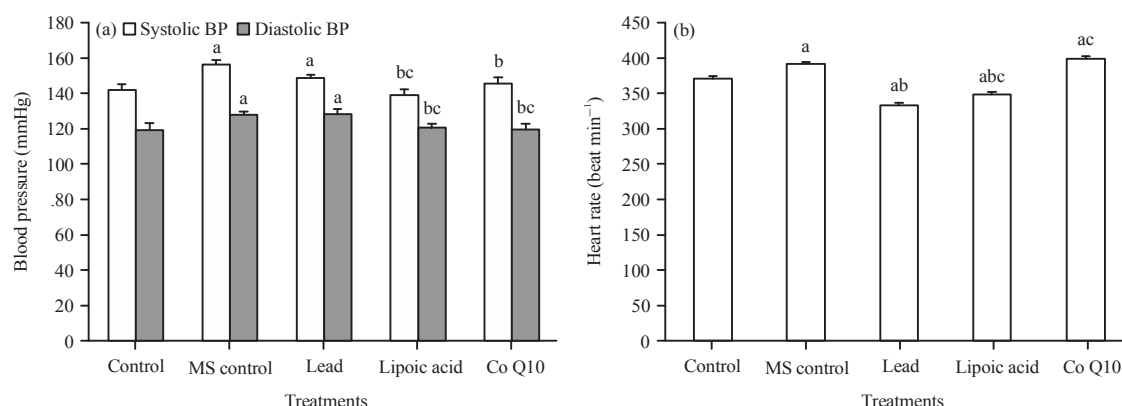


Fig. 2(a-b): Effects of LA and CoQ10 on (a) Blood pressure and (b) Heart rate in rats with MS and treated by lead. The animals were either vehicle or 20% fructose in drinking water and high fat diet for 90 days. After induction of Metabolic Syndrome (MS) the rats were further subdivided into four groups to receive lead (150 ppm) plus lipoic acid (100 mg kg⁻¹) or Co enzyme Q10 (10 mg kg⁻¹) for additional 30 days. Values are Mean $\pm$ SEM (n = 6), ^aSignificantly different from control group, ^bSignificantly different from MS group, ^cSignificantly different from lead group

Table 2: Effects of LA and CoQ10 on lipid profile in rats with MS and treated by lead

Groups	Serum concentration (mg dL ⁻¹)			
	TG	LDL	HDL	Chlo
Control	60.9 $\pm$ 0.5	94.9 $\pm$ 2.9	62.3 $\pm$ 0.4	124.1 $\pm$ 0.3
MS	102.6 $\pm$ 0.5 ^a	111.3 $\pm$ 0.9 ^a	25.3 $\pm$ 0.7 ^a	173.2 $\pm$ 0.5 ^a
Lead	90.8 $\pm$ 0.8 ^{ab}	152.4 $\pm$ 0.4 ^{ab}	20.2 $\pm$ 0.6 ^a	197.7 $\pm$ 0.7 ^{ab}
Lipoic acid	105.9 $\pm$ 0.4 ^{abc}	106.5 $\pm$ 1.4 ^{abc}	36.8 $\pm$ 0.4 ^a	161.5 $\pm$ 0.4 ^{abc}
CoQ10	151.8 $\pm$ 0.6 ^{abc}	89.7 $\pm$ 1.2 ^{bc}	82.3 $\pm$ 0.1 ^a	153.3 $\pm$ 0.2 ^{abc}

Animals were either vehicle or 20% fructose in drinking water and high fat diet for 90 days. After induction of Metabolic Syndrome (MS) the rats were further subdivided into four groups to receive lead (150 ppm) plus lipoic acid (100 mg kg⁻¹) or coenzyme Q10 (10 mg kg⁻¹) for additional 30 days. Values are Mean $\pm$ SEM (n = 6), ^aSignificantly different from control group, ^bSignificantly different from MS group, ^cSignificantly different from lead group.

