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Original Research

Assessing the Levels of L-Carnitine and Total Antioxidant Capacity in Adults With Newly Diagnosed and Long-Standing Type 2 Diabetes

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Key Messages

- This study is a correlative study that examined the potential of reduced levels of L-carnitine to add to the pathophysiology of type 2 diabetes.
- Multivariate logistic regression analysis showed that L-carnitine was significantly positively associated with total antioxidant capacity and negatively correlated with fasting blood sugar, triglycerides and body mass indexes in patients with type 2 diabetes.
- Setting the value of L-carnitine content to prevent diabetes through the use of effective drugs or nutrition therapy can be useful in monitoring diabetes.

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ABSTRACT

Objectives: This study is essentially a correlative study that examines the potential of reduced levels of L-carnitine (LC) when combined with the pathophysiology of type 2 diabetes. The aim of the study was to assess the levels of LC, total antioxidant capacity (TAOC), fasting blood sugar (FBS), triglycerides and cholesterol in people with newly diagnosed and long-standing type 2 diabetes and in healthy controls.
Methods: The study was done in 90 adult subjects, including 30 with newly diagnosed diabetes, 30 with long-standing type 2 diabetes and 30 healthy controls. Plasma samples were used to assay the biochemical parameters.
Results: In this study, both groups (newly diagnosed and long-standing type 2 diabetes) were significantly different in baseline characteristics, such as age, height, weight, body mass index, FBS, cholesterol and triglycerides, compared to the healthy controls. Plasma LC levels in patients with newly diagnosed and long-standing type 2 diabetes were significantly lower than in healthy controls ($p<0.001$). Also, the mean plasma TAOC level in the patients with newly diagnosed and long-standing type 2 diabetes was slightly lower than in the healthy controls. Nevertheless, TAOC levels were not significantly different across all the groups ($p=0.87$).

The plasma LC levels were significantly positive when compared to the plasma TAOC levels ($r=0.516$), which means that an increase in LC levels is associated with an increase in TAOC levels. However, a negative correlation was observed between LC levels and FBS ($r=-0.387$), triglycerides (-0.159) and body mass indexes ($r=-0.068$). This means that a decrease in LC levels is associated with increases in FBS, triglyceride and body mass index levels.
Conclusions: According to the effects of reduced LC levels on the metabolic profiles of patients with long-standing type 2 diabetes, setting the LC content value to prevent diabetes through the use of effective drugs or nutrition containing LC can be useful in managing diabetes.

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Mots clés :
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RÉSUMÉ

Objectifs : Cette étude est essentiellement une étude de corrélations qui examine le potentiel des niveaux réduits de L-carnitine (LC) en association avec la physiopathologie du diabète de type 2. Le but de l'étude était d'évaluer les niveaux de LC, la capacité antioxydante totale (TAOC), la glycémie à jeun (FBS), les triglycérides et le cholestérol chez des personnes atteintes d'un diabète de type 2 de longue date ou récemment diagnostiqué, et chez des témoins sains.
Méthodes : L'étude a été réalisée chez 90 sujets adultes, dont 30 avec un diabète nouvellement diagnostiqué, 30 avec un diabète de type 2 de longue date et 30 contrôles sains. Des échantillons de plasma ont été utilisés pour mesurer les paramètres biochimiques.
Résultats : Dans cette étude, les deux groupes (diabète de type 2 nouvellement diagnostiqué et diabète de type 2 de longue date) présentaient des caractéristiques de base significativement différentes, telles que l'âge, la taille, le poids, l'indice de masse corporelle, le FBS, le cholestérol et les triglycérides. Les taux plasmatiques de LC chez les patients atteints de diabète de type 2 nouvellement diagnostiqué et de longue date étaient significativement plus faibles que chez les témoins en bonne santé ($p<0,001$). En outre, le niveau moyen de TAOC plasmatique chez les patients atteints de diabète de type 2 nouvellement diagnostiqué et de longue date était légèrement inférieur à celui des témoins sains. Néanmoins, les niveaux de TAOC n'étaient pas significativement différents pour l'ensemble des groupes ($p=0,87$).

