Original Article

Comparing the Protective Effect of L-carnitine, Chromium, and Vitamin D with Metformin on Kidney Parameters, Lipid Profiles, and Antioxidant Indices in Streptozotocin-diabetic Rats

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Abstract

Introduction: Type 1 diabetes mellitus is believed to be caused by decline of insulin secretion because of destruction of the pancreatic β cell, which is characterized with symptoms such as hyperglycemia, polyuria, polydipsia, weight loss, and other symptoms. Due to the lack of sufficient data about protective effect of L-carnitine, chromium, and vitamin D as compared with metformin on biochemical indices in streptozotocin-diabetic rats, it seems necessary to determine the effects of these medications on diabetes. **Materials and Methods:** Sixty Wistar rats were divided into 12 diabetic and healthy groups, and 10 groups of witness, metformin)150 mg/kg(, L-carnitine)200 mg/kg(, and chromium)2 mg/kg(, vitamin D (0.06 µg) and a group treated with simultaneous combined therapy of L-carnitine, chromium, and vitamin D. Diabetes mellitus was induced by streptozotocin. Rats with glucose levels of more than 300 mg/dL were considered as diabetic. After 30 days of treatment, the serum concentrations of renal parameters, lipid profile, malondialdehyde, and activity of superoxide dismutase were measured in the studied groups. **Results:** Malondialdehyde had a significant decrease in all diabetic groups but an increase in nondiabetic metformin and L-carnitine groups ($P < 0.05$). In all groups, a significant reduction of triglyceride was observed ($P < 0.05$). Urea increased in the diabetic metformin and chromium treatment groups, whereas in the other groups it decreased ($P < 0.05$). Among diabetic metformin groups, a significant increase in serum creatinine was found ($P < 0.05$). High-density lipoprotein also decreased in the combined group of L-carnitine, chromium, and vitamin D ($P < 0.05$). Cholesterol in diabetic L-carnitine, chromium treatment, and combined group showed a significant decrease ($P < 0.05$). **Conclusion:** These data showed that all three drugs of L-carnitine, chromium, and vitamin D such as metformin seemed appropriate, which had the hypoglycemic, antilipidemic, and antioxidant effects.

Keywords: *Chromium, diabetes mellitus, L-carnitine, metformin, vitamin D*

Introduction

Diabetes is a progressive disease resulting from high blood glucose levels due to the lack of appropriate physiological response to glucose.[1] Type I diabetes is created as a result of the interaction between genetic, environmental, and immunological factors that ultimately resulted in the destruction of pancreatic β cell and insulin deficiency.[2] Diabetic nephropathy is one of the most common causes of kidney failure. This complication can be found in both insulin and non-insulin-dependent types of diabetes.[3] L-Carnitine is the physiologically active form of carnitine in the body.[4] Carnitine reduction increases fatty acids in the blood, which is followed by increased insulin resistance and will pave the way for diabetes. Therefore, diabetic patients especially those with chronic complications of diabetes will have a greater need to carnitine, and thus carnitine supplement may be useful in diabetic patients.[5] One of the damaging factors in diabetics is the presence of reactive oxygen species (ROS) that antioxidants consumption can reduce their effects to some extent.[6] Chromium is an antioxidant mineral, which has recently been considered and seems necessary for normal glucose and lipid homeostasis.[7] Chromium by binding to low-molecular-weight oligopeptides increases their insulin receptors and phosphorylation and leads to regulation of blood glucose and glycated hemoglobin levels.[8] In the last decades, many non-bone diseases associated with vitamin D deficiency have been included in diabetes. Animal studies have shown that vitamin D is an essential component for the natural secretion of insulin, which decreases insulin resistance through

