The Effects of L-Carnitine, Acetyl-L-Carnitine, and Propionyl-L-Carnitine on Body Mass in Type 2 Diabetes Mellitus Patients

Dong-Dong Wang 1*, Tian-Yun Wang 2†, Yang Yang 3†, Su-Mei He 4* and You-Mei Wang 2*

1 Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy & School of Pharmacy, Xuzhou Medical University, Xuzhou, China, 2 Department of Pharmacy, Huaiyan Hospital of Huaiyan City, Huaiyin, China, 3 Department of Pharmacy, The Affiliated Changzhou Children's Hospital of Nantong University, Changzhou, China, 4 Department of Pharmacy, The Affiliated Suzhou Science & Technology Town Hospital of Nanjing Medical University, Suzhou, China

Purpose: The study aimed to explore the effects of l-carnitine, acetyl-l-carnitine, and propionyl-l-carnitine on Body Mass in type 2 diabetes mellitus (T2DM) patients.

Methods: Randomized controlled trial (RCT) studies of l-carnitine, acetyl-l-carnitine, and propionyl-l-carnitine in T2DM patients were searched. The change rates of Body Mass index (BMI) from baseline values were used as an evaluation indicator. The maximal effect ($E_{\text{max}}$) model by non-linear mixed-effect modeling (NONMEM) was used as the evaluation method.

Results: A total of 10 RCT studies, 1239 T2DM patients were included for analysis, including eight studies of l-carnitine, one study of acetyl-l-carnitine, and one study of propionyl-l-carnitine. The study found that l-carnitine could reduce the Body Mass of T2DM patients. Based on only one study each for acetyl-l-carnitine and propionyl-l-carnitine, no significant effects were found in acetyl-l-carnitine or propionyl-l-carnitine. In addition, in order to achieve a plateau of efficacy (80% $E_{\text{max}}$), 2 g/day l-carnitine was required for at least 2 weeks.

Conclusions: Two g/day l-carnitine was required for at least 2 weeks to affect Body Mass in T2DM patients, and no significant effects were found in acetyl-l-carnitine or propionyl-l-carnitine.

Keywords: l-carnitine, acetyl-l-carnitine, propionyl-l-carnitine, Body Mass, type 2 diabetes mellitus

HIGHLIGHTS

- The present study analyzed the effects of l-carnitine, acetyl-l-carnitine, and propionyl-l-carnitine on Body Mass in T2DM patients.
- L-carnitine could reduce the Body Mass of T2DM patients, in which 2 g/day l-carnitine was required for at least 2 weeks.
- No significant effects on Body Mass were found from acetyl-l-carnitine or propionyl-l-carnitine in T2DM patients.
INTRODUCTION

Type 2 diabetes mellitus (T2DM), a chronic degenerative disease where the pancreas cannot produce enough insulin and/or the insulin produced is inefficient, causing hyperglycemia, is a major health problem and one of the top 10 causes of mortality worldwide (1). According to the International Diabetes Federation (IDF) (2019), 9.3% of adults around the world, amount to 463 million people, have T2DM (1). This number is expected to increase to 700 million people by 2045, which is equivalent to 10.90% of the adult population worldwide (1). In addition, T2DM is also an important risk factor for chronic kidney disease, cardiovascular disease, and mortality (2).

From a clinical point of view, T2DM patients are often accompanied by obesity, atherosclerotic disease, dyslipidemia, and hypertension (3, 4), in which more than 50% of T2DM patients have been reported to be obese (3, 5). Overweight or obesity in T2DM can increase the cardiovascular disease risk and further increase the risk of death, which are important determinants of the prognosis in T2DM patients (5, 6). Therefore, intensive therapy for T2DM patients with overweight or obesity is crucial (2).

