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ORIGINAL ARTICLE

Effect of L-Carnitine on Serum Parameters in Alloxan-induced Diabetic male rats

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ABSTRACT

L-carnitine (LC) is an essential nutrient. It has vitamin-like qualities and it is considered essential in helping to transport fatty acids into mitochondria. The benefit effect of L-carnitine is proposed for treatment of obesity as long time periods. The objective of this study was to determine the effects of supplementation of LC on serum parameters in alloxan-induced diabetic rats. The animals were made diabetic using by alloxan (120 mg/kg, i.p.). The LC at doses 7, 14 and 28 mg/kg were administered for 16 days, intraperitoneally. Blood samples were obtained from heart after 16 days. The group of control diabetic rats was administered saline as vehicle. Serum glucose, cholesterol, triglycerides, LDL, HDL, urea, uric acid, creatinine, alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) enzymes levels were measured by kit. The results showed the LC treatment decreased raise of serum glucose, cholesterol, triglycerides, LDL, urea, uric acid, ALT and AST levels, while increased serum HDL level in alloxan-induced diabetic rats compared to saline control diabetic rats. The present data indicated that LC has anti-diabetic effect on diabetic animals. So, it should be considered in future therapeutic researches.

Keywords: L-carnitine, diabetes, rat, alloxan

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INTRODUCTION

Carnitines are widely distributed in nature and their potential health benefits have been popularized. Free carnitine (3-hydroxy-4-N-trymethylaminobutyric acid) was first isolated from bovine muscle by Russian scientists in 1905 and only the L-isomer (L-carnitine, LC) was found bioactive (1). In fact, LC could be biosynthesized *de novo* by human body. However, LC present in human tissues is mainly of exogenous origin from meat, poultry and fish in dietary (2,3). It has long been assumed that carnitine is not an essential component of diet as humans have the ability to synthesize this compound. In 1973, Engel reported the first case of carnitine deficiency and treated it with carnitine supplementation (2). In 1985, carnitine was identified as an essential nutrient of multifunction for the body by the International Nutritional Conference held in Chicago (4). Considering their safety and multifunction, carnitines, including LC and L-acetyl-carnitine (LAC), are widely used in various diseases including diabetes (5). So, the aim of the present study was to evaluate the effect of LC administration on serum parameters in diabetic rats.

MATERIALS AND METHODS

Male Wistar rats initially weighing 200 to 250 g purchased from the Pasteur Institute (Karaj, Iran) were used in the experiments. The animals were housed in groups of 5 per cage with free access to standard laboratory chow (35% carbohydrates, 25% proteins, 7% lipids, and 3% vitamins) and tap water. The diet

was purchased from Pars-Dam food service, Tehran, Iran. The animal room was maintained at 22°C ± 2°C with timed lighting on from 7 AM to 19 PM and relative air humidity of 40% to 60%. Eight animals were used for each group of study. Each animal was used once only. The study was conducted in accordance with ethical procedures and policies approved by the Animal Care and Use Committee of Islamic Azad University, Tehran, Iran. The animals were made diabetic using by alloxan (120 mg/kg, i.p.) After 7 days, the rats with fasting blood glucose higher than 180 mg/dl were used for the experiments.
L-carnitine tartarate (Sigma, Germany) was dissolved in saline and prepared its different doses (7, 14 and 28 mg/kg body weight) and treated to the experimental animals, interperitoneally. Animals in the control group received only the 0.5 ml saline as vehicle. The food and water were removed from cages 12 h before testing.
After 16 days, rats were fasted overnight, and blood samples were drawn from heart under light ether anaesthesia. The animals were removed after blood collection. Fasting serum glucose, cholesterol, triglycerides, LDL, HDL, urea, uric acid, creatinine, alanine aminotransferase and aspartate aminotransferase levels were determined by kit (Parsazmoon Company, Iran).
Statistical analyses were carried out by SPSS. Data were expressed as mean ± SEM. Statistical analysis was performed using one-way analysis of variance followed by Tukey post hoc test. The criterion for statistical significance was $p<0.05$.