Les taux plasmatiques de LC étaient significativement positifs par rapport aux taux de TAOC plasmatiques ($r=0,516$), ce qui signifie qu'une augmentation des taux de LC est associée à une augmentation des niveaux de TAOC. Cependant, une corrélation négative a été observée entre les niveaux de LC et la FBS ($r=–0,387$), les triglycérides ($–0,159$) et les indices de masse corporelle ($r=–0,068$). Cela signifie qu'une diminution des taux de LC est associée à une augmentation des niveaux de FBS, de triglycérides et de l'indice de masse corporelle.
Conclusions : En accord avec les effets de taux réduits de LC sur les profils métaboliques des patients atteints de diabète de type 2 de longue durée, la détermination d'une valeur de la teneur en LC pour prévenir le diabète par l'utilisation de médicaments efficaces ou une alimentation riche en LC peut être utile dans la gestion du diabète.

Introduction

It is widely accepted that type 2 diabetes is 1 of the most important health problems in the modern world, and it requires new diagnostic tools to assess early detection (1). Researchers have reported that L-carnitine (LC) exhibits significant Ca^{2+} chelating activity. LC can affect the calcium-dependent biologic systems because Ca^{2+} is important in the biochemical and physiological processes of living cells (2). Much evidence has been accumulated in recent years that indicates that LC seems to improve glucose metabolism and, thus, has been recommended as a useful therapeutic agent for treating patients with type 2 diabetes (3). Previous studies have shown that plasma LC levels are reduced in patients with type 2 diabetes (3). In another study, it was demonstrated that LC plays a role in the increase of fasting plasma glucose levels, and it increases triglyceride concentrations in patients with type 2 diabetes (3). It has been said that diabetes mellitus is a global metabolic disorder described by hyperglycemia, dyslipidemia and dysfunction of protein metabolism (4). Supplementation with LC improves glycemic control in people with type 2 diabetes (5). LC is an endogenous metabolite and an exogenous nutrient that plays a pivotal role in lipid metabolism. Plasma levels of carnitine are reduced in type 2 diabetes. The administration of LC in type 2 diabetes mellitus is associated with an improvement in glycemia and plasma lipid levels (6). Administration of LC causes a decrease in glucose concentration levels but an increase in triglycerides (7). Higher LC (3-hydroxy-4-N-trimethylammonio-butanoate) concentrations do not prevent late complications of diabetes in patients with type 1 and type 2 diabetes (8).

Orlistat plus LC showed better improvement in body weight and glycemic and lipid profiles than orlistat alone. Furthermore, a faster and better improvement in inflammatory parameters was observed with orlistat plus LC as compared to orlistat only (9). LC affects the regulation of cellular respiration as well as the activity of enzymes that defend against oxidative damage and prevent oxidative stress. LC plays an important role as an antioxidant (10). Moreover, recent evidence has indicated that oxidative stress plays a major role in the pathogenesis of diabetes mellitus (11). Increasing evidence shows that hyperglycemia and oxidative stress play important roles in elevating the complications of diabetes, possibly by utilizing their effects through hyperglycemia-induced reactive oxygen species and overproduction by the mitochondrial electron-transport system. In chronic diabetes mellitus, high plasma levels of glucose and the production of reactive oxygen species at this stage damage the islet cells through oxidative stress (12,13). The main aims of this study were 1) to investigate changes in the biochemical factors in patients with newly diagnosed and long-standing type 2 diabetes; and 2) to analyze the association of LC levels with body mass index (BMI), fasting blood sugar (FBS), cholesterol (Chol), triglycerides (TG) and total antioxidant capacity (TAOC) levels that were involved in both newly diagnosed and long-standing type 2 diabetes.

Methods

In this case-controlled study, plasma LC, TAOC, FBS, TG, Chol, weight (kg), height (m) and BMI (calculated as weight divided by height squared) were determined. To inspect the relationship between LC and TAOC in patients with diabetes, 3 groups were recruited. Group 1 included 30 patients with long-standing type 2 diabetes (9 male, 21 female) and with complications related to type 2 diabetes for at least 2 years at the time of diagnosis. Group 2 included 30 newly diagnosed patients (7 male, 23 female). Group 3 included 30 healthy controls (9 male, 21 female). The groups were between 25 and 75 years of age. The patients were from Iran and were diagnosed according to the principles of the American Diabetes Association.

