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Protective Effects of L-carnitine and Co-enzyme Q10 Against Oxidative Stress Damage in Hypertension

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Abstract: In this study, it was aimed to investigate the effects of L-carnitine and Co-enzyme Q10 administration together with ACE Inhibitor (ACE inh.) on oxidative stress parameters in liver, brain and kidney tissues in L-NAME hypertensive rats. At the study, divided all rats into eight groups, four groups with 14 days of experiment time and four groups with 28 days of experiment time. At the end of the experiment, the rats were euthanized and their liver, brain and kidney tissues were taken. Malondialdehyde (MDA), glutathione (GSH) and nitric oxide (NO) activities were measured in tissue supernatants. While NO and MDA levels increased in all tissues, a significant decrease was observed in GSH levels ($P<0.001$). In conclusion, it is suggested that supplementation of L-carnitine and CoQ10 can be considered as a combination therapy strategy for patients prone to higher levels of oxidative stress and inflammation.
Keywords: ACE inhibitor, Co-enzyme Q10, hypertensive, L-carnitine

Hipertansiyonda L-karnitin ve Ko-enzim Q10'un Oksidatif Stres Hasarına Karşı Koruyucu Etkileri

Öz: Bu çalışmada, L-NAME hipertansif sıçanlarda ACE İnhibitörü (ACE inh.) ile birlikte L-carnitine ve Co-enzyme Q10 uygulamasının karaciğer, beyin ve böbrek dokularında oksidatif stres parametreleri üzerine etkilerinin araştırılması amaçlanmıştır. Çalışmada,14 günlük deney süresine sahip dört grup ve 28 günlük deney süresi sahip olan dört grup olmak üzere sekiz gruba ayrıldı. Deney sonunda sıçanlara ötenazi uygulanarak karaciğer, beyin ve böbrek dokuları alındı. Doku süpernatanlarında malondialdehit (MDA), glutatyon (GSH) ve nitrik oksit (NO) aktiviteleri ölçüldü. Tüm dokularda NO ve MDA seviyeleri yükselirken, GSH seviyelerinde belirgin bir düşüş gözlendi ($P<0.001$). Sonuç olarak L-karnitin ve CoQ10 takviyesinin, daha yüksek düzeyde oksidatif stres ve inflamasyona eğilimli hastalar için bir kombinasyon tedavisi stratejisi olarak düşünülebileceği önerilmektedir.
Anahtar kelimeler: ACE inhibitörü, hipertansif, koenzim Q10, L-karnitin

Introduction

Hypertension is a cardiovascular illness seen in 25-43% of the world's population over the age of 18. Hypertension is defined as the force generated by the blood pumped into the arterial wall from the heart, which is high enough to cause heart illness. It can also be defined as a blood pressure level greater than or equal to 280/90 mmHg (Yusuf et al., 2004). Hypertension occurs for many reasons such as environmental, genetic, anatomical and endocrine system problems. Sodium hypothesis and endothelial dysfunction are the most common views when considering pathogenesis (Adrogué and Madias, 2007). Endothelial cells perform functions such as smooth muscle tone, angiotensin-I and angiotensin-II, thrombomodulin, thromboxane A2 and endothelin release. NO is considered one of the most important substances secreted by endothelium. NO is a free radical that acts widely in the cardiovascular system, neurological system and immune system (Maddu, 2019). NO is secreted under normal conditions and adjusts vascular tone, and can also be secreted by exogenous and endogenous stimuli. In addition to its cell protective effect, proliferation inhibitory and tumor cell-killing effects have also been reported in smooth muscle (Du et al., 2019). NO synthesis is provided from L-arginine. NO stimulates the production of cyclic guanosine monophosphate (cGMP) by activating vascular intracellular guanylate cyclase. It relaxes vascular muscle cells by reducing the concentration of cGMP in the sarcoplasmic reticulum. It is known that the renin-angiotensin system (RAS) is a determinant in