Effects of LA and CoQ10 on the kidney function in rats with MS and treated by lead: Metabolic syndrome caused kidney damage as indicated by significant increase in serum

creatinine and urea as biomarkers of kidney damage. Giving MS rats lead for one month worsen kidney injury where urea level significantly elevated compared to MS rats given lead.

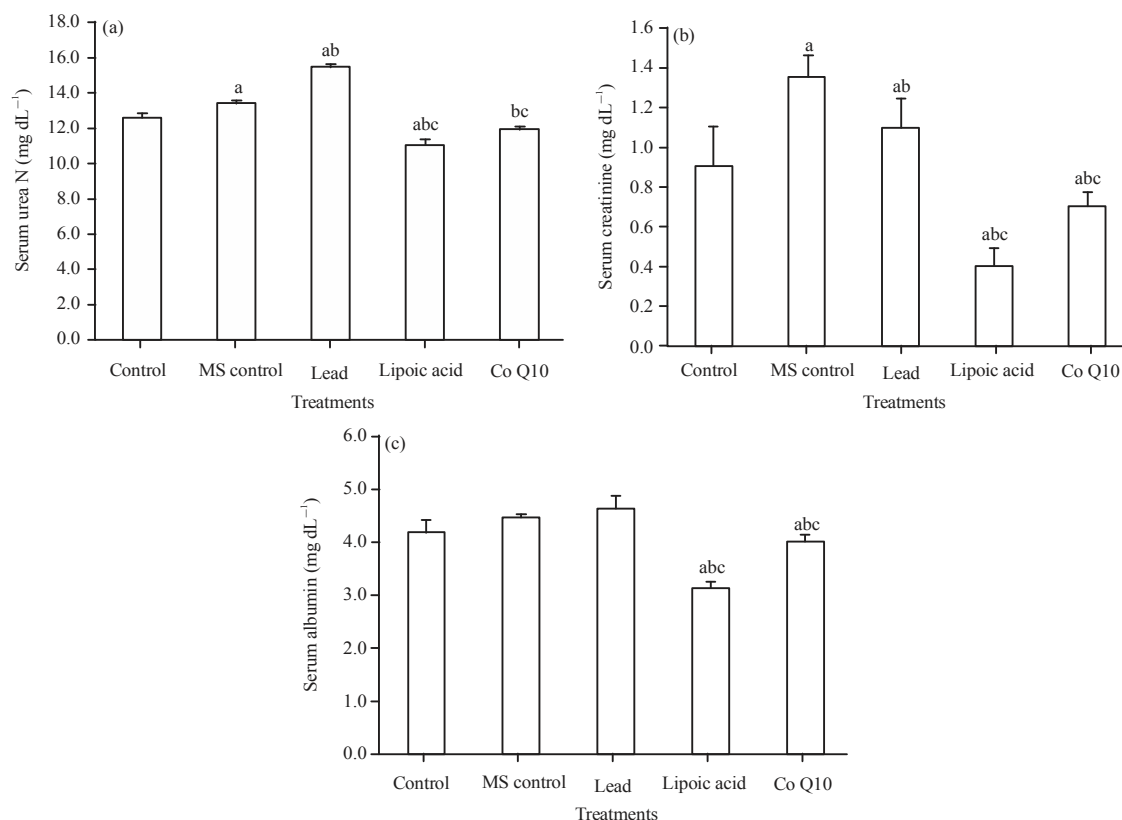


Fig. 3(a-c): Effects of LA and CoQ10 on kidney function, (a) Serum urea nitrogen, (b) Creatinine and (c) Albumin in rats with MS and treated by lead. The animals were either vehicle or 20% fructose in drinking water and high fat diet for 90 days. After induction of Metabolic Syndrome (MS) the rats were further subdivided into four groups to receive lead (150 ppm) plus lipoic acid (100 mg kg⁻¹) or coenzyme Q10 (10 mg kg⁻¹) for additional 30 days. Values are Mean $\pm$ SEM (n = 6). ^aSignificantly different from control group, ^bSignificantly different from MS group, ^cSignificantly different from lead group

The LA and CoQ10 improved kidney function, where they significantly reduce serum creatinine and urea (Fig. 3).