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affecting on calcium metabolism and regulating insulin receptor gene.[9] Metformin, another hypoglycemic drug that reduces blood glucose level through decreasing gluconeogenesis, has also antioxidant effects associated with increasing of glutathione and reducing of lipid peroxidation in diabetes mellitus.[10] Free radicals are considered important agents causing abnormalities in general and diabetes in particular. Free radicals trigger lipid peroxidation in the membrane, in which its end result would be production of harmful substances that aldehydes are the most important. Malondialdehyde (MDA) is one of the most important organic compounds that can be used as a marker for measuring lipid peroxidation.[11] Oxidative stress is caused by overproduction or incomplete removal of highly ROS or reactive nitrogen species (RNS). Superoxide dismutase (SOD) plays an important role not only in antioxidant defense against free radicals but also in conversion of O_2 superoxide anion to oxygen and hydrogen peroxide.[12] Lipoproteins play a key role in the absorption of dietary cholesterol, long-chain fatty acids, and fat-soluble vitamins along with transferring of triglycerides (TGs), cholesterol, and fat-soluble vitamins from the liver to peripheral tissues and cholesterol from peripheral tissues to the liver.[13] Due to the lack of data about positive or negative effects of L-carnitine, chromium, and vitamin D in type 1 diabetes and taking a safe dietary supplement to reduce the effects of diabetes, determining the effects of these compounds as compared with metformin on lipid peroxidation, renal parameters, and oxidative stress indexes seems necessary.

Materials and Methods

Experimental protocol

Sixty male Wistar rats weighing about 250–300 g, after sustainability at standard conditions of the animals' nest, were divided into 12 groups. One group was used as the control group and the other groups received metformin, L-carnitine, vitamin D, chromium or combination of L-carnitine, chromium, and vitamin D (combined group). L-carnitine, chromium, and metformin were dissolved in physiological saline and injected intraperitoneally daily into study groups.

Diabetes was induced in animals by an intraperitoneal injection of 60 mg/kg of streptozotocin (STZ) (Sigma, Taufkirchen, Germany). Six witness groups were considered, that is, the nondiabetic group, metformin group, L-carnitine group, chromium group, and combined group. STZ leads to the destruction of pancreatic cells and insulin decrease. Rats with blood glucose levels of more than 300 mg/dL were considered as diabetic. To measure blood sugar, blood samples were taken from the tails of the rats and a glucometer and a glucose strip (Bionime GM 110, Taichung, Taiwan) were used. Intraperitoneal injections of 200 mg/kg of L-carnitine, 2 mg/kg of chromium, and 150 mg/kg of metformin to each group were performed daily at a certain time. 0.06 µg vitamin D in almond oil was fed orally to groups daily at certain hour.

Biochemical analysis

After 30 days, serum was separated from collected blood samples. Serum samples were used to determine glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol, TG, Na, K, creatinine, uric acid, urea, MDA, and SOD activity. Kits for HDL, LDL, cholesterol, TG, Na, K, creatinine, uric acid, and urea were purchased from the Pishtaz -Teb Company (Tehran, Iran). However, the estimation of MDA levels was performed using Elisa kit (ZellBio, Ulm, Germany) and the activity of SOD was estimated by Elisa kit (ZellBio, Germany).

Statistical analysis

The data were analyzed by one-way analysis of variance (ANOVA) and independent *t*-test using the SPSS software version 18.0, IBM Corp. USA, New York. A value of $P < 0.05$ was considered statistically significant.

Results

Effects of treatment on renal function

According to Table 1 that shows the serum levels of sodium and potassium (mg/dL), no significant differences were observed in the mean serum levels of sodium and potassium between diabetic and nondiabetic groups ($P > 0.05$). The mean serum creatinine was not significantly different among the nondiabetic groups but in diabetic metformin group as compared with other diabetic groups significantly increased ($P < 0.01$). Average serum uric acid in nondiabetic and diabetic vitamin D groups as compared with all other groups had a significant increase ($P < 0.01$). Serum urea in nondiabetic control group as compared with other groups significantly increased. In both diabetic chromium and diabetic metformin groups, a significantly higher amount of urea was found ($P < 0.01$).

Effects of treatment on lipid profile

According to Table 2, HDL in nondiabetic groups had no significant differences ($P > 0.05$), whereas in the combined group it showed a significant decrease ($P < 0.05$). No significant differences were observed in the LDL and cholesterol between the nondiabetic and diabetic groups ($P > 0.05$). Cholesterol in the combined group, diabetic chromium, and diabetic L-carnitine groups significantly decreased ($P < 0.05$). The TG levels in the nondiabetic L-carnitine groups as compared with other groups significantly decreased, whereas in all the diabetic groups TG levels significantly increased ($P < 0.001$).

