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Research Article

THE EFFECTS OF MAGNESIUM AND L-CARNITINE ON SOME BIOCHEMICAL PARAMETERS IN EXPERIMENTAL DIABETIC RATS

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ABSTRACT. In this study, the effects of magnesium (Mg) and L-carnitine on body weight, blood glucose, plasma lipase and paraoxonase activities, serum lipids, lipid peroxidation (MDA) and total antioxidant capacity (TAC) were determined in rats with experimental diabetes mellitus induced by streptozotocin. Eighty Wistar albino male rats (200-250 g) were divided into eight groups of ten. First group (control) received 2 ml distilled water; group 2 received 50 mg/kg (b.w., i.p.) STZ; Group 3 received 125 mg/kg (b.w.) Mg; group 4 received 300 mg/kg (b.w.) L-carnitine; group 5 received 125 mg/kg (b.w.) Mg+300 mg/kg (b.w.) L-carnitine; group 6 received 50 mg/kg (b.w.) STZ+125 mg/kg (b.w.) Mg; Group 7 received 50 mg/kg (b.w.) STZ+300 mg/kg (b.w.) L-carnitine; Group 8 received 50 mg/kg (b.w.) STZ+125 mg/kg (b.w.) Mg+300 mg/kg (b.w.) L-carnitine for four weeks. In rats with diabetes, oral administration of 125 mg/kg Mg and 300 mg/kg L-carnitine separately, was found to have no effect on body weight, blood glucose, serum total cholesterol, HDL and LDL-cholesterol and TAC. In diabetic rats, serum MDA levels decreased with the administration of both substances separately and/or in combination, and triglyceride levels decreased with only L-carnitine and Mg+L-carnitine administration. Especially with the combined application of Mg and L-carnitine, the high blood glucose levels determined in rats with diabetes decreased significantly. As a result, it was concluded that Mg and L-carnitine may have antidiabetic effects, especially in combination.

Keywords: *Biochemical parameters, diabetes, L-Carnitine, magnesium, rat.*

INTRODUCTION

Diabetes mellitus, one of the most common types of endocrine diseases in the world, is a metabolic disease characterized by insufficient insulin secretion, increased insulin degradation, lack of insulin activity and resistance to metabolic effects of insulin in the target tissues. In the mechanism of diabetes mellitus, hyperglycemia is associated with excessive hepatic glycogenolysis and glyconeogenesis, and the use of glucose by tissues is reduced, so that the pathology of diabetes is accompanied by disorders of carbohydrate, lipid and protein metabolism [1, 2, 3].

Since the side effects of synthetic drugs are high in the treatment of diabetes, it is of great importance to discover and investigate alternative hypoglycemic agents in recent years. For this purpose various vitamins [4, 5, 6, 7], minerals [5, 8, 9, 10, 11, 12], plant and its seeds are used [13, 14, 15, 16, 17, 18].

Magnesium (Mg) is an important cofactor of more than 300 enzymatic reactions. This element, which has important functions in the metabolism of carbohydrates, lipids, proteins, and nucleic acids, is also involved in the synthesis of adenosine triphosphate (ATP) [19, 20, 21]. L-carnitine, which acts as a major carrier in the transport of long-chain fatty acids from the mitochondrial membrane, has an important role in metabolism of energy and antioxidant activity by affecting the oxidation of free fatty acids and glucose in cells [22, 23, 24].

The role of both Mg and L-carnitine in mitochondria and their role in the regulation of membrane permeability is well known [19, 20, 21, 25]. There are several studies on the positive effects of L-carnitine [26, 27, 28, 29, 30] and Mg [5, 8, 31, 32] on diabetes. The combined effect of L-carnitine and Mg was only found in patients with β-thalassemia, and it was found to have a positive effect on cardiac functions and hematological parameters [33]. In order to contribute to the studies in this field, in this study, the effects of Mg and L-carnitine on body weight, blood glucose, plasma lipase and paraoxonase activities, serum triglyceride, total cholesterol, HDL and LDL-cholesterol and malondialdehyde (MDA) levels, as lipid peroxidation parameter, and total antioxidant capacity (TAC) were evaluated in STZ induced diabetic rats.

