Abstract

To assess the effect of L-carnitine administration as an additional useful supplement, its modulating effect on glycaemic state, and its effect on certain parameters of renal function in type 2 diabetics with or without nephropathy. Patients and Methods: Fifty-four patients (32 males, 22 females) with type 2 diabetes mellitus who were attending Al-Waffa Diabetic Clinic, Mosul, Iraq; during the period from 1st October 2005 to 31st March 2006 were included in this study. L-carnitine was given to each of these diabetics for 45 days in a dose of 550 mg, in form of tablets in two doses orally, in addition to their other hypoglycaemic drugs. Blood samples were taken from each patient for the measurement of fasting plasma glucose (FPG), HbA1c, serum creatinine and urea before the first administration of L-carnitine, then after 15, 30 and 45 days from the commencement of the study. Mean FPG showed significant decrease (p<0.001) between the four intervals with a mean of 11.15 mmol/L before starting carnitine administration, 8.55 mmol/L after 15 days, 8.30 mmol/L after 30 days and 7.85 mmol/L after 45 days from the administration of carnitine. This study also shows a significant decrease in mean HbA1 and HbA1c when compared to that before administration (p<0.001) with mean of 8.99% and 6.78% respectively before starting administration, and 7.65% and 5.71% respectively 45 days after carnitine administration. Serum creatinine showed a significant decrease (p<0.001) with a mean of 114.9 µmol/L and 100.6 µmol/L before and 45 day from starting carnitine administration respectively. Serum urea showed also a significant decrease (p<0.01) from a mean of 6.61 mmol/L before carnitine administration and 6.03 mmol/L 45 days from starting carnitine administration. L-carnitine can be useful as an additional dietary supplement and pharmaceutical agent that complement other hypoglycaemic drugs for the management of type 2 diabetics. It has a lowering effect on fasting plasma glucose and blood HbA1c as well as its effect on improving renal function.

Keywords: Diabetes mellitus, carnitine, glucose, HbA1c, creatinine, urea

Introduction

Carnitine is considered as one of the dietary supplement, which is synthesized from the amino acids methionine and lysine(1). It is β-hydroxy γ-trimethyl ammonium butyrate, a naturally occurring compound inside the body that facilitates the transport of fatty acid inside the mitochondria. L-carnitine, or so-called levo carnitine is one of the important derivatives for mitochondrial β-oxidation system of fatty acids(2). It increases the production of energy through stimulating fats oxidation. This will result in the reduction of total fat mass and serum lipid with increase in the percentage of total muscle mass. Hence, carnitine can improve the nutritional state and body mass index, and promote positive protein balance(3).

Moreover, carnitine can decrease the oxidative stress and inhibit apoptosis (programmed cell death) by preventing ceramide formation (4). It also plays a role in membrane repairing process especially in the erythrocytes (5). Moreover, carnitine can stimulate the immune response (6), promote maturation of the fetus and sperm (7), and correct receptors abnormalities in aging brain, and heart (8). Diabetes mellitus is a common disease that is characterized by disturbed metabolism of carbohydrates and fats which leads to the development of long-term microvascular and macrovascular complications(9, 10). As carnitine...
contributes in the metabolism of fats and glucose, therefore any deficiency may cause a defect in their metabolism (11).

Decreased plasma carnitine level has been well reported in type 2 diabetics, but less in type 1 diabetics (12) with a reduction in plasma carnitine starts with the development of complications(13). The decrease in plasma free carnitine may be attributed to insulin deficiency and to unopposed glucagon excess(14). In concern with diabetic complications, Tamamogullari et al., (9) shows that carnitine deficiency may aggravate the appearance of complications while carnitine supplementation improves the progression of retinopathy and sural nerve conduction and sensory symptoms in patients with diabetic polyneuropathy (15). Also, carnitine stimulates the use of glucose by peripheral tissues and increases the sensitivity of the cells to insulin (17). It is recommended that plasma free carnitine should be determined in diabetics, even if they have good metabolic control (19). On the other hand, hypoglycemia induced by insulin over-therapy could be elevated by the administration of L-carnitine (18).

The objectives of this work were to assess the effect of L-carnitine administration in type 2 diabetics: 1. As an additional useful supplement with its possible pharmaceutical therapy when used with other hypoglycaemic drugs; 2. Its modulating effect on glycaemic state (plasma glucose and HbA1c), and 3. Its effect on certain parameters of renal function in diabetics with or without nephropathy.