RESULTS AND DISCUSSION

Type 2 diabetes mellitus represents a major public health issue all over the world. Diabetes prevalence in adults 20 years and older was 4.0% in 1995, and it is expected to increase to 5.4% in 2030 (6).
The present results showed administration alloxan elevated of serum glucose ($p<0.01$), triglycerides ($p<0.01$), cholesterol ($p<0.05$), LDL ($p<0.05$), urea ($p<0.01$), uric acid ($p<0.01$), ALT ($p<0.05$) and AST ($p<0.01$) levels, while attenuated serum HDL level ($p<0.01$) in alloxan- induced diabetic rats compared normal animal. Long term treatment of L-carnitine decreased serum glucose ($p<0.01$), triglycerides ($p<0.01$), cholesterol ($p<0.001$), LDL ($p<0.01$), urea ($p<0.01$), uric acid ($p<0.001$), ALT ($p<0.01$) and AST ($p<0.001$) levels, while elevated serum HDL ($p<0.05$) level in alloxan- induced diabetic rats compared to diabetic control group, significantly (Table 1).
Carnitine metabolism is aberrant in diabetes and plasma concentration of free L-carnitine is diminished (7). L-Carnitine or acetyl-L-carnitine treatment corrects some changes of function in diabetic rats (8,9). The mechanism(s) of LC effects are not known in detail (10), although there have been several suggestions.
Carnitine plays an important role in lipid metabolism, acting as an obligatory cofactor for β-oxidation of fatty acids by facilitating the transport of long-chain fatty acids across the mitochondrial membrane as acylcarnitine esters. Furthermore, because carnitine behaves as a shuttle for acetyl groups from inside to outside the mitochondrial membrane, it covers also a key role in glucose metabolism (11). Carnitine acts as a carrier of activated acyl groups across the mitochondrial membrane of all cells (12-14).
On the other hand, cellular energy production may be improved as carnitine increases the transport of long-chain fatty acids into mitochondria for β-oxidation. The acetate moiety could also act as an energy source and may further enhance mitochondrial lipid handling (15). Moreover, increasing the metabolism of long-chain acyl derivatives, which accumulate in diabetes, could be beneficial, since these amphipathic molecules interfere with many membrane processes (16). Treatment with L-carnitine attenuates the accumulation of long-chain fatty acid esters. An increased mitochondrial NADH/NAD + ratio inhibit β-oxidation of fatty acids. Together with a reduction in tissue L-carnitine, which is necessary for mitochondrial long-chain fatty acid transport, this may be responsible for accumulation of long chain fatty acid esters (17,18).
L-carnitine plays an important role in the mitochondrial uptake of long-chain fatty acids by facilitating their transportation across the inner mitochondrial membrane to undergo β-oxidation. L-carnitine also affects glucose metabolism by activating pyruvate dehydrogenase, thus enhancing the flux of pyruvate into the citric acid cycle (19). This agent by stimulating fatty acid breakdown at the mitochondrial level (20) could reasonably reduce liver fatty acid inflow for lipoprotein production, thus distinctly lowering levels in the subjects presumably affected by excess production of lipoprotein [19-20].
L-carnitine supplementation also has cholesterol-lowering effects. This may depend on its triglyceride-lowering effect that consequently alters the lipoprotein composition that is adversely changed in diabetes. The decreased synthesis of triglyceride lowers the triglycerides content of LDL, which results in an enhanced uptake of LDL by its receptors (21).

Table 1 – Effect of i.p. administration of L-carnitine at doses 7, 14 and 28 mg/kg on serum parameters in diabetic rats.

			L-carnitine (mg/kg)		
Parameters	Control	Saline	7	14	28
Glucose (mg/dl)	105±7	330±57**	270±35+	170±46++	129±39++
Triglycerides (mg/dl)	275±32	454±17**	338±27	293±36++	285±37++
Cholestrol (mg/dl)	179±2	242±16*	161±10++	163±7++	128±18+++
LDL (mg/dl)	48±13	98±15*	49±5+	39±19++	38±6++
HDL (mg/dl)	97±11	39±10**	54±12**	73±12 **	85±7+
AST (UI/l)	927±39	1198±28**	1164±36	953±59+	770±74+++
ALT (UI/l)	894±63	1279±22*	996±112	902±100+	855±66++
Urea (mg/dl)	193±26	523±93**	364±23	305±64	201±75++
Uric acid	5.8±0.34	7.74±0.14**	6.43±0.64	5.34±0.27+++	4.42±0.29+++
Creatinine (mg/dl)	1.575±0.17	2.1±0.5	1.99±0.63	1.92±0.44	1.45±0.4

*p<0.05, **p<0.01, ***p<0.001 different from control group.
+p<0.05, ++p<0.01, +++p<0.001 different from saline group.

CONCLUSION

In conclusion, the investigation demonstrates a significant improvement in serum parameters including glucose, cholesterol, triglyceride, LDL, HDL, urea, uric acid, AST and ALT but not creatinine in diabetic animal in response to L-carnitine treatment. So, the study confirms usage of L-carnitine for therapeutic studies of diabetes.

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