MATERIALS AND METHODS

Chemicals

Magnesium as magnesium sulphate ($MgSO_4$) is provided from Merck (Cat. No 105886), L-carnitine as L-carnitine fumarate is purchased from SOLGAR (USA) and STZ is provided from Sigma-Aldrich (Cat. No S0130). All other reagents were obtained from commercial sources.

Animals, Diets and Experimental Design

Eighty male Wistar albino rats (200-250 g), were divided into eight groups of 10 in each group. Rats were housed in polycarbonate cages (3-4 rats in each cage), rough sawdust litter, under conventional animal shelter conditions owned by the research center [controlled temperature (21±2 °C), humidity (50±5%), air exchange (12 per hour) cycle, light (12 hours light, 12 hours dark)]. The groups received the following treatment: group 1: control group; group 2: 50 mg/kg (b.w.) intra peritoneally (i.p.) STZ induced diabetes, group 3: 125 mg/kg (b.w.) Mg, group 4: 300 mg/kg (b.w.) L-carnitine, group 5: 125 mg/kg (b.w.) Mg+300 mg/kg (b.w.) L-carnitine, group 6: diabetes +125 mg/kg (b.w.) Mg, group 7: diabetes+300 mg/kg (b.w.) L-carnitine and group 8: diabetes+125 mg/kg (b.w.) Mg+300 mg/kg (b.w.) L-carnitine. Magnesium and L-carnitine were given to the animals by oral gavage for four weeks. Animals fed with commercial pellet feed to meet their daily nutritional needs received water and feed *ad libitum* throughout the experiment.
Doses of Mg [4, 8, 32, 34] and L-carnitine [26, 27, 28] used in the study were determined according to the results of previous studies.

A five-week preliminary trial using 40 [35], 50 [36] and 60 [37, 38] mg / kg STZ doses to determine the dose of STZ to be administered before starting the study was performed. Diabetes was created by monitoring the general condition of the animals and measuring their weekly tail blood glucose levels by a glucometer (One Touch Lifescan, USA). It was decided that the most appropriate dose was 50 mg/kg.

Streptozotocin (50 mg/kg. b.w/day) dissolved in 0.1 ml. citrate buffer (pH: 4.5) was given to rats as a single dose (i.p.). Streptozotocin, which destroys the beta cells of the pancreas within 3 days after the application, causes the formation of diabetes. [36, 39]. Therefore, fasting blood glucose levels were started to be monitored by glucometer 3 days after STZ administration. Of the animals with polyuria, polyphagia and polydipsia, those with a fasting blood glucose of 200 mg/dl and above were considered as diabetic [16, 35, 40, 41]. Eight animals in the study did not develop diabetes, and three animals died due to improper gavage. Body weights and blood glucose levels of the rats were recorded weekly during the four-week trial.

Blood Collection and Biochemical Analyzes

At the end of the experiment, after pentobarbital (40 mg/kg, b.w.) anesthesia, which did not affect the levels of the parameters to be analyzed, from the animals that were fasted for 12 hours, an average of 2-3 ml blood was collected from their hearts by puncture method into tubes with no anticoagulant for serum and Li-heparin for plasma. Blood were centrifuged at 1300 x g for 10 minutes at 4 ℃ and then serum and plasma were separated. Plasma lipase (Spinreact, Spain, cat. no: 1001275) activities and serum MDA (Cayman, USA, cat no: 10009055) levels were determined with ELISA (Bio-Tek, ELx50, USA), plasma PON1 (Rel Assay, Turkey, cat no: 0031) activities, serum triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol (Spinreact, Spain, cat no: 41031, 41021, 1001098, 41023, respectively), TAC (Rel Assay, Turkey, cat no: 0017) and Mg (Spinreact, Spain, cat no: 1001285) levels were determined with spectrophotometer (Shimadzu UV Model 1208, Japan) by using commercial kits.

Statistical Analysis

Statistical analysis of the data was made with the SPSS 20.0 package program for Microsoft. The difference between the groups was also revealed by one-way analysis of variance (ANOVA). When the F value was found to be significant, Duncan's Multiple Range Test was applied to determine which group caused the difference. Data were given as the mean and standard error of the means. ($P<0.001$) was considered as statistically significant.