Effects of LA and CoQ10 on oxidative stress biomarkers in rats with MS and treated by lead: Rats with MS showed a significant increase in oxidative stress biomarkers in rats with MS and MS treated by lead showed further damage. These biomarkers included the increase in NO, TNF- α , LDH and MDA with a significant decrease in the antioxidant capacity of tissues as indicated by the decrease of GSH and SOD. Both LA and CoQ10 could ameliorate this damaging effect of lead on kidney tissues as indicated by the restoration of NO, TNF- α and MDA to normal levels and replenishing the normal levels of GSH and SOD (Fig. 4a-e).

DISCUSSION

The administration of high fructose/fat to rats caused a significant increase in rats body weight and the development

of biochemical characteristics associated with MS such as hyperglycemia and hyperlipidemia these results are in accordance with those reported before (Basciano *et al.*, 2005; Stanhope and Havel, 2008). Lead administration to rats with MS worsens the pathophysiological changes in MS by the induction of oxidative stress damage. The induction of oxidative stress in kidney tissues is among the mechanisms involved lead-induced kidney injury (Al-Otaibi *et al.*, 2015; Hasanein and Teimuri-Far, 2015).

To correct the damaging effect of lead in rats with MS, two standard antioxidants were selected LA and CoQ10 to test their potential protective effects. The LA is a potent antioxidant that can correct the oxidative stress as well as it appreciable preventive and therapeutic effects in atherosclerosis and vascular disorders. It also has a high capacity to antagonize the elevated total nitrate/nitrite levels rats with increased oxidative stress (DeMarco *et al.*, 2004). In the present study, LA could partially ameliorate some of the negative effects of lead in MS rats like the significant