Effects of treatment on MDA level and SOD activity

As shown in Figure 1, MDA in nondiabetic metformin and vitamin D groups had a significant increase but in all the diabetic groups it significantly decreased ($P < 0.01$).

According to Figure 2, the SOD activity did not show any significant changes in the nondiabetic and diabetic groups.

Discussion

High-dose STZ injection strongly suppresses the insulin secretion and creates a situation similar to type 1diabetes. It also affects destructively on the liver and kidneys because of oxidative stress. Researchers showed that because of inducing diabetes by STZ the average amount of creatinine and urea

Table 1: Comparison of renal parameters in nondiabetic and diabetic groups

Group		Na (mg/dL)	K (mg/dL)	Creatinine (mg/dL)	Uric acid (mg/dL)	Urea (mg/dL)
Control	Nondiabetic	125.60 ± 18.87	4.52 ± 0.13	0.76 ± 0.04	1.64 ± 0.20	53.90 ± 7.52
	Diabetic	118.40 ± 0.82	4.47 ± 0.11	0.84 ± 0.01	1.44 ± 0.11	98.55 ± 7.51
Metformin	Nondiabetic	142.20 ± 18.39	4.52 ± 0.08	0.69 ± 0.10	1.66 ± 0.46	47 ± 6.29
	Diabetic	118.40 ± 5.72	4.53 ± 0.51	1.04 ± 0.19	1.86 ± 0.48	124.90 ± 15.93
Vitamin D	Nondiabetic	141.20 ± 11.98	4.50 ± 0.16	0.85 ± 0.20	4.11 ± 0.62	40.60 ± 3.32
	Diabetic	128 ± 12.96	4.48 ± 0.16	0.87 ± 0.06	2.42 ± 0.52	102.10 ± 26.91
Chromium	Nondiabetic	122.60 ± 1.94	4.66 ± 0.23	0.67 ± 0.04	2.08 ± 0.35	46.30 ± 7.62
	Diabetic	124.80 ± 2.16	4.55 ± 0.05	0.85 ± 0.02	2.05 ± 0.54	146.40 ± 18.47
L-Carnitine	Nondiabetic	111.10 ± 29.09	4.60 ± 0.07	0.79 ± 0.01	1.51 ± 0.06	45.60 ± 4.08
	Diabetic	124.80 ± 7.72	4.65 ± 0.15	0.92 ± 0.03	1.65 ± 0.41	116.30 ± 12.76
L+C+D	Nondiabetic	137.80 ± 17.56	4.44 ± 0.08	0.79 ± 0.05	1.81 ± 0.29	39.60 ± 4.01
	Diabetic	118.40 ± 5.22	4.52 ± 0.17	0.76 ± 0.18	1.80 ± 0.40	61.70 ± 10.55

Table 2: Comparison of lipid profile in nondiabetic and diabetic groups

Group		HDL (mg/dL)	LDL (mg/dL)	Cholesterol (mg/dL)	TG (mg/dL)
Control	Nondiabetic	23.84 ± 3.32	10.06 ± 1.33	45 ± 7.41	86.30 ± 7.64
	Diabetic	34.79 ± 0.18	13.31 ± 0.08	74.28 ± 0.19	326.20 ± 18.79
Metformin	Nondiabetic	25.50 ± 4.91	14.48 ± 0.57	52.50 ± 9.38	105.10 ± 22.45
	Diabetic	38.10 ± 2.24	17.18 ± 3.49	68.40 ± 3.64	53.60 ± 5.38
Vitamin D	Nondiabetic	25.30 ± 3.70	13.53 ± 3.82	53.90 ± 9.76	106.80 ± 22.03
	Diabetic	41.80 ± 8.52	17.38 ± 2.98	78 ± 7.87	98.50 ± 15.15
Chromium	Nondiabetic	23.94 ± 3.85	13.28 ± 3.64	49.30 ± 11.78	78.10 ± 16.05
	Diabetic	33.80 ± 4.19	19.78 ± 2.90	62.80 ± 7.91	32.40 ± 9.16
L-Carnitine	Nondiabetic	26.20 ± 2.65	11.92 ± 2.66	47.80 ± 5.80	57.10 ± 16.82
	Diabetic	34.40 ± 2.21	15.58 ± 2.34	62.80 ± 7.91	51.70 ± 7.54
L+C+D	Nondiabetic	24.70 ± 1.75	11.76 ± 1.37	48 ± 4.04	92 ± 20.72
	Diabetic	27.26 ± 9.42	15.04 ± 5.87	54.70 ± 5.90	67.70 ± 19.92