RESULTS AND DISCUSSION

Live weight and blood glucose levels

At the end of the experiment, while no statistically significant difference was found between the control group and the groups given Mg, L-carnitine and Mg + L-carnitine. Body weight decreased in all diabetic groups ($P<0.001$) compared to control, Mg and Mg+L-carnitine groups (Table 1).

Blood glucose values measured on the 3rd day after STZ administration were considered as the baseline. At the end of the experiment, blood glucose levels in diabetic groups were found to be significantly higher compared to the control, Mg, L-carnitine and Mg+L-carnitine groups. However, it was observed that the blood glucose levels of the diabetes+Mg+L-carnitine group were still higher than the control group, these decreases were significant compared to diabetes, diabetes+Mg and diabetes+L-carnitine groups (Table 2; $P<0.001$).

Table 1. *Effect of Mg and L-carnitine on live weight (g) in control and trial groups. (Mean ± Standart error)*

Weeks	Control N=10	Diabetes N=10	Mg N=7	L-carnitine N=7	Mg+L-carnitine N=8	Diabetes+Mg N=10	Diabetes+L-carnitine N=8	Diabetes+Mg+L-carnitine N=9	P
Beginning	202.70±2.37	214.60±6.07	208.86±4.65	202.71±1.02	204.62±5.29	202.40±3.42	216.00±2.79	202.67±4.45	-
1	221.30±3.34^{a}	204.20±6.67^{ab}	221.28±6.15^{a}	204.71±5.49^{ab}	211.37±6.06^{ab}	183.80±4.87^{c}	199.87±3.16^{bc}	196.55±7.59^{bc}	***
2	238.80±2.99^{a}	207.70±8.67^{bc}	235.43±6.62^{a}	219.86±4.83^{ab}	223.25±5.97^{ab}	181.70±5.82^{d}	198.12±4.42^{cd}	203.55±9.02^{bc}	***
3	252.00±4.71^{a}	212.00±11.07^{bc}	239.43±7.23^{a}	233.71±5.47^{ab}	238.62±6.89^{a}	197.60±11.06^{c}	197.00±3.72^{c}	197.00±11.83^{c}	***
4	255.90±3.06^{a}	210.20±10.46^{b}	247.00±6.93^{a}	236.14±5.47^{a}	243.62±7.27^{a}	193.20±9.68^{b}	196.00±4.46^{b}	202.67±4.48^{b}	***

*$^{a-d}$: Values within each row with different superscripts differ significantly. -: not significant; ***: P<0.001.*

Table 2. *Effect of Mg and L-carnitine on blood glucose levels (mg/dL) in control and trial groups. (Mean ± Standart error)*

Weeks	Control N=10	Diabetes N=10	Mg N=7	L-carnitine N=7	Mg+L-carnitine N=8	Diabetes+Mg N=10	Diabetes+L-carnitine N=8	Diabetes+Mg + L-carnitine N=9	P
Beginning	116.50±6.77^{a}	378.70±22.17^{a}	116.43±4.17^{b}	110.14±8.30^{b}	103.12±5.27^{b}	352.90±14.90^{a}	351.88±13.07^{a}	351.78±39.82^{a}	***
1	102.30±2.27^{c}	390.20±22.42^{ab}	135.00±14.09^{c}	97.71±7.04^{c}	101.75±2.89^{c}	447.60±19.49^{a}	397.75±17.76^{ab}	338.11±57.69^{b}	***
2	105.80±1.31^{b}	341.40±26.55^{a}	124.28±8.99^{b}	109.57±6.12^{b}	107.25±8.18^{b}	364.70±26.77^{a}	348.25±11.13^{a}	352.67±51.06^{a}	***
3	107.30±2.71^{c}	416.60±29.88^{a}	109.57±9.46^{c}	103.28±5.91^{c}	124.50±11.57^{c}	374.00±18.69^{a}	396.25±34.20^{a}	279.78±36.42^{b}	***
4	134.50±8.66^{c}	435.30±27.98^{a}	96.57±5.16^{c}	100.86±3.40^{c}	96.25±1.76^{c}	458.90±22.10^{a}	401.87±25.36^{a}	271.22±63.92^{b}	***

*$^{a-c}$: Values within each row with different superscripts differ significantly. ***: P<0.001*

Plasma lipase activities, PON1 levels

No statistically significant difference was found between the Mg and Mg+L-carnitine groups in terms of plasma lipase levels. However, the lipase levels of diabetic groups were found to be significantly higher ($P<0.001$) than the control groups. On the other hand, no difference was determined between the groups in terms of plasma PON1 levels (Table 3; $P>0.05$).