Subjects and Methods

Patients: Fifty-four diabetic patients (32 males and 22 females) were volunteered in this study. Their ages were ranged from 25-70 years with a mean of 45 years. All of them were known to have type 2 diabetes mellitus and were regularly consulting Al-Wafaa Diabetic Clinic, Al-Zahrawi Hospital, Mosul, Iraq during the period from 1st October 2005 to 31st March 2006. All of them have already been diagnosed to have type 2 diabetes mellitus by a specialist physician, and have developed certain complications of diabetes. Ethically, all these diabetics agreed to cooperate in this study by taking orally 550 mg of L-carnitine twice daily for 45 days and to give blood samples every 15 days from the commencement of the treatment.

This form of medicine is produced under the name of Health Aid L-carnitine manufactured by PHARMADASS Limited, health aid house company (UK). The patients continued the use of other oral hypoglycaemic drugs such as Glibenclamide or/and Metformine or any other drug such as antihypertensive, which have already been prescribed to them before starting this study.

Specimens and methods: Fasting blood samples were obtained from all patients included in this study by antecubital venepuncture between 9.00 am and 1.00 pm. About 4 ml of venous blood specimens were collected from each subject and separated into three parts according to the test to be measured. For HbA1c, 1 ml of blood was transferred into an EDTA tube, with gentle shaking for proper mixing with the anticoagulant. For glucose, 1 ml of blood was transferred into a tube containing sodium fluoride-potassium oxalate (antiglycolytic-anticoagulant).

Following separation by centrifugation, the resultant plasma was used for glucose determination. For creatinine and urea, the remaining 2 ml of blood was transferred into a plain tube, allowed to clot for 15 min in a water bath at 37°C, then serum was separated by centrifugation and used for creatinine and urea determination. Fasting plasma glucose (FPG) was measured by oxidase-peroxidase method which is highly specific for D-glucose, using a kit supplied from Biocon (Germany)(19). HbA1c was measured in whole blood sample by ion-exchange resin quantitative colorimetric determination using a kit supplied from Stanbio (USA) (20). Serum creatinine was measured by Jafe end point method using a kit supplied from Bioemix (France) (21) and serum urea was measured by urease method using kit supplied by biomerix (France) (22). Statistical analysis: The experimental data were subjected to Analysis of Variance, Duncan Multiple Range Tests, and Trend Analysis using Statistical Analysis System(SAS) according to Littell et al., (23).
**Results**

One of the parameters studied in this work was the fasting plasma glucose concentration.

The samples were taken from the patients at four intervals as follows:
1. Before taking the first dose of L-carnitine (at 0 times).
2. After 15 days from administration of L-carnitine.
3. After 30 days from administration L-carnitine.
4. After 45 days from administration L-carnitine.

Whereas the samples of the other parameters (Serum; Urea, Creatinine, HbA1 and HbA1c) were taken at 0 time and after 45 days from commencing the administration of L-Carnitine.

The results of this study shows that there is a significant decrease in FPG at all the four intervals ($P<0.001$) from 11.15 mmol/L (222.7 mg/dl) before starting treatment to 8.55 mmol/L (171.07 mg/dl) after 15 days, 8.30 mmol/L (165.93 mg/dl) after 30 days and 7.85 mmol/L (157.05 mg/dl) after 45 days of commencement of Carnitine therapy respectively (Table 1).

In addition, there is also a significant decrease ($P<0.001$) in the mean of HbA1c from 8.99% before starting treatment to 7.65% at the end of 45 days of using carnitine (Table 2). This finding is in agreement with that of Rahbar el al., (27) who found that L-carnitine when administered in a dose of 3 gm daily to previous treatment by Glypride and Metformine over 12 weeks period resulted in reducing FPG in type 2 diabetics by 13%. In addition, a significant decrease in HbA1c was also observed.

The reduction in FPG following L-carnitine administration may be accounted to that L-carnitine increases the use of glucose either by peripheral tissues (16), or by activating pyruvate dehydrogenase, and decreasing inter mitochondrial acetyl-CoA/CoA ratio (28). This hypothesis is approved by full saturation of plasma by lactate after L-carnitine administration, and increased cellular glucose uptake (29). Another hypothesis may be that, L-carnitine can play a role in the treatment of type 2 diabetics by improving insulin resistance that is caused by post-receptors defect (30). This means that L-carnitine may be useful for cell membrane repairing and, removal of harmful lipid from the cells may improve or decrease the resistance to insulin action by photoreceptor defect either at the membrane level or intracellularly (31).