nitrogen in diabetic control group as compared with the control group increased such a finding that is expected due to the fact that one complication of diabetes is kidney damage.[14] In this study, in the tested nondiabetic groups no significant changes were observed in creatinine levels and even in the combined group protective role in relation to this factor was shown more. In line with our findings, Samadi *et al.*[15] found that STZ significantly increased the amount of urea in the diabetic group. In this study, the most increase of creatinine was seen in the diabetic metformin group, whereas its significant increase in the diabetic L-carnitine group as compared with the control group indicated kidney damage. Javadi *et al.*[16]reported a significant increase in serum levels of urea and creatinine in diabetic rabbits that reached its maximum in the twelfth week. These observed changes are in accordance with the results of our studies especially in the L-carnitine group. In this study, we saw significant reduction of uric acid in all groups but increase of it in vitamin D group. However, the level of uric acid significantly decreased in nondiabetic groups than diabetic groups; it was significantly lower in the diabetic vitamin D group as compared with nondiabetic vitamin D group.[17] Vitamin D acts through activation by 1α-hydroxylase expressed in the β cell. Vitamin D may directly enhance insulin sensitivity either through stimulating the expression of insulin receptors or activating peroxisome proliferation-activated receptor (PPAR-y), the regulating agent of fatty-acid metabolism in adipose and muscular tissues.[18] In a seven-year study on 21,475 patients, increased levels of uric acid from 7 to 9.8 mg/dL nearly doubled the risk of kidney disease. In the study of Momeni *et al.*,[19] mean serum uric-acid levels in diabetic patients treated with insulin were more than patients treated with glucose-lowering pills that there is no justification for it now but it is consistent with the results of our study in the metformin group. High levels of blood urea can indicate dehydration and renal failure that occurs during diabetes because of renal cell damages and disruption in the glomerular filtration process. In this study, in the group receiving combination therapy of three drugs lowered serum level of urea was seen that can be justified in this way that in this group injection drug by removing free radicals prevented from this increasing trend and led to significant reduction of serum urea. In agreement with our findings, Rowe *et al.*[20]stated that uric-acid levels in nondiabetic group were lower than in diabetic group and no significant differences existed among uric-acid levels of diabetic and nondiabetic groups. Diabetes development disturbs the electrolyte balance of sodium and potassium in the blood and causes diabetic ketoacidocis. In patients with diabetic ketoacidosis, water movement through the intracellular fluid, dilutes the blood concentration of sodium and potassium. According to our results, no significant differences were found in the levels of sodium and potassium between the diabetic and nondiabetic groups. One of the most important indicators for determining the extent of lipid peroxidation is MDA level.