Serum MDA levels and TAC

While there was no statistically significant difference between the control, Mg and Mg+L-carnitine groups in terms of serum MDA levels, there was a significant increase ($P<0.001$) in MDA levels only in the diabetic group compared to the control, Mg and Mg+L-carnitine groups. Separate and / or combined administration of both Mg and L-carnitine to diabetic animals was found to significantly reduce diabetes-induced increased lipid peroxidation ($P<0.001$). On the other hand, there was no significant difference between the control and experimental groups in terms of serum TAC (Table 3; $P>0.05$).

Serum lipid levels

There was no difference between control groups, Mg and Mg+L-carnitine groups in terms of serum triglyceride levels, but triglyceride levels were found statistically high only in diabetes group and diabetes+Mg group (Table 3; $P<0.001$). Administration of Mg to rats with diabetes did not affect the increase caused by diabetes, however, L-carnitine and Mg+L-carnitine combination decreased the triglyceride levels significantly and brought them closer to the control group values.

While no difference was observed between the control, Mg and Mg+L-carnitine groups in terms of serum total cholesterol levels, total cholesterol levels in the diabetic group increased ($P<0.001$) statistically. Administration of Mg, L-carnitine and Mg+L-carnitine to diabetic rats brought the increased total cholesterol levels ($P<0.01$) due to diabetes closer to the control group values, although it was not statistically significant (Table 3).

In terms of serum HDL-cholesterol levels, there was no difference between the control group and those given only Mg, L-carnitine and Mg+L-carnitine. On the other hand, HDL-cholesterol levels were significantly lower in diabetic groups compared to control, Mg, L-carnitine and Mg+L-carnitine groups (Table 3; $P<0.001$). Adding Mg and / or L-carnitine to diabetic groups did not affect HDL-cholesterol levels.

There was no difference in serum LDL-cholesterol levels between control, Mg, L-carnitine and Mg+L-carnitine groups. Likewise, no statistically significant difference was found between the control and diabetic groups in terms of serum LDL-cholesterol levels. On the other hand, it was observed that the LDL-cholesterol levels of the groups that were given only Mg, L-carnitine and Mg+L-carnitine were statistically lower ($P<0.001$) compared to diabetes-induced groups. The addition of Mg, L-carnitine and Mg+L-carnitine to diabetic groups did not cause a significant change in LDL-cholesterol values (Table 3).

Serum Mg levels

Serum Mg levels were significantly lower in the diabetic group than the control and Mg groups only ($P<0.001$). The highest serum Mg levels were determined in the groups

given Mg. Compared to the diabetic group alone, there was a significant increase in Mg levels in the diabetes+Mg group ($P<0.001$), while no significant increase was observed in the diabetes+L-carnitine and diabetes+Mg+L-carnitine groups, however, it was observed that the Mg levels in these groups approached the control group values numerically (Table 3).

Diabetes

In the presented study, in accordance with the findings of some researchers [13, 14, 16, 17, 37, 38, 41, 42, 43, 44, 45], experimentally diabetic rats were observed to have lower body weight compared to other groups. This may be due to degeneration in DNA synthesis due to the cytotoxic effect of STZ on pancreatic tissue and hyperglycemia developing as a result of low hexokinase enzyme activity from STZ in all tissues. Because hyperglycemia causes a decrease in ATP synthesis and also an increase in muscle loss due to increased protein breakdown [13, 14, 16, 17, 38, 42, 43, 44]. However, as in previous experimental diabetes studies with rats [23, 43, 44], in this study, higher blood glucose levels in diabetic rats may be attributed to decreased insulin synthesis and release due to the damage caused by the STZ in pancreatic langerhans islets' beta cells [13, 14, 16].