At present, many drugs have been used to control blood glucose and Body Mass in T2DM patients, among which Wang et al. report the quantitative efficacy of l-carnitine supplementation on glycemic control in T2DM patients (7). However, the effects of l-carnitine, as well as its other forms of existence, acetyl-l-carnitine, and propionyl-l-carnitine on Body Mass in T2DM patients are still unclear. The present study is to explore the effects of l-carnitine, acetyl-l-carnitine, and propionyl-l-carnitine on Body Mass in T2DM patients.

METHODS

Literature Search and Data Extraction

We searched and extracted the Pubmed database (https://pubmed.ncbi.nlm.nih.gov/) with the deadline of April 2021. Only English publications were included. The terms “l-carnitine,” “acetyl-l-carnitine,” “propionyl-l-carnitine,” and “type 2 diabetes mellitus” were used in the present search strategy. Inclusion criteria included: (I) randomized controlled trial (RCT), (II) with Body Mass Index (BMI) information, (III) exact dose and duration of l-carnitine, acetyl-l-carnitine, and propionyl-l-carnitine. Source, country, grouping, sample size, age, duration of treatment et al were extracted from the above-included studies.

In order to eliminate the potential baseline effect, the efficacy of l-carnitine, acetyl-l-carnitine, and propionyl-l-carnitine were evaluated using BMI change rate from the baseline value. The Formula (1) was as follows:

\[
E\% = \frac{E_t - E_b}{E_b} \times 100\%
\]  

Formula (1)

E\_t, the value of BMI at time t; E\_b, the value of BMI at baseline.

Model Establishment

The E\_max model was used to evaluate the effects of l-carnitine, acetyl-l-carnitine or propionyl-l-carnitine on Body Mass in T2DM patients. In addition, in order to acquire the actual effects on BMI from l-carnitine, acetyl-l-carnitine, and propionyl-l-carnitine, the control effects need to be subtracted from the sum effects. The Formulas (2) and (3) were as follows:

\[
E_{D,ij} = E_{t,ij} - E_{c,ij}
\]  

Formula (2)

\[
E_{D,ij} = \frac{E_{\text{max,}i,j}}{E_{50, i,j}} \times \text{Time} + \frac{\epsilon_{i,j}}{\sqrt{N_{i,j}}} \times 100
\]  

Formula (3)

E\_D\_ij, the sum effects on BMI from l-carnitine, acetyl-l-carnitine or propionyl-l-carnitine, including actual effects and control effects; E\_D\_ij, the actual effects on BMI; E\_C\_ij, the control effects on BMI; E\_max, the maximal effects on BMI; E_{50}, the treatment duration to reach half of the maximal effects on BMI; \epsilon\_ij, the residual error of study i with j time; N\_ij, the sample size in study i with time point j. \epsilon\_ij was weighted by sample size, assumed to be normally distributed, with a mean of 0 and variance of \sigma^2/(N\_ij/100).

The inter-study variability was described by exponential or additive error models. The Formulas (4)–(7) were as follows:

\[
E_{\text{max,}i,j} = E_{\text{max}} \times \exp(\eta_{1,i,j})
\]  

Formula (4)

\[
E_{50, i,j} = E_{50} \times \exp(\eta_{2,i,j})
\]  

Formula (5)

\[
E_{\text{max},i,j} = E_{\text{max}} + \eta_{1,i,j}
\]  

Formula (6)

\[
E_{50, i,j} = E_{50} + \eta_{2,i,j}
\]  

Formula (7)

\eta\_1\_i\_j, \eta\_2\_i\_j were the inter-study variabilities, when available, they would be added into E\_max, and E\_50, respectively. \eta\_1\_i, \eta\_2\_i were assumed to be normally distributed, with a mean of 0 and variance of \sigma^2\_1\_i, \sigma^2\_2\_i, respectively.