The inclusion criteria were as follows. In patients newly diagnosed with diabetes, FBS levels >125 mg/dL and BMIs >25 kg/m^2 were established. The duration of diabetes in subjects with long-standing diabetes was 2 years at the time of diagnosis and they had long-term complications resulting from type 2 diabetes. The diabetes statuses in each group were diagnosed by an expert endocrinologist. The exclusion criteria were taking any drug or suffering from other

Table 1
Baseline demographic characteristics of the patients with newly diagnosed and long-standing type 2 diabetes and the healthy control group

Variables	Long-standing type 2 diabetes	Newly diagnosed type 2 diabetes	Control group	p value
Age (y)	58.03 (9.03)	49.43 (10.77)	43.96 (13.04)	<0.001
Height (m)	155 (8.42)	159.73 (10.56)	170.89 (8.51)	<0.001
Weight (kg)	75.73 (15.56)	74.7 (15)	80.68 (9.85)	<0.2
BMI (kg/m^2)	31.39 (4.60)	29.22 (4.04)	27.54 (2.04)	0.001
FBS (mg/dL)	183.13 (42.93)	155.7 (82.25)	84.43 (5.63)	<0.001
Chol (mg/dL)	198.6 (44.98)	179.9 (72.04)	164.5 (25.68)	0.027
TG (mg/dL)	187.6 (74.36)	174.2 (74.71)	117.2 (32.43)	<0.001

Note: Results represent mean ± SD obtained from 3 separate experiments.
BMI, body mass index; *Chol*, cholesterol; *FBS*, fasting blood sugar; *TG*, triglycerides.

Table 2
Laboratory parameters in patients with newly diagnosed and long-standing type 2 diabetes and healthy control groups

Groups/ variables	Long-standing type 2 diabetes	Newly diagnosed type 2 diabetes	Control	p value
LC	49.51 (4.82)	56.09 (5.09)	68.51 (9.40)	<0.001
TAOC	26.23 (3.67)	28.68 (3.17)	29.84 (10.93)	0.87

Note: Results represent mean ± SD obtained from 3 separate experiments.
LC, L-carnitine; *TAOC*, total antioxidant capacity.

diseases as well. Informed consent was obtained from all the patients for subsequent use of their blood samples. This study was cleared by the University Ethics Review Board for human studies (p/J/30/5262,93/12/23), and all the patients signed informed consents. The experiment's protocols were approved by the Babol University of Medical Sciences (#2637).

Laboratory assessment

Blood samples were obtained from all subjects and were collected in acid-washed pipes. Plasma was obtained from these blood samples by adding 1 mg/mL Na_2-EDTA. The samples were centrifuged at 3000*g* for 5 min. Immediately after this, the plasma samples were stored at –20°C for 4 weeks and then moved to –80°C until use. FBS levels were measured using the glucose-oxidation method (14), and TG and Chol levels (15) were measured by the enzymatic method (Pars Azmoon Sanat Pooya, Tehran, Iran). LC and TAOC concentrations were measured using the sandwich enzyme-linked immunosorbent assay (ELISA) method, following the manufacturer's instructions (Bioassay Technology Laboratory, Shanghai, China). These assays were validated using other complementary methodology to confirm the outcomes determined by the ELISA assay.

Statistical analysis

The data were expressed as the mean ± standard deviation. All data are presented as adjusted predictive values based on a linear regression model, using age and BMI as independent variables. The endpoint level for statistical significance was set at $p<0.05$, and the analysis of variance (ANOVA) test was used to define differences among dependent groups. The strength of association between pairs of variables was assessed using the Pearson correlation coefficient.

Results

Based on the results presented in Table 1, we can conclude that subjects with long-standing type 2 diabetes had higher levels of some characteristics such as age, as compared to the newly diagnosed patients with diabetes. BMI levels were higher but only in patients with long-standing diabetes. Nonetheless, those with long-standing type 2 diabetes had lower levels of such characteristics as height. Laboratory parameters, such as FBS, Chol and TG levels, were higher in those with long-standing type 2 diabetes than in those with newly diagnosed type 2 diabetes and healthy controls.