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the formation of hypertension by acting as NO in vascular metabolism and pathology. RAS begins in the macula densa, near distal tubule cells passing between glomerular afferent and efferent arterioles. The amount of renin released from juxtamedullary cells formed by afferent arteriole cells depends on the amount of sodium and chlorine ions in the macula densa. In RAS, at lung angiotensin-converting enzyme (ACE) converts Ang-I to Ang-II during cycling. ANG-II narrows the efferent arteriole and keeps the filtration rate constant by increasing the glomerular hydrostatic pressure (Perez-Loret et al., 2017; Labandeira-Garcia et al., 2017). ACEinhibitors have clinically taken place in antihypertensive and vascular sparing therapy. These inhibitors have been reported to be more effective than other antihypertensive drugs (Arnett et al., 2019). MDA is the end product of lipid peroxidation and its presence is evaluated as an indicator of damage due to oxidative stress. MDA diffuses easily and binds to lipids and proteins in the cell membrane and disrupts the structural integrity of the cell membrane. In studies conducted in organ system models, it has been reported that the level of MDA in ischemia increases and L-carnitine has a preventive effect on the over expression of MDA (Khosla et al., 2004).

Stress factors due to changing living standards and dietary habits lay the groundwork for hypertension (Taşar et al., 2012). The homeostasis of the cell deteriorates due to these stress factors and causes the increase of free radicals. The permeability of the cell membrane increases due to reasons related to lipid peroxidation, and due to this increase, the equilibrium state is disturbed and cell metabolism is at risk (Forouzanfar and Asgharzade, 2020). Antioxidant systems are important and effective mechanisms in cell protection against metabolic disorders caused by free radicals. For this reason, a balance between free radicals and antioxidant systems should be achieved in cell and tissue metabolism. For this balanced state, antioxidants such as propolis, L-carnitine, CoQ10 and α-tocopherol are used as antioxidant system agents effective against the negative effects of free radicals (Alaedin 2021). L-carnitine is a protein synthesized from amino acids such as lysine and methionine. L-carnitine is an antioxidant that eliminates superoxide. It is synthesized from the liver and kidney and is involved in the transport of long-chain fatty acids to the mitochondrial matrix. L-carnitine, which is high in circulating lymphocytes, is known to show activity in the conjugation of organic acids with strong metabolic toxic effects. The peroxidation reactions of fatty acids that occur with the effect of free oxygen radicals formed during metabolic activities are reversed by L-carnitine (Alaedin, 2021). With its antioxidant properties, L-carnitine retains free oxygenradicals and has a protective effect against oxidative damage. It is known that L-carnitine taken externally as a supplement supports the metabolic energy need and is used in cases of diphtheria and hypoglycemia and dialysis patients (Thakur et al., 2021). Studies have shown that L-carnitine increases the expression of genes involved in the release of NO and this effect increases its protection on the cardiovascular system, is effective in cell defense with its antioxidant effect and prevents oxidative stress by regulating enzyme activities (Guerreiro et al., 2018).

CoQ10 is a compound called ubiquinone that is synthesized as a co-factor in the intercellular electron transport chain. CoQ10, a highly effective antioxidant, is located in the mitochondrial membrane. With its antioxidant effect, it prevents lipid peroxidation and protects the cell against free oxygen radicals. CoQ10 expression varies with disease and age. The amount of CoQ10 decreases considerably in cardiovascular-based diseases. CoQ10, is very important for elderly people because it helps strengthen skeletal muscles and prevents the oxidation of important molecules in the cell. CoQ10, has recently been used as an effective nutritional supplement among alternative medicine options, has been stated that it can be used as a support in energy metabolism, strengthening muscles, supporting the immune system, cardiological protection and hypertensive conditions (Sener et al., 2004).

This study, it was aimed to reveal the effects of L-carnitine and CoQ10 application in chronic experimental hypertensive rats formed with L-NAME, which are nitric oxide synthetase enzyme inhibitors, on NO, GSH and MDA values in brain, kidney and liver tissues.

Materials and Methods

The study was confirmed by the Institutional and Animal Care and Ethics Committee of Kafkas University (KAU-HADYEK/2010-27). In this study, 80 adult male Sprague Dawley rats 8 weeks old and weighing 200-250 g were used. Rats were randomly fed with water and fed at 25°C for 12 hours a day/12 hours dark under standard light for 38 days.

Experimental groups

It is divided into 8 experimental experiences used in the study. These groups are:

Group 1 [Control (n= 10)]: No application was made to rats for 14 days.

