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ORIGINAL RESEARCH

Quantitative efficacy of L-carnitine supplementation on glycemic control in type 2 diabetes mellitus patients

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ABSTRACT

Objectives: This study aimed to explore the quantitative efficacy of L-carnitine supplementation on glycemic control in type 2 diabetes mellitus patients using model-based meta-analysis (MBMA).

Methods: Literatures were retrieved from the public database and data from these trials were extracted. The quantitative efficacy of L-carnitine on fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) in type 2 diabetes mellitus patients were evaluated by maximal effect (E_{max}) models with nonlinear mixed effects modeling (NONMEM).

Results: In the model of FPG, E_{max} and $_{treatment}$ duration to reach half of the maximal effects (ET