Lipase is an enzyme that is secreted from the pancreas and hydrolyzes triglycerides, and its activity increases in pancreatic inflammations [46]. In the study, plasma lipase activities were higher in the all diabetic animals than in other group animals. In various studies, it was found that lipase activity was higher in diabetic rats by applying 60 [14, 47], 75 [48, 49, 50] mg/kg STZ compared to healthy rats. Increasing the lipase in patients with diabetes has highlighted the use of lipids instead of carbohydrates as an energy source [48]. In addition, it has been suggested that increased LDL-cholesterol and triglyceride levels in plasma are inevitable since elevated lipase enzyme increases lipid absorption [51]. It has been reported that the increase in lipase enzyme levels in diabetic rats is responsible for the increase in the number of Langerhans islets in pancreatic tissue and hyperplasia of beta cell [47]. Ebrahimi et al. [14] stated that after STZ injection, changes occurred in pancreatic exocrine secretion due to the destruction of beta cells, an increase in serum lipase activity, this change could be corrected with insulin injection, and insulin absence could be effective in lipolytic enzyme activity in the gastrointestinal tract.

The most common known lipid disorders in diabetes are hypertriglyceridemia and hypercholesterolemia [13, 42, 47]. Insulin deficiency inactivates the lipoprotein lipase enzyme, which allows the conversion of phospholipids and cholesterol into free fatty acids in the liver, and thus these lipids enter the blood [13, 41]. Insulin has a inhibiting effect of hydroxy methyl glutaryl coenzyme A reductase (HMG-CoA reductase), a key enzyme in the metabolism of cholesterol rich in LDL particles [41, 45]. In the present study, the cause of high serum triglyceride, total cholesterol and LDL-cholesterol levels and low HDL-cholesterol levels in the diabetic group, due to hypoinsulinemia, may be HMG-KoA reductase, an important key enzyme in cholesterol metabolism, may also be the result of lipolysis and lipids into the blood as a result of inactivation of the lipoprotein lipase enzyme [7, 13, 45].

Table 3. *Effect of Mg and L-carnitine on plasma PON1 and lipase (U/L) activities and serum MDA (µmol/L), TAC (mmol/L), triglyceride, total cholesterol, HDL and LDL-cholesterol ang Mg levels (mg/dL) in control and trial groups. (Mean ± Standart error)*

Parameters	**Control N=10**	**Diabetes N=10**	**Mg N=7**	**L-carnitine N=7**	**Mg+L-carnitine N=8**	**Diabetes+Mg N=10**	**Diabetes+L-carnitine N=8**	**Diabetes+Mg+ L-carnitine N=9**	**P**
Lipase	10.03±1.33^{c}	18.62±0.75^{a}	12.73±0.96^{bc}	12.81±0.98^{bc}	11.75±1.27^{c}	21.41±3.01^{a}	18.57±1.18^{a}	16.98±2.71^{ab}	***
PON1	120.71±20.75	132.70±26.90	97.37±18.45	83.03±12.35	98.33±18.22	76.93±11.98	90.15±27.40	84.50±21.56	-
MDA	5.04±0.42^{cd}	9.95±1.05^{a}	4.43±0.15^{d}	4.23±0.29^{d}	4.01±0.44^{d}	7.39±0.87^{b}	7.09±0.63^{bc}	5.56±0.90^{bcd}	***
TAC	2.54±0.51	2.42±0.44	4.07±0.81	3.17±0.66	4.08±0.36	3.22±0.49	3.91±0.33	3.44±0.57	-
Triglyceride	153.66±14.25^{b}	771.55±98.53^{a}	131.66±19.64^{b}	96.53±13.11^{b}	98.65±10.35^{b}	961.15±172.88^{a}	234.94±38.87^{b}	332.16±125.30^{b}	***
Total Cholesterol	68.36±3.85^{bcd}	100.59±8.01^{a}	72.14±4.82^{bcd}	54.92±3.17^{d}	62.91±6.83^{cd}	88.42±11.80^{ab}	80.49±6.55^{abc}	78.47±11.88^{abcd}	***
HDL- Cholesterol	43.87±3.96^{a}	24.88±1.76^{b}	47.56±9.17^{a}	39.21±4.44^{a}	38.07±4.87^{a}	17.06±1.23^{b}	14.76±0.57^{b}	14.90±0.93^{b}	***
LDL- Cholesterol	29.62±1.95^{ab}	37.45±3.76^{a}	21.50±0.99^{b}	23.02±2.30^{b}	22.37±1.79^{b}	39.89±3.84^{a}	37.69±5.56^{a}	31.01±4.77^{ab}	***
Mg	2.43±0.17^{b}	1.77±0.17^{c}	3.06±0.21^{a}	2.14±0.03^{bc}	2.10±0.01^{bc}	3.05±0.36^{a}	2.05±0.12^{bc}	2.32±0.08^{bc}	***