Group 2 [ACE Inhibitor (n= 10)]: 10 mg/kg ACE inhibitor was applied intraperitoneally for 14 days. The rats were brought into a hypertensive state by given 75 mg/kg L-NAME (Dogrell and Brown, 1998) intraperitoneally for 10 days.

Group 3 [ACE Inhibitor + L-carnitine (n= 10)]: 10 mg/kg ACE inhibitor + 100 mg/kg L-carnitine applied intraperitoneally for 14 days. The rats were brought into a hypertensive state by given 75 mg/kg L-NAME (Dogrell and Brown, 1998) intraperitoneally for 10 days.

Group 4 [ACE Inhibitor + CoQ10 (n= 10)]: 10 mg/kg ACE inhibitor + 100 mg/kg CoQ10 applied intraperitoneally for 14 days. The rats were brought into a hypertensive state by given 75 mg/kg L-NAME (Dogrell and Brown, 1998) intraperitoneally for 10 days.

Group 5 [Control (n= 10)]: No application was made to rats for 28 days.

Group 6 [ACE Inhibitor (n= 10)]: 10 mg/kg ACE inhibitor was applied intraperitoneally for 28 days. The rats were brought into a hypertensive state by given 75 mg/kg L-NAME (Dogrell and Brown, 1998) intraperitoneally for 10 days.

Group 7 [ACE Inhibitor + L-carnitine (n= 10)]: 10 mg/kg ACE inhibitor + 100 mg/kg L-carnitine applied intraperitoneally for 28 days. The rats were brought into a hypertensive state by given 75 mg/kg L-NAME (Dogrell and Brown, 1998) intraperitoneally for 10 days.

Group 8 [ACE Inhibitor + CoQ10 (n= 10)]: 10 mg/kg ACE inhibitor + 100 mg/kg CoQ10 applied intraperitoneally for 28 days. The rats were brought into a hypertensive state by given 75 mg/kgL-NAME (Dogrell and Brown,1998) intraperitoneally for 10 days.

When the experiment period ended, the rats were sacrificed under ether anesthesia by the cervical dislocation method and stored under suitable conditions to analyze the GSH, MDA and NO levels from the brain, liver and kidney tissues by spectrophotometric method colorimetrically.

Homogenization of liver, brain and kidney tissues

Rats were euthanized under ether anesthesia. Tissue samples taken from brain, liver and kidney were immediately fixed with PBS (7.4 pH) at +4 °C and homogenized at 290 g for 3 minutes with the help of a cooling homogenizer (Wiggen-Hauser D-500, Germany). During homogenization, the samples were kept in ice for 15-20 seconds once a minute to prevent heating. The homogenates were centrifuged for 15 minutes at 4 °C at 2400 rpm (Hermle Z 326 K, Germany), and the supernatants obtained were stored at -25 °C until analyzed.

Biochemical analysis

Concentrations of NO, GSH and MDA, respectively, Miranda et al. (2001) Beutler et al. (1963) and Yoshoiko et al. (1979) spectrophotometrically measured (UV-1201, Shimadzu, Japan) according to the method reported.

Statistical analysis

Statistical analyzes were performed using SPSS Statistics 26 package program. Shapiro-Wilk normality test and Levene Homogenity test were applied to all parameters. Independent parametric data were evaluated with One-way ANOVA and Tukey posthoc test. Also Paired Samples T-test was used to compare the 14^{th}-28^{th}days of each groups. $P< 0.05$ was considered significant in all analyzes. As a result of the analysis, the significance values were divided into 3 groups ($P<0.05$; $P<0.01$; $P<0.001$). Because the data are parametric, mean and ± standard deviation (X ± SD) was used for statistical analysis and graphing.