The result of this study disagrees with that of Derosa et al., (32) who found no effect on FPG level in type 2 diabetics following oral L-carnitine in a dose 2 gm daily. This may be accounted by that, the disease in their series of patients was diagnosed early before the development of diabetic complications, while the patients in the present study had the disease for long duration (even before diagnosis) and were presented with complications and also most of them were with poor control. The differences in the results of these two studies consequences on organs and tissues functions, should be regularly done (26).

**Discussion**

Diabetes mellitus is a major health problem worldwide (24). The major key for prevention and slowing the progression of its complications is by achieving good metabolic control that aids proper management(25). In the follow-up, frequent assessment of glycaemic state and its
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may be supported also by the study of Tamamogullari et al., (9) who indicated that plasma L-carnitine is reduced more in diabetics with complications especially neuropathic, retinopathic and nephropathic than in diabetics without complications. L-carnitine deficiency causes a defect in energy metabolism and decrease in energy production(33). The insufficient control of metabolism leads to the development of diabetic complications (10) so, such complications may be considered as indicator of L-carnitine deficiency. However, early L-carnitine supplementation prevents the occurrence of chronic diabetic complications (9). This is also enforced by the study of Ido et al., (34) who reported decreased plasma L-carnitine level in diabetic rats with neuropathy. The patients in the study of Rahbar et al., (27) have similar specifications to that shared in this study in term of the duration of the disease and its complications, suggesting that these two groups of patients have L-carnitine deficiency. However, patients in Derosa et al., (32) study did not yet develop L-carnitine deficiency.

In the present study, following 45 days of administration of L-carnitine, significant decrease in serum creatinine (p<0.01) and urea (p<0.0001) was observed (Table 2). Mean serum creatinine decreased from 114.9 µmmol/L to 100.6 µmol/L and urea decreased from 6.6 mmol/L to 6.04 mmol/L. The study on the effects of carnitine on these indicators of renal function is regarded as pioneer study as limited work on human has been done. This result agrees with other studies on the effect of carnitine on these indices in rats, as all of them showed significant decrease in both serum creatinine and urea (35,36).

This finding in the present study may be accounted to that carnitine system is present in high concentration in the kidney (37), and supplementation of L-carnitine activates the receptors in the kidney for carnitine and increase β-oxidation and action of the kidney in this concern. Carnitine deficiency usually occurs in diabetics (9), in addition, urinary excretion of carnitine is higher in diabetics than non-diabetics (38). Therefore, in different renal diseases there may be secondary carnitine deficiency resulting from its excessive loss. This explains why supplementation of carnitine in patients with kidney diseases and in diabetics improves serum creatinine and urea levels (39).

Conclusion:

L-carnitine can be useful as an additional dietary supplement and pharmaceutical agent that complement other hypoglycaemic drugs for the management of type 2 diabetics. It has a lowering effect on fasting plasma glucose and blood HbA1c as well as its effect on improving renal function by decreasing serum creatinine and urea.

References

5. Arduini A, Mancinelli G, Radatti GL, Dottori S, Molajoni F, and Ramsay RR. Role of carnitine and carnitine palmitoyltransferase as integral components of the pathway for membrane phospholipids fatty – acid turnover in intact human
Table 1: Mean fasting plasma glucose (FPG) at different intervals/periods of administration of L-carnitine for 45 days

<table>
<thead>
<tr>
<th>Biochemical measurement</th>
<th>Intervals of periods of measurements</th>
<th>Before L-carnitine</th>
<th>After 15 Days</th>
<th>After 30 Days</th>
<th>After 45 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG mmol/L (mg/dl)</td>
<td></td>
<td>11.15 (222.7)</td>
<td>8.55 (171.2)</td>
<td>8.30 (165.9)</td>
<td>7.85 (157.1)</td>
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</tbody>
</table>

Table 2: Means of certain biochemical values before and after L-carnitine treatment (with letters of Duncan's test)

<table>
<thead>
<tr>
<th>Biochemical measurements</th>
<th>Before</th>
<th>After 45 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum urea mmol/L (mg/dl)</td>
<td>6.61 * (39.59)</td>
<td>6.04 * (36.14)</td>
</tr>
<tr>
<td>Serum creatinine µmol/L (mg/dl)</td>
<td>114.9 * (1.30)</td>
<td>100.6 * (1.14)</td>
</tr>
<tr>
<td>HbA1 (%)</td>
<td>8.99 %a</td>
<td>7.65 %b</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.79 %a</td>
<td>5.72 % b</td>
</tr>
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