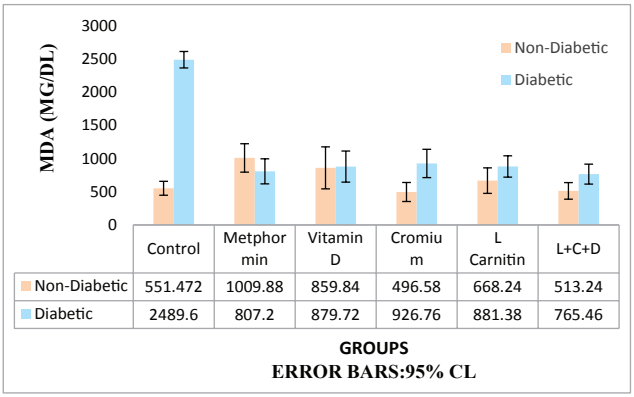

Figure 1: Comparison of the MDA in diabetic and nondiabetic groups

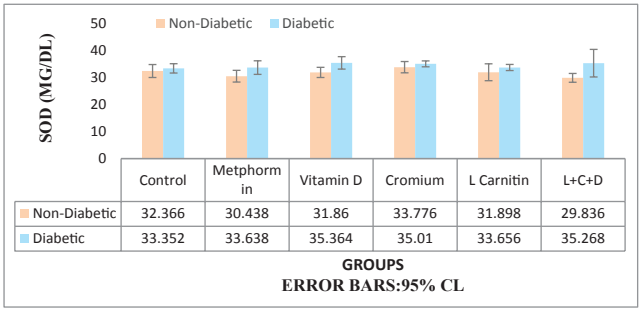

Figure 2: Comparison of the activity of SOD in diabetic and nondiabetic groups

In this research, the MDA was significantly increased in the diabetic group than the nondiabetic group, and this result is consistent with studies of Salimnejad *et al.*.[21] Asadollahi *et al.*[22] found that thiols and uric acid were significantly lower in diabetic patients, whereas MDA was significantly higher in them as increased production of free radicals causes various diseases such as diabetes, weakening of the antioxidant system, and thus reducing the amount of antioxidants. In our study, significant changes of SOD enzyme activity in diabetic group as compared with the control group revealed the destructive effects of oxidative caused by diabetes. Also, decreased SOD activity was seen in all groups as compared with the healthy groups but among diabetic L-carnitine, vitamin D, and chromium groups no significant differences were detected. In agreement with our findings, Garo *et al.*[23] stated that reducing the activity of antioxidant enzymes increased concentrations of oxidative stress markers. Malidis *et al.*[24] reported that in diabetic rats creatine, choline, and carnitine decreased, whereas lactate, alanine, and myo-inositol increased. It seems that carnitine because of its antioxidant property plays an important role not only in protecting sperm membrane against free radicals and oxidative stress phenomenon but also in the fatty-acid metabolisms for transporting of Acyl-CoA across the mitochondrial membrane. L-carnitine deficiency may give rise to reduced long-chain free fatty-acid oxidation and carbohydrate use. L-carnitine treatment increases the activity of glutathione and inhibits lipid peroxidation in the old rats. L-carnitine protective functions can be conveyed by mitochondrial production of energy via changes in cell membrane viscosity. The increase of fats raises toxic radical's production and decreased body's antioxidant defense power in the face of free radicals. Hajinejad *et al.*[25] found that an increase in serum lipid levels correlated with increased levels of serum MDA. In other words, the lipid peroxidation process is related to free radicals because the uncontrolled self-addition mechanism is quite harmful and brings about disturbances in membranes structures, lipids, and other cellular components.[26] According to available studies, cholesterol and TG levels are higher in diabetic patients as compared with nondiabetic patients, and this is consistent with the results of our study.[27] In this study, metformin has anti-lipidemic property and makes a significant reduction in serum cholesterol levels and TGs, and this result is in agreement with findings of Shafi *et al.*[28] Metformin activates adenosine monophsphate-activated protein kinase (AMPK) and inhibits the Acetyl Co-carboxylase (ACC) by phosphorylation. Reduction of malonyl-CoA level removed its inhibitory effect on CTP-1 therefore lipogenesis is prevented.[29] In diabetes, the balance between the body's antioxidant defense system and free radical production is eliminated and the amount of free radicals such as ROS increases in the body. Free radicals similar to ROS reduce peroxidase enzyme and increase LDL oxidation rate. According to Vinson and Bose,[30] chromium in diabetic patients significantly decreased LDL but it is not consistent with our results in the chromium group and this reduction is only consistent with TG level. In addition, Ravanshad *et al.*[31] concluded that in diabetic patients chromium had an anti-lipidemic role and increased the HDL level. In our study in diabetic chromium group, the HDL levels did not change significantly but there was a significant decrease in LDL in the diabetic chromium group as compared with cholesterol and TG.

Conclusion

The results of this study implied that in terms of pharmaceutical combination all three drugs of L-carnitine, chromium, and vitamin D such as metformin seemed appropriate, which had the hypoglycemic and antioxidant effects. The group receiving chromium, among all other groups, had more effective and significantly different results. In the group receiving the combination of L-carnitine, chromium, and vitamin D had also more effective and positive effects. Also, it became clear that synergistic effect of these three factors had a more effective protective role. At the end, it is recommended that more studies are needed to explore comparatively the protective effects of other hypoglycemic drugs with supplement such as chromium, L-carnitine, and vitamin D.

Ethical approval

This research proposal approved in Islamic Azad University of Falavarjan with code 17230520941014.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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