Results

Malondialdehyde, glutathione and nitric oxide levels on the kidney

We were founded that, NO levels of all groups in experimental groups were increased when compared to control groups (Table 1). Significant increases in NO levels were observed in the analysis on the 28^{th} day of all groups. A statistically impressive difference was observed in the ACE inh. group on the both 14^{th} and the 28^{th} days compared to the control group ($P<0.001$). On the Ace inh. group was observed difference meaning between the 14^{th} day and 28th day ($P<0.001$). At NO levels on the ACE inh.+ L-carnitine groups and control groups significantly differences were observed ($P<0.001$). At the same time between the 14^{th} and 28^{th} days meaning differences were observed ($P<0.001$). Similarly, significant differences were observed in the ACE inh+CoQ10 groups compared to the control group ($P<0.001$, $P<0.01$), and also on the 14^{th} and 28^{th} days ($P<0.001$). Statistically significant differences were determined in NO levels in all groups when the 14^{th} and 28^{th} days were compared. It was observed that NO levels increased in all groups on the 28th day. While the highest increase occurred in the ACE inh.+CoQ10 group, the lowest ACE inh. detected in the group ($P<0.001$). There was no statistically significant difference in GSH and MDA levels between the 14^{th} and 28^{th} days (Table 1).

Table 1. Malondialdehyde (MDA), Glutathione (GSH) and Nitric Oxide (NO) parameters in kidney

Kidney	Days	Control (X±SD, n=10)	ACE INH (X±SD, n=10)	ACE INH+L-Carnitine (X±SD, n=10)	ACE INH+CoQ10 (X±SD, n=10)	*P**
GSH (µg/g Protein)	**14th day**	9.34±0.56^{a}	5.84±0.73^{b}	6.43±0.64^{bc}	6.68±0.49^{c}	$^{a-b,a-bc,a-c}$P<0.001, $^{b-c}$P<0.05
	28th day	9.55±1.13^{a}	5.27±0.33^{b}	5.93±0.25^{b}	5.99±0.48^{b}	$^{a-b}$P<0.001
	P**	NS	NS	P<0.05	P<0.05	
MDA (nmol/g Protein)	**14th day**	10.71±0.57^{a}	14.37±1.64^{bc}	12.83±1.9^{bd}	13.32±1.33^{be}	$^{a-bc}$P<0.001, $^{a-be}$P<0.01,$^{a-bd}$P<0.05
	28th day	11.19±1.51^{a}	15.39±1.77^{bc}	14.02±2.79^{bd}	13.87±2.53	$^{a-bc}$P<0.01, $^{a-bd}$P<0.05
	P**	NS	NS	NS	NS	
NO (nmol/g Protein)	**14th day**	261.51±14.81^{a}	489.31±20.61^{b}	289.82±15.29^{c}	301.74±17.74^{cd}	$^{a-b,a-cd,b-c,b-cd}$P<0.001,$^{a-c}$P<0.01
	28th day	257.81±15.23^{a}	624.97±31.92^{b}	546.73±26.81^{c}	574.48±19.12^{c}	$^{a-b,a-c,b-c}$P<0.001
	P**	NS	P<0.001	P<0.001	P<0.001	

*SD: Standart Deviation, ACE INH: Angiotensin Converting Enzyme inhibitors, CoQ10: Co-enzyme 10, µg: microgram, g: gram, nmol: nanomole, NS: Not significant. Different letters indicate statistical significance among the groups. The presence of the same letter in double lettering indicates that there is no statistical difference (*P: PostHoc Tukey, **P: Paired Samples T-test).*

According to the analysis, a decrease in reduced GSH levels was found in all experimental groups compared to the control groups. Significant increases in reduced GSH levels were observed on day 14 in all groups compared to day 14 and day 28. In the ACE inh. group was no observed difference meaning on the 14th and 28th days but statistically significant differences were observed when compared to the control group and ACE inh. group (P<0.001). There was a significant decrease in ACE inh.+L-carnitine groups when compared with the control group (P<0.001; P<0.01). Statistically, there was a significant decrease of reduced GSH levels on the ACE inh.+CoQ10 group (P<0.001) when compared with control group.

Malondialdehyde, glutathione and nitric oxide levels on brain

NO levels on the brain were found that increased in all experimental groups but were higher 28th day than the 14th day. According to the analysis, NO levels were found to increase significantly in the ACE inh. group. Significant differences were observed on days 14 and 28 when looking at the analysis of the ACE+L -carnitine group according to the control group (P<0.001, P<0.01). There was found that significant difference between the ACE inh.+CoQ10 group and with the control group (P<0.001; P<0.01) (Table 2).