Table 2 indicates that the LC levels were significantly different across all the groups ($p<0.001$). Plasma LC levels in patients with newly diagnosed and long-standing type 2 diabetes were significantly lower than those in healthy controls ($p<0.001$). Also, the mean

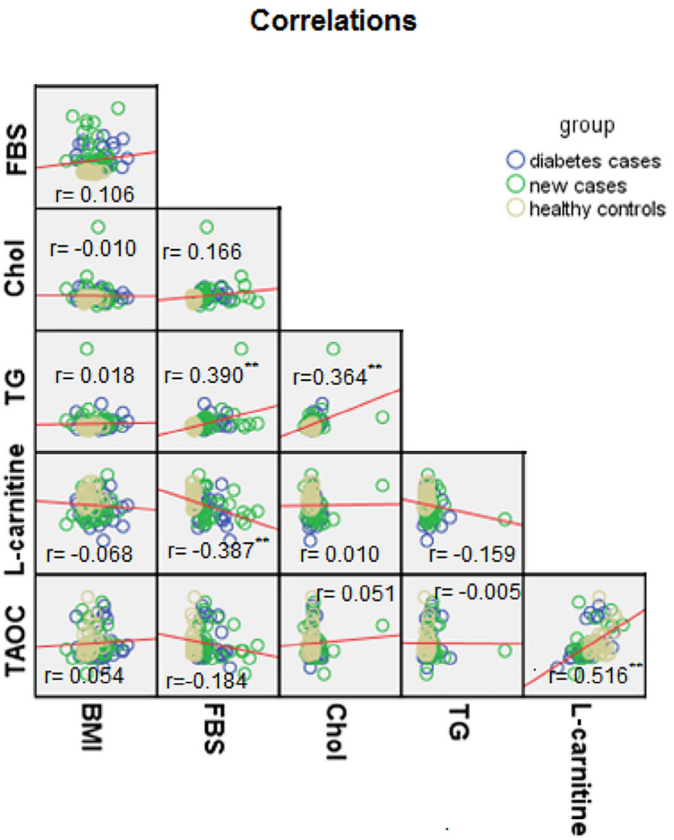

Figure 1. Correlation among L-carnitine, triglycerides (TG), cholesterol (Chol), fasting blood sugar (FBS) and body mass index (BMI) in patients with type 2 diabetes. *TAOC*, total antioxidant capacity.

plasma TAOC levels in the patients with newly diagnosed and long-standing type 2 diabetes were slightly lower than those of the healthy controls. Nevertheless, TAOC levels were not significantly different among the groups ($p=0.87$).

In addition, the correlation between LC levels and BMI, FBS, Chol, TG and TAOC levels in patients with newly diagnosed and long-standing type 2 diabetes was analyzed using correlation curve analysis (Figure 1). Plasma LC levels were significantly positive as compared to plasma TAOC levels ($r=0.516$). Hence, an increase in the LC level is associated with an increase in the TAOC level. However, there is a negative correlation between LC level and FBS ($r=-0.387$), TG (–0.159) and BMI level ($r=-0.068$). This means that a decrease in the LC level is associated with an increase in FBS, TG and BMI. (Supplementary Figure 1)

Discussion

The most important findings of this research were the effects of reduced LC levels in the patients with long-standing type 2

diabetes; the effects were greater than those in the newly diagnosed patients. The amount of FBS, Chol and TG contents were higher in the patients with long-standing type 2 diabetes than in the newly diagnosed patients. Our results show that with lower LC levels, the chance of getting diabetes increases more in patients with long-standing type 2 diabetes than in patients with newly diagnosed diabetes. This effect may be due to the accumulation of various metabolites in the mitochondria or may be related to insulin resistance. It is well known that LC is necessary for the transfer of long-chain fatty acids into the mitochondrial matrix and for the efflux of acyl groups out of the mitochondria. The accumulation of intracellular lipid derivatives within the mitochondria plays a major role in the development of insulin resistance. It is important to emphasize that insulin resistance is a key element in the pathogenesis of newly diagnosed and long-standing type 2 diabetes. Because of this effect, the role of LC has gained attention as a tool for the treatment of insulin resistance in patients with type 2 diabetes. The findings of this study indicate that a decrease in the LC levels in patients with newly diagnosed and long-standing type 2 diabetes has a negative effect on plasma lipid levels. A significant negative correlation was observed between the levels of LC and TG (r=–0.159).