*$^{a-d}$: Values within each row with different superscripts differ significantly. -: not significant; ***: P<0.001*

In diabetes, the antioxidant defense system is disrupted and the increased reactive oxygen species cause breaks in DNA [13, 52]. It has been reported that there is an increase in serum concentrations of MDA, which is the most prominent marker of lipid peroxidation in rats with diabetes, and this is an indirect evidence of high free radical production in diabetes [5, 15, 18]. In this study, the increases in serum MDA concentration without affecting serum TAC, and in plasma PON1, which protects HDL and LDL cholesterol from oxidation and acts as an antioxidant against free radical formation in the cell membrane [53, 54] may be due to the increase in β- oxidation due to insulin deficiency, Increases of β-oxidation causes the accumulation of hydrogen peroxide in tissues, thus enzyme inactivation during the glycation process [5, 11, 15].

Diabetes and Magnesium

In recent years, the interest in nutritional, plant and food supplements that have beneficial effects on health as an alternative to modern medicine has been increasing. Especially in the case of diabetes, natural resources such as vitamins and minerals are needed. It has been stated that Mg, one of the microelements, is not directly related to the mechanism of diabetes, but can help prevent complications from the disease [3]. Magnesium is an important ion in glucose homeostasis. Magnesium, as a cofactor in the glucose transport system of plasma membranes, has an important role in the activity of glucose oxidation enzymes, and is an element that plays a role in insulin release and can regulate the energy transfer mechanism from high-energy phosphate bonds [55, 56].

In the presented study, body weight loss due to diabetes could not be prevented by adding Mg in agreement with the findings of Rondon et al. [40], Aboyami et al. [32] and Ige et al. [12]. This may be due to the fact that diabetes mellitus is a disease characterized by rapid and significant weight loss, as reported by Aboyami et al [32], and therefore the reduced body weight cannot be restored easily. In addition, the significant decrease in high serum MDA levels determined due to diabetes by administering Mg to diabetic rats supports the findings of some researchers [11, 31, 57]. This suggests that due to the scavenging effect of free radicals, Mg may act as an antioxidant by preventing lipid peroxidation [11, 32].

Trace elements have important functions in glucose metabolism, especially as the cofactor of the enzymes involved in the synthesis, release and storage of insulin, the formation of the insulin receptor complex and thus the activation of insulin sensitivity [10, 58]. Diabetic patients have lower serum Zn, Cr, Mn and Mg levels than healthy groups. It has been reported that there is a significantly negative correlation between serum glucose levels and Zn, Cr, Mn and Mg levels in diabetics [9, 10, 59]. In the presented study, it was determined that serum Mg levels in diabetic rats were significantly lower as a result of increased excretion of Mg due to polyuria caused by hyperglycemia, compared to healthy rats constituting the control group, supporting the findings of some researchers [9, 10, 40, 57, 59]. Administration of Mg to the diabetic group caused a significant increase in serum Mg levels, which indicates that Mg can positively affect the mineral balance. On the other hand, the fact that the addition of Mg to diabetic animals did not affect blood glucose and plasma lipase, PON1 and serum lipid (triglyceride, total cholesterol, LDL and HDL cholesterol) levels and TAC, it was determined that the administration of Mg in different doses and forms to rats, and may also be due to the nutritional content of their diets or individual differences in animals, race or sex.