Table 2. Malondialdehyde (MDA), Glutathione (GSH) and Nitric Oxide (NO) parameters in brain

Brain	Days	Control (X ± SD,n=10)	ACE INH (X ± SD, n=10)	ACE INH + L-carnitine (X ± SD, n=10)	ACE INH + CoQ10 (X ± SD, n=10)	*P**
GSH (µg/g Protein)	**14th day**	13.85±1.33^{a}	8.69±0.57^{b}	9.57±0.25^{b}	9.51±0.39^{b}	$^{a-b}$P<0.001
	28th day	14.19±2.27^{a}	7.64±0.73^{b}	9.44±0.51^{c}	10.24±0.82^{cd}	$^{a-b, a-c, a-cd}$P<0.001, $^{b-c}$P<0.05, $^{b-cd}$P<0.01
	P**	NS	P<0.01	NS	P<0.05	
MDA (nmol/g Protein)	**14th day**	7.27±0.86^{a}	10.52±0.55^{b}	9.12±0.74^{c}	8.97±0.73^{cd}	$^{a-b, a-c, a-cd, b-cd}$P<0.001, $^{b-c}$P<0.01
	28th day	6.98±0.87^{a}	11.23±1.67^{b}	9.56±0.98^{c}	9.74±0.78^{cd}	$^{a-b, a-c, a-cd}$P<0.001, $^{b-c, b-cd}$P<0.05
	P**	NS	NS	NS	NS	
NO (nmol/g Protein)	**14th day**	273.47±14.83^{a}	569.41±31.35^{b}	321.72±26.94^{c}	338.52±29.38^{cd}	$^{a-b, a-cd, b-c, b-cd}$P<0.001, $^{a-c}$P<0.01
	28th day	266.59±12.83^{a}	732.56±24.49^{b}	667.20±53.69^{c}	694.58±35.15^{bd}	$^{a-b, a-c, a-bd}$P<0.001, $^{b-c}$P<0.01
	P**	NS	P<0.001	P<0.001	P<0.001	

*SD: Standart Deviation, ACE INH: Angiotensin Converting Enzyme inhibitors, CoQ10: Co-enzyme 10, µg: microgram, g: gram, nmol: nanomole, NS: Not significant. Different letters indicate statistical significance among the groups. The presence of the same letter in double lettering indicates that there is no statistical difference (*P: PostHoc Tukey, **P: Paired Samples T-test).*

It was found that MDA values were statistically higher in all experimental groups. MDA levels were observed to increase in the ACE inh. group on both the 14th day and the 28th day (P<0.001, P<0.05). There was found that statistically difference meaning on ACE inh + L-carnitine group when compared with the control group both 14th day and 28th day (P<0.05). Similar differences were observed in group Ace inh.+CoQ10 (P<0.01).

According to analysis was found that in all experimental groups' statistically decreased reduced GSH levels in the brain. On the brain, reduced GSH levels were observed ACE inh., ACE inh.+L-carnitine and ACE inh.+CoQ10 groups compare the control group (P<0.001).

It was found that MDA levels statistically increase in all groups when to compared with the control group. There were significant increases in three groups ACE

inh., ACE inh.+L-carnitine and ACE inh.+CoQ10 group on 14th day (P<0.001). On the 28th day MDA levels were found that statistically different meaning on all experimental groups when compared with the control group in the brain (P<0.001). When the comparison between the 14th and 28th days was made, the GSH levels in the brain decreased in all groups compared to the control group and statistical significance was determined (P<0.05). No statistical changes were detected in MDA levels in the brain between days 14 and 28. On the other hand, an increase in NO levels was determined on the 28th day compared to the 14th day. The highest increase was ACE inh. while the lowest increase occurred in the +CoQ10 group, ACE inh. detected in the group (P<0.001).

Malondialdehyde, glutathione and nitric oxide levelson liver

NO levels were found that significantly higher in all experimental groups when compared to the control group. According to the analysis, NO levels increased on the 14th and 28th day in all groups when compared with the control group, ACE inh. and ACE inh.+L-carnitine and ACE inh.+CoQ10 (P<0.001) (Table 3).