An important finding in this study was that LC levels in patients with long-term and newly diagnosed type 2 diabetes were lower compared to the healthy control group. This result is in accordance with the findings of other studies (7). Because of the role played by LC in lipid and carbohydrate metabolism, decreases in the LC level could cause complications for patients with type 2 diabetes. This study also demonstrated that Chol and TG levels in patients with long-standing type 2 diabetes are considerably higher than in patients with newly diagnosed type 2 diabetes and the healthy control group. These results suggest that LC levels have a reverse relationship with Chol and TG levels. Such findings correlate with other results, which claim that LC deficiency causes abnormalities in lipid metabolism and may cause dyslipidemia (16). An explanation could be related to the fact that a reduction in fatty acid transport inside the mitochondria following the reduction of LC levels results in the cytosolic accumulation of TG and Chol. The results of this study are in accordance with other research (7,17,18). Conversely, the study by Derosa et al of patients with diabetes and that of Huang et al of patients undergoing hemodialysis showed that LC supplementation did not have any significant effect on serum total Chol or TG levels (16,19).

This study showed that FBS levels in patients with newly diagnosed and long-standing type 2 diabetes were higher than those in the healthy controls. On the other hand, LC had a negative correlation with FBS levels (r=–0.387). The explanation for this could be related to the role of LC. First, low LC levels decrease the level of cytoplasmic acetyl-CoA due to an inhibition of pyruvate dehydrogenase activity. Second, there is a decrease in metabolism due to the effect of LC, which plays a regulatory role in the synthesis and degradation of important glycolytic and gluconeogenic enzymes related to carbohydrate metabolism. The roles of LC suggest that decreased LC levels cause a rise in the FBS levels and increase the risk for diabetes in patients with diabetes because it causes a decrease in acetyl-CoA and diminishes glucose-induced insulin secretion. This observation correlates with other findings: low LC levels affect the metabolism of glucose (20,21). The patients in the Mingrone study showed that in type 2 diabetes, LC increases glucose uptake and regulates the synthesis of glycolytic and gluconeogenic enzymes (22).

This study indicated that TOAC concentration in patients with newly diagnosed and long-standing type 2 diabetes was significantly lower than its mean concentration level in the controls. These findings are in accordance with the results of other studies (23). These results could be related to the fact that reactive oxygen species are more numerous in patients with diabetes (12). However, in this issue, there was no significant difference between patients with newly diagnosed diabetes and long-standing type 2 diabetes compared with the controls. On the contrary, Savu et al showed that in patients with diabetes, antioxidant levels decrease more than in healthy subjects (12). This might be due to the ages of the subjects. As age increases, oxidative damage has an inverse effect on total body antioxidants.

TAOC levels had a positive relationship with LC levels according to their significant correlations. LC averts oxidative stress and normalizes the activity of enzymes involved in the body's defense system. In contrast to oxidative damage, it shows that LC has an effective antioxidant activity, including reducing the power of superoxide anion radical scavenging, hydrogen peroxide scavenging and metal-chelating activities (11).

In addition, the association of LC with other components involved in both newly diagnosed and long-standing type 2 diabetes, such as BMI, FBS, Chol, TG and TAOC levels, were analyzed by correlation curve analysis. It is suggested that the association of LC levels with TAOC levels might be due to the high prevalence of free radicals in these patients.