Diabetes and L-Carnitine

L-carnitine is preferred as a very popular food supplement due to its effects on energy metabolism and its antioxidant activity and safe profile. L-carnitine is involved in both the metabolic pathways of fatty acid transport and the separation of acetyl groups from mitochondria. L-carnitine is an essential transporter involved in the transport of long-chain fatty acids across the mitochondrial membrane [22, 23, 24]. Although serum L-carnitine levels were not determined in this study, it has been reported that serum L-carnitine levels decreased in diabetes patients in various studies [24, 60, 61]. It has been stated that regular intake of L-carnitine can be used to improve insulin sensitivity in diabetic patients who are resistant to insulin [24, 62].

Bazotte and Bertolini [61] evaluated the changes in performance and biochemical parameters in male Wistar albino rats that were added 200 and 400 mg/kg L-carnitine daily to their drinking water. These researchers revealed that carnitine administration did not affect body weight and blood glucose and triglyceride, total cholesterol, HDL and LDL cholesterol levels. Same researchers [61] found that the 200 and 400 mg/kg doses of L-carnitine did not affect body weight and blood glucose, total cholesterol, HDL and LDL cholesterol levels in male Wistar albino rats in which they had experimental diabetes with 40 mg / kg alloxan, but the triglyceride levels increased due to diabetes were given 400 mg/kg L-carnitine. They reported that 200 mg/kg L-carnitine had no effect on this parameter. In another study [63] experimental diabetes was induced with 120 mg/kg alloxan in rats of the same race and ip. Serum glucose, cholesterol, triglyceride, LDL and HDL-cholesterol levels were evaluated 16 days after L-carnitine tartrate was administered at 7, 14 and 28 mg / kg doses. With long-term administration of L-carnitine in diabetic rats, increased glucose, cholesterol, triglyceride, LDL-cholesterol levels and decreased HDL-cholesterol concentrations were determined, and it was stated that L-carnitine may have an antidiabetic effect due to its active roles in glucose and lipid metabolism.

Rodrigues et al. [64] found that in rats with experimental diabetes with STZ, decreased body weight and blood insulin levels with diabetes did not change with the administration of 3 g/kg (i.p.) L-carnitine, and lipid levels decreased with increasing plasma glucose, and based on these findings, the application of high-dose L-carnitine administration They have suggested that it can reduce the complications of diabetes.

In another study [65], in hypertensive male albino rats with diabetes induced by 50 mg/kg STZ, L-carnitine was added to the ration at 0.5 g/100 mg doses for 6 weeks, and serum glucose, total cholesterol, LDL-cholesterol. It was determined that total cholesterol and MDA levels decreased numerically, triglyceride levels decreased statistically, serum HDL-cholesterol, NO levels and erythrocyte SOD activity increased numerically, and blood GSH levels significantly increased. It is concluded that L-carnitine may delay or reduce oxidative stress in diabetic hypertensive rats.

Uysal et al. [60] also induced experimental diabetes in animals with 65 mg/kg STZ after administering 500 mg / kg (ip.) L-carnitine to male Wistar albino rats for 30 days and examined changes in blood glucose and lipid peroxidation and antioxidant parameters in pancreatic tissue after 18 days. Researchers found that L-carnitine did not have a protective effect in decreasing blood glucose levels to normal values, which increased with STZ administration. However, in the STZ group, increased pancreatic TBARS levels and GSH-Px activity decreased with L-carnitine administration, and SOD activity was not affected by any of the applications. It has been concluded that the index of lipid peroxidation increased with diabetes decreased with L-carnitine administration, possibly due to the decreased availability of lipids for peroxidation, since this substance plays an

active role in the transport of fatty acids for energy production. The decrease in pancreatic GSH-Px activity was also attributed to the decrease of these free oxygen radicals with L-carnitine administration.

Wang et al. [52] in male Wistar rats with experimental diabetes with 55 mg/kg STZ, L-carnitine given 1 g/L with drinking water did not cause changes in blood glucose levels, however, there was an increase in live weight values in the diabetes+L-carnitine group compared to diabetics, They emphasized that the increase in plasma free fatty acids due to diabetes and the increase in cardiac tissue MDA levels also decreased. These researchers suggested that the decrease in plasma free fatty acids and cardiac tissue MDA levels may result from the prevention of myocardial contraction, which is a diabetes-related damage, by L-carnitine administration.