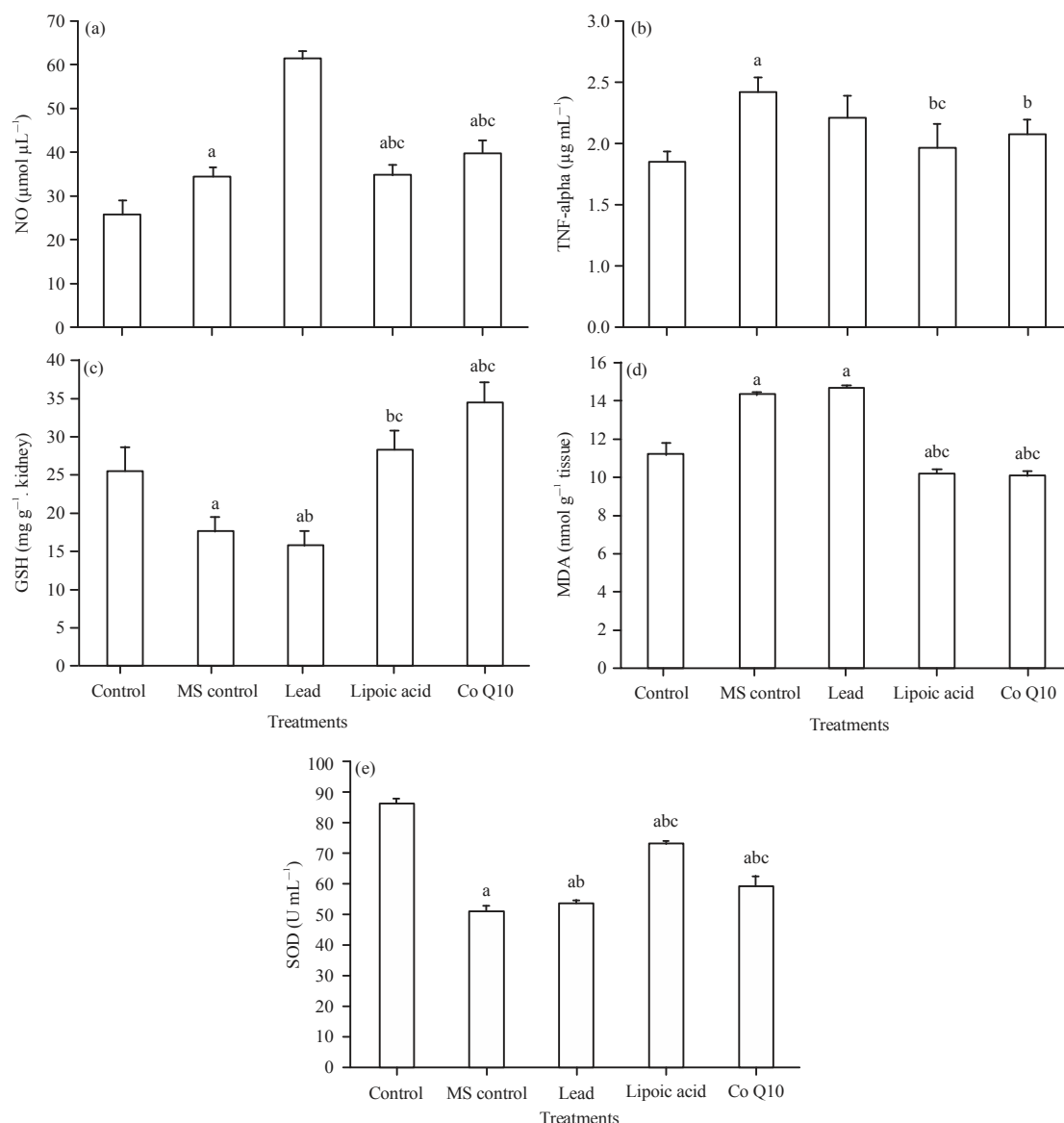


Fig. 4(a-e): Effects of LA and CoQ10 on oxidative stress biomarkers in rats with MS and treated by lead. The animals were either vehicle or 20% fructose in drinking water and high fat diet for 90 days. After induction of Metabolic Syndrome (MS) the rats were further subdivided into four groups to receive lead (150 ppm) plus lipoic acid (100 mg kg^{-1}) or coenzyme Q10 (10 mg kg^{-1}) for additional 30 days. Values are Mean $\pm$ SEM ($n = 6$). (a) NO, (b) TNF-alpha, (c) GSH, (d) MDA and (e) SOD were measured as described under materials and methods. ^aSignificantly different from control group, ^bSignificantly different from MS group, ^cSignificantly different from lead group.

restoration of lipid profile, blood glucose and insulin levels. These effects could be attributed to its antioxidant capacity. The beneficial effects of LA on lipid profile were reported by others and they were explained based on the antioxidant properties of LA (Budin *et al*, 2007; Zhang *et al*, 2011).

The CoQ10 is an oil-soluble, vitamin-like antioxidant synthesized by the body. It has the ability to improve the

diabetic control and blood pressure control via multiple mechanisms including its ability to decrease the oxidative stress (Hodgson *et al*, 2002; Littarru and Tiano, 2010). In the current study, the use of CoQ10 was associated with decreased lipid peroxidation which could be due to its ability to decrease oxidative stress. In addition, the use of CoQ10 corrected some of the harmful effects of lead in MS rats such

as the blood glucose and insulin levels. These results are similar to the reported significant reduction in thiobarbituric acid reactive substances, MDA caused by CoQ10 supplementation (Singh and Niaz, 1999).

CONCLUSION

In conclusion, the use of both LA and CoQ10 were associated with statistically significant beneficial effects in rats with MS and treated by lead. These appreciable effects are mediated through their antioxidant capabilities.

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