In addition, continuous covariates and categorical covariates were evaluated by Formulas (8)–(10):

\[
P_p = P_T + (COV - COV_m) \times \theta_c
\]  

Formula (8)

\[
P_p = P_T \times (COV/COV_m)^\alpha
\]  

Formula (9)

\[
P_p = P_T + COV \times \theta_c
\]  

Formula (10)

P\_p, the parameter for a patient with a covariate value of COV; P\_T, the typical value of the parameter; COV, covariate; COV\_m, the median value of covariable in the population. \theta\_c, a correction coefficient of the covariate to the model parameter.

The model development was done using non-linear mixed-effect modeling (NONMEM, edition 7, ICON Development Solutions, Ellicott City, MD, USA). When a basic model was built, potential covariates were considered for adding into E\_max. The change of objective function value (OFV) was used as the covariate inclusion criteria. When the decrease of OFV was > 3.84 (\chi^2, \alpha = 0.05, d.f. = 1), it was considered sufficient for inclusion. When the increase of OFV was > 6.63 (\chi^2, \alpha = 0.01, d.f. = 1), it was considered sufficient for significance in the final model (8).

Model Validation and Prediction

The goodness-of-fit plots of the model (individual predictions vs. observations), distribution of conditional weighted residuals (CWRES) for the model (density vs. CWRES, and quantiles
of CWRES vs. quantiles of normal), and individual plots from different studies were used to estimate the final model. Prediction-corrected visual predictive check (VPC) plots were used to assess the predictive performance of the final model. In addition, the medians and 2.5th—97.5th percentiles of the results from bootstrap (Simulation, \( n = 1,000 \)) were used to compare with final model parameters. The efficacy prediction of L-carnitine on BMI in T2DM patients was simulated by the Monte Carlo method.

**RESULTS**

**Included Studies**

Figure 1 was the retrieval process and a total of 10 RCT studies, comprising 1,239 T2DM patients were included for analysis, including 8 studies of L-carnitine (9–16), 1 study of acetyl-L-carnitine (17), and 1 study of propionyl-L-carnitine (18). The dosages of L-carnitine, acetyl-L-carnitine, and propionyl-L-carnitine were 2–3, 2, and 2 g/day, respectively, in the included studies, and the details were shown in Table 1, and part of the literature was retrieved from the previous study (7). The risk of bias analysis was shown in Figure 2. As both acetyl-L-carnitine, and propionyl-L-carnitine had only 1 study, model-based meta-analysis (MBMA) could not be performed at this time for them. Further analysis found that no significant effects on BMI in acetyl-L-carnitine or propionyl-L-carnitine in T2DM patients. Therefore, the following MBMA analysis was mainly aimed at L-carnitine.

**Modeling and Validation**

The actual drug effects of L-carnitine on BMI in T2DM patients is shown in Table 2, the \( E_{\text{max}} \) of L-carnitine on BMI in T2DM patients was \(-1.51\%\) and the \( ET_{50} \) of L-carnitine on BMI in T2DM patients was 0.5 weeks. In addition, no covariate

![Image](https://example.com/image.png)

**TABLE 1** | Included randomized controlled studies.

| Study         | Country | Group                              | Sample size | Age            | Duration |
|---------------|---------|------------------------------------|-------------|----------------|----------|
|               |         | Intervention                        | Control     | Intervention   | Control   |          |
| El-Sheikh et al. (16) | Egypt   | 2 g/day L-carnitine + 4 mg/day glimepiride | 31          | 50.9 ± 8.6     | 6 months |
| Derosa et al. (14)       | Italy   | 2 g/day L-carnitine + 360 mg/day orlistat | 132         | 51.0 ± 4.0     | 12 months|
| Malaguarnera et al. (13) | Italy   | 2 g/day L-carnitine + 10 mg/day sibutramine | 129         | 54.0 ± 5.0     | 12 months|
| Malaguarnera et al. (12) | Italy   | 2 g/day L-carnitine + placebo       | 41          | 49.0 ± 13.0    | 3 months |
| Galvano et al. (11)      | Italy   | 2 g/day L-carnitine + 20 mg/day simvastatin | 38          | 52.1 ± 8.1     | 4 months |
| Derosa et al. (10)       | Italy   | 2 g/day L-carnitine + Placebo       | 46          | 52.0 ± 6.0     | 6 months |
| Liang et al. (9)         | China   | 3 g/day L-carnitine + Placebo       | 23          | 59.4 ± 1.7     | 12 weeks |
| Parvanova et al. (17)    | Italy   | 2 g/day Acetyl-L-carnitine + Placebo | 109         | 64.9 ± 7.7     | 6 months |
| Santo et al. (18)        | Italy   | 2 g/day Propionyl-L-carnitine + Placebo | 37          | 61.75 ± 3.03   | 12 months|