Al-Malki and Moselhy [30] determined that in albino male rats with diabetes induced by 65 mg/kg STZ, L-carnitine administration caused a numerical increase in body weight and increased blood glucose levels numerically approached the values of the control group.

Supporting the findings of some researchers in the present study [30, 61, 64], L-carnitine supplementation did not have a positive effect on body weight loss due to diabetes, possibly because diabetes mellitus is a disease characterized by rapid and significant weight loss (56). In this study, as some researchers reported [52, 60, 61, 65], the blood glucose levels did not decrease in the diabetes+L-carnitine group, showing that the 300 mg/kg dose of L-carnitine could not have a protective effect in the case of diabetes.

On the other hand, the fact that only triglyceride levels in serum lipid profile decreased with L-carnitine administration in this study is consistent with the findings of Bazotte and Bertolini [61], Abuzahra and Mustafa [65] and Mansour [29]. In addition, the significant decrease in high serum MDA levels determined due to diabetes with the administration of L-carnitine to diabetic rats supports the findings of some researchers [30, 52, 60, 64]. This suggests that L-carnitine may be associated with an active role in the transport of fatty acids for energy production, possibly by reducing the availability of lipids for peroxidation [29, 60].

Limited studies have been available on the effects of L-carnitine on serum/plasma lipase [66, 67] enzyme activity and PON 1 [68, 69] activity. Arafa et al. [66] reported that 200 mg/kg (ip.) L-carnitine administration did not affect lipase enzyme activity in rats with acute pancreatitis, Zhang et al. [67] reported that 300, 600 and 900 mg/kg L-carnitine added to broiler feeds increased serum lipase enzyme activity depending on the dose. In the present study, plasma lipase enzyme activity did not change with L-carnitine administration to diabetic groups. Likewise, PON 1 activity, which is one of the oxidative stress markers, was found to be increased in 200 mg/kg in rabbits fed high fat diet [69] and with 100 mg/kg L-carnitine administered (ip.) to in intense exercise rats [68]. Although it has been demonstrated that it increases; In this study, this parameter was not affected by L-carnitine treatments.

In this study, the addition of L-carnitine to diabetic animals did not affect serum lipid levels and TAC, except plasma lipase, PON1 and triglycerides, and the administration of L-carnitine in different doses and forms to rats, the way of administration of L-carnitine, and also the nutritional content of their rations or individual differences in animals, can also be caused by the breed.

Diabetes and Magnesium+L-Carnitine Combination

The combined effect of L-carnitine and Mg has been investigated only in patients with-thalassemia, and it has been found that they have positive effects on cardiac functions and hematological parameters [33], but no studies on the effects of this combination in diabetes cases have been found. In the present study, it was observed that administration of Mg and L-carnitine to rats with experimental diabetes did not cause any changes in body weight changes, plasma lipase, PON 1 activities and serum total cholesterol, LDL and HDL cholesterol levels and TAC. However, it was determined that this combination significantly decreased blood glucose levels, which increased with diabetes, compared to only the diabetic group, although it did not approach the values of the control group, and brought serum triglyceride levels closer to the control group values. In addition, the lowering effect of the combination of Mg + L-carnitine on serum MDA levels was found to be numerically more significant than the lowering effect of Mg and L-carnitine alone.

CONCLUSION

In rats with diabetes, oral administration of 125 mg/kg Mg and 300 mg/kg L-carnitine separately, was found to have no effect on body weight, blood glucose, serum total cholesterol, HDL and LDL-cholesterol and total antioxidant capacity. In diabetic rats, serum MDA levels decreased with the given of both substances separately and/or in combination. On the other hand, serum triglyceride levels decreased with only L-carnitine and Mg+ L-carnitine administration. However, the significant decrease in high blood glucose levels in diabetic rats, especially with the combined administration of Mg and carnitine, may suggest that this combination may have a potential therapeutic effect in the treatment of diabetes mellitus. As a result; in order to fully determine the antidiabetic effects of Mg and L-carnitine, especially in combination, new studies can be conducted in which different doses and forms of these substances can be used.

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