Conclusions

In conclusion, multivariate logistic regression analysis showed that LC had a significant positive association with TAOC, while it had a negative correlation with FBS, TG and BMI levels in the patients with newly diagnosed and long-standing type 2 diabetes. LC levels were found to be lower in patients with newly diagnosed and long-standing type 2 diabetes as compared to the healthy controls. Patients with long-standing type 2 diabetes had worse metabolic profiles when compared with the healthy controls. According to our results the most effective of reduced LC levels on the metabolic profiles of patients with long-standing type 2 diabetes, setting the LC content so as to prevent diabetes through the use of effective drugs or nutrition therapy containing LC can be useful in controlling diabetes. These results might be used in the prevention of diabetes or the improvement of complications of diabetes. However, further studies are needed to elucidate the mechanism in this regard, and more comprehensive investigations are being carried out in our laboratory.

This study has some limitations. The small sample size might have led to discrepancies in the results of statistical analyses. Nonetheless, the study is sufficient to demonstrate novel associations of LC with FBS, Chol, TG and TAOC levels in patients with newly diagnosed and long-standing type 2 diabetes.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of *Canadian Journal of Diabetes* at https://www.canadianjournalofdiabetes.com.

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Author Disclosures

Conflicts of interest: None.

Author Contributions

All authors of this article directly participated in the planning, execution and analysis of the study. DQ designed the study; MR, ZM and DQ conducted the research; MR analyzed the data and performed the statistical analyses; MR and DQ wrote the article; DQ takes primary responsibility for the final content. All authors read and approved the final manuscript.

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Supplementary Material

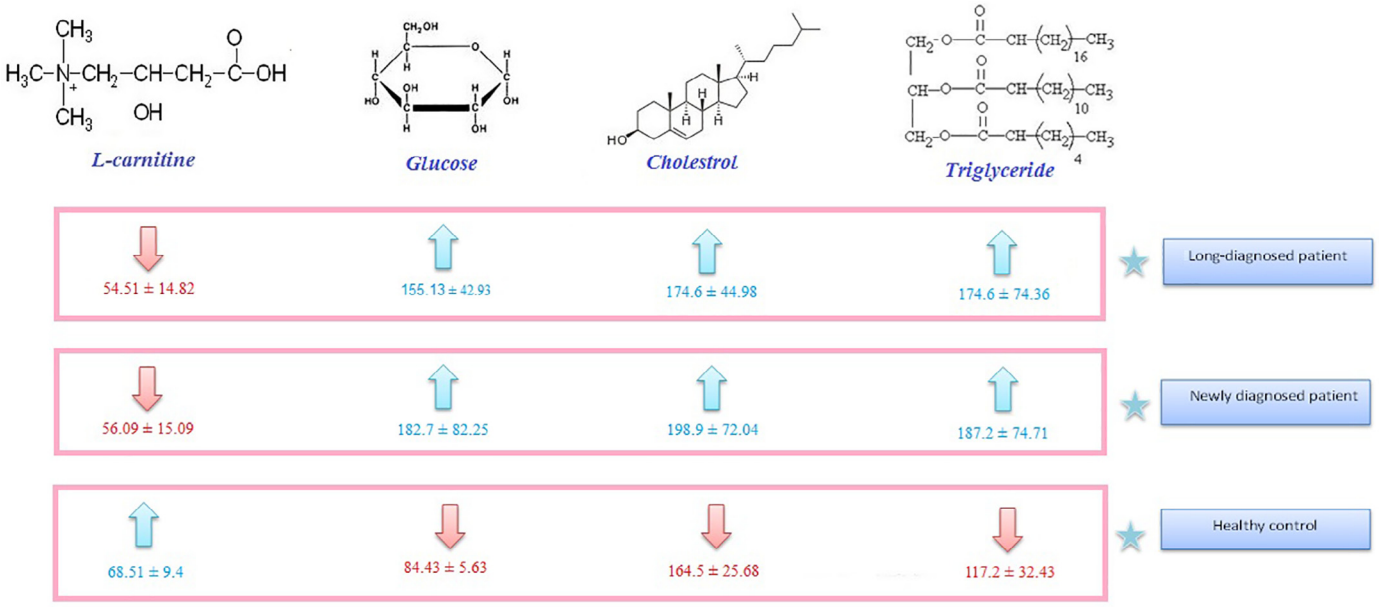

Figure S1. L-carnitine, glucose, cholesterol and triglyceride level changes in the patients with newly diagnosed, long-standing type 2 diabetes and in healthy controls.