Part of the literature was retrieved from the previous study (7).
TABLE 2 | Parameter estimates of final model and 95% confidential interval.

| Parameter     | Estimate | Simulation (n = 1,000) | Bias (%) |
|---------------|----------|------------------------|----------|
| $E_{\text{max}}$, % | $-1.51$ | $-1.51 \ [\ -8.82, -0.62]$ | $0$ |
| $ET_{50}$, week | $0.5$   | $0.5 \ [0.5, 3.72]$ | $0$ |
| $\omega_{E_{\text{max}}}$ | $1.345$ | $1.200 \ [0.003, 6.982]$ | $-10.781$ |
| $\omega_{ET_{50}}$ | $0.003$ | $0.003 \ [0.003, 9.788]$ | $0$ |
| $\epsilon$     | $0.414$ | $0.415 \ [0.159, 0.789]$ | $0.242$ |

95% confidential interval was showed with 2.5th, 97.5th percentile; $E_{\text{max}}$ was the maximal effects; $ET_{50}$ was the treatment duration to reach half of $E_{\text{max}}$; $\omega_{E_{\text{max}}}$ was the inter-study variability of $E_{\text{max}}$; $\omega_{ET_{50}}$ was the inter-study variability of $ET_{50}$; $\epsilon$ was the residual error; Bias = (Median-Estimate)/Estimate x 100%.

By simulation data, which shows the predictive power of the final models.

**Prediction**

We also simulated the curve of the final model for the effect of l-carnitine on BMI via the Monte Carlo method. The trend of the efficacy of l-carnitine on BMI in T2DM patients is shown in Figure 5. As we could see from the curve, the efficacy of l-carnitine on BMI at 0.5 weeks was 50% of the $E_{\text{max}}$, at 2 weeks was 80% of the $E_{\text{max}}$ (plateau stage), at 4.5 weeks was 90% of the $E_{\text{max}}$, at 9.5 weeks was 95% of the $E_{\text{max}}$. In the current study, the dose range was 2–3 g/day and there was no significant dose-dependence from l-carnitine efficacy on BMI in T2DM patients, so the lower dose of 2 g/day was selected as recommended dose. In addition, in order to achieve a plateau of efficacy (80% $E_{\text{max}}$), 2 g/day l-carnitine was required for at least 2 weeks.

**DISCUSSION**

Carnitine is derived from amino acids and is found in almost all cells in the body (19). Its name comes from the Latin *carnus*, meaning meat, because the compound is extracted from meat (19). Carnitine is a generic term, which includes l-carnitine, acetyl-l-carnitine, and propionyl-l-carnitine (20). l-Carnitine plays an important role in energy metabolism (21). It transfers long-chain fatty acids to cell mitochondria for oxidation, which produces energy needed by the body (21, 22). It also transports harmful substances out of the organelle, preventing them from accumulating in the cell (21). Because of these functions, carnitine is found in high concentrations in skeletal muscle and cardiac muscle cells, which allow them to use fatty acids as an energy source (20). For most people, the body can make enough to meet its needs, but for some people, because of genetic or pharmaceutical reasons, the body cannot produce enough, it is, therefore, an essential nutrient for these individuals (23).