We found that statistically meaning in all groups when compared with the control group. Levels of reduced GSH was observed a significant decrease in ACE inh., ACE inh.+L-carnitine, ACE inh.+CoQ10 groups according to control group (P<0.001). According to the analysis, statistically significant differences were observed between all groups and the control group. It was found that MDA levels were higher when compared to the ACE inh., ACE inh.+L-carnitine and ACE inh.+CoQ10 groups with the control group (P<0.001, P<0.05). When the levels of GSH and MDA in the liver were examined, no statistical difference was determined between the 14th and 28th days. There was an increase in NO levels on the 28th day compared to the 14th day. The highest increase on day 28 was ACE inh. detected in the group. ACE inh.+L-carnitine, ACE inh. The same level of increase was detected in the +CoQ10 groups (P<0.05) (Table 3).

Discussion and Conclusion

Hypertension is defined as a blood pressure level greater than or equal to 280/90 mmHg (Yusuf et al., 2004). CoQ10 is both a potent lipophilic antioxidant and an endogenously synthesized compound that can recycle and also regenerate other antioxidants such as ascorbate and tocopherol after metabolic activity (Mustafa et al., 2017). Biosynthesis of L-carnitine, which is produced naturally, is formed from lysine amino acids in the kidney and liver. There are studies that talk about the anti-inflammatory, antioxidant and anti-apoptotic protective effects of L carnitine (Sener et al., 2004, Abdel-Emam and Ali, 2022). In recent studies, very rapid upregulation of reactive oxidative species has been implicated in the pathogenesis of endothelial dysfunction in several disease states, including increased O2- production, diabetes mellitus, and spontaneously hypertensive rats (Ülker et al., 2003). In this study, it was observed that NO levels increased in liver, brain and kidney tissues of hypertensive rats induced with ACE inhibitor L-NAME in both the 14-day experimental group and the 28-day experimental group. However, when the NO levels of the 28-day study group were examined, it was determined that the brain and kidney tissues increased more than the 14-day study group. This may be because that prolonged injection with L-NAME causes more oxidative stress and endothelial damage in rats. L-carnitine is synthesized endogenously from the essential amino acids lysine and methionine, which are also synthesized in the liver, kidney and brain, and is additionally supplied through animal food products. L-carnitine biosynthesis provides only 25% of the amount needed and is used in metabolism daily. Therefore, the full amount of L-carnitine needs to be supplemented either in the diet or as a supplement (Fielding et al., 2018). In our study, a significant decrease in NO levels was observed in rats treated with L-carnitine and CoQ10. Contrary to our study, Bueno et al. (2005) found that serum NO levels were significantly lower in the normotensive Wistar-Kyoto group in their study of spontaneously hypertensive rats (P<0.01). L-carnitine or

Table 3. Malondialdehyde (MDA), Glutathione (GSH) and Nitric Oxide (NO) parameters in liver

Liver	Days	Control (X ± SD, n=10)	ACE INH (X ± SD, n=10)	ACE INH + L-carnitine (X ± SD, n=10)	ACE INH + CoQ10 (X ± SD, n=10)	P*
GSH (µg/g Protein)	**14th day**	15.77±0.75[a]	9.22±0.39[b]	11.71±0.96[b]	12.23±1.72[b]	[a-b]P<0.001
	28th day	15.23±0.74[a]	9.56±0.61[b]	10.98±1.55[b]	10.83±2.03[b]	[ab]P<0.001
	P**	NS	NS	NS	NS	
MDA (nmol/g Protein)	**14th day**	16.28±1.58[a]	23.68±3.13[b]	19.53±2.17[ac]	20.18±3.53[c]	[a-b]P<0.001, [a-c, b-ac, b-c]P<0.05
	28th day	16.58±1.97[a]	22.87±1.34[b]	20.12±2.74[bc]	19.78±3.26[bc]	[a-b]P<0.001, [a-bc]P<0.05
	p**	NS	NS	NS	NS	
NO (nmol/g Protein)	**14th day**	281.01±16.14[a]	1058.45±81.61[b]	886.63±65.82[cd]	923.09±45.63[cd]	[a-b, a-cd, b-cd]P<0.001
	28th day	286.08±11.36[a]	1138.21±79.47[b]	897.46±41.59[cd]	934.98±24.80[cd]	[a-b, a-cd, b-cd]P<0.001
	P**	NS	P<0.05	NS	NS	

*SD: Standart Deviation, ACE INH: Angiotensin Converting Enzyme inhibitors, CoQ10: Co-enzyme 10, µg: microgram, g: gram, nmol: nanomole, NS: Not significant. Different letters indicate statistical significance among the groups. The presence of the same letter in double lettering indicates that there is no statistical difference (*P: PostHoc Tukey, **P: Paired Samples T-test).*

propionyl-L-carnitine administration increased serum NO levels. This may be related to the fact that NO is characterized by an imbalance between vasoconstrictor and vasodilator (vasodilation) endothelial factors. In a study on the role of the L-arginine/NO pathway in the formation of hypertension in spontaneously modeled hypertensive rats, significant increases were found in thoracic aortic NO synthase (NOS) activity and kidney, aorta, inducible NOS (iNOS) activity, and the modeled hypertensive endothelial NOS (eNOS) proteins have been observed in rats (Vaziri et al. 1998). In the analysis made with the conclusion of our study, we found that the main factor involved in the improvement of endothelial function after treatment with L-carnitine. One known and practiced method to assess the damage caused by oxidative stress is to confirm lipid peroxidation through TBARS content, of which MDA levels are major components (Cardoso et al., 2013). MDA is a physiological ketoaldehyde produced by peroxidative degradation of unsaturated lipids. MDA can be produced as a result of metabolic activity in the metabolism under normal conditions, but it has been reported that high MDA production occurs as a result of oxidative stress. In this study, remarkable increases in lipid peroxidation occurring in the liver, kidney and brain were observed in hypertensive rat models induced with L-NAME. This caused a significant increase in MDA concentrations compared to the control group. It was determined that this increase in the tissues caused serious damage due to hypertensive. On the other hand, MDA levels decreased in groups treated with L-carnitine and CoQ10. Demirdag et al. (2004) showed in their studies that L-carnitine affects acute liver injury by reducing or preventing lipid peroxidation against oxidative damage caused by carbon tetrachloride. In a similar study, it was reported that the increase in MDA levels in rats modeled with chronic renal failure decreased as a result of L-carnitine administration. Again, according to the analyzes made in the same study, it was stated that GSH levels increased (Sener et al., 2004). In another study, researchers found that the hypertensive model established in rats significantly increased oxidative stress with depletion of GSH and increased serum MDA levels (Khan et al., 2016). As the damage duration increases, the effect of L-carnitine decreases. In our study, there was less decrease in MDA liver, kidney and brain levels on the 28th day compared to 14th day in the group treated with L-carnitine. L-carnitine shows its activation by reducing lipid peroxidation and thus reduces damage in tissues. However, as the toxic effect continues, L-carnitine activation decreases and its effectiveness decreases.

Compared with non-enzymatic antioxidants, GSH is both the first to protect plasma membrane lipids from lipid peroxidation and is known as the most important non-enzymatic antioxidant (Sener et al., 2004). In this study, a significant decrease was observed in GSH concentrations in liver, kidney and brain in hypertensive rats induced by L-NAME compared to the control group. This reduction in tissues indicated that hypertensive caused severe damage. On the other hand, L-carnitine and CoQ10 treated groups were found to improve GSH levels close to control. These results showed that GSH scavenges O2- and protects tissues against oxidative stress. Besides all its known antioxidant properties, GSH also plays a vital role in restoring other important free radical scavengers and antioxidants such as vitamin E and ascorbic acid to their reduced normal state (Sener et al., 2004). Despite statin induction in rats, co-administration of L-carnitine and CoQ10 for 2 weeks significantly protected the pancreas against statin toxicity (Sadighara et al., 2017). In another study, it was shown that L-carnitine effectively reduced the liver damage caused by lead acetate in rats (Ozsoy et al., 2011). As oxidative stress is the main cause and an important marker in almost all diseases, it is also very important in the pathogenesis of hypertension or arterial damage due to hypertension (Jaarin et al., 2015). For this reason, current concentrations of oxidative stress-related damage markers in tissues are of great importance in investigating the sources of diseases such as hypertension as well as all diseases.

In conclusion, the dysregulation resulting in oxidative stress due to L-name-induced hypertension in liver, brain and kidney tissues contributes to the pathophysiology of endothelial dysfunction in hypertensive rats. It has been demonstrated that L-carnitine and Co-enzymeQ10 play an important role as regulators in reversing NO, MDA and GSH levels.

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