As is well-known, l-carnitine can adjust many events, such as metabolism of glucose and fatty acids, and has the
potential to protect these cellular events in several manners including decreasing the production of reactive oxygen species at different points and maintaining mitochondrial functions (24). In addition, it has been reported that l-carnitine had many important pharmacological actions (24–31), for example, l-carnitine has a potential therapeutic effect in treating insulin resistance (32). It is also reported that l-carnitine can improve glycemia in T2DM patients (33). Wang et al.’s report provides valuable quantitative information for the efficacy of l-carnitine supplementation on glycemic control in T2DM patients (7).
They find that for the efficacy of l-carnitine on fasting plasma glucose (FPG), 2 g/day l-carnitine is required for at least 36.1 weeks; For the efficacy of l-carnitine on glycated hemoglobin (HbA1c), 2 g/day l-carnitine is required for at least 106 weeks (7). However, the effects of l-carnitine, as well as its other forms of existence, acetyl-l-carnitine, and propionyl-l-carnitine on Body Mass in T2DM patients are still unclear. The purpose of this study is to explore the effects of l-carnitine, acetyl-l-carnitine, and propionyl-l-carnitine on Body Mass in T2DM patients by MBMA.

In the present study, a total of 10 RCT studies comprising 1,239 T2DM patients were included for analysis, including 8 studies of l-carnitine (9–16), 1 study of acetyl-l-carnitine (17), and 1 study of propionyl-l-carnitine (18). The dosages of l-carnitine, acetyl-l-carnitine, and propionyl-l-carnitine were 2–3, 2, and 2 g/day, respectively, in the included studies. Of course, when investigating the efficacy of a drug on Body Mass, important factors should be stable such as diet, antglycemic drugs, and duration of T2DM. Fortunately, since our study was from RCTs, conditions in the intervention group and the control group were similar in each study. In this way, the control group effects were deducted from the intervention group, and the actual l-carnitine drug effects were obtained. In addition, we also considered the impact of various indicators in different studies on baseline values. In addition, as for both acetyl-l-carnitine, and propionyl-l-carnitine had only 1 study, MBMA analysis could not be performed at this time for them. Further analysis found no significant effects on BMI in acetyl-l-carnitine or propionyl-l-carnitine in T2DM patients.

In further analysis of the effects of l-carnitine on Body Mass in T2DM patients, we found the $E_{\text{max}}$ of l-carnitine on BMI in T2DM patients was $-1.51\%$ and the $ET_{50}$ of l-carnitine on BMI in T2DM patients was 0.5 weeks. In addition, no covariate (in particular dosage) was incorporated into the $E_{\text{max}}$ model, showing there was no significant dose-dependence from l-carnitine efficacy on BMI in T2DM patients. In the current study, the dose range was 2–3 g/day, and there was no significant dose-dependence from l-carnitine efficacy on BMI in T2DM patients, and the lower dose of 2 g/day was selected as recommended dose. In addition, in order to achieve a plateau of efficacy (80% $E_{\text{max}}$), 2 g/day l-carnitine was required for at least 2 weeks. From the current view, l-carnitine could play an important role in glucose metabolism and increase energy expenditure, meanwhile, l-carnitine had a role in lipid metabolism as well (34–36). For these two reasons, l-carnitine helps Body Mass loss by increasing energy expenditure (36). However, this study had some limitations. The number of studies currently included was limited, and additional studies were needed in the future.

**CONCLUSIONS**

Two gram per day l-carnitine was required for at least 2 weeks to affect Body Mass in T2DM patients, and no significant effects were found in acetyl-l-carnitine or propionyl-l-carnitine.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

**AUTHOR CONTRIBUTIONS**

D-DW, S-MH, and Y-MW conceived and designed the study. D-DW, T-YW, YY, and S-MH collected and analyzed data. D-DW wrote the paper. S-MH reviewed and edited the manuscript. All authors read and approved the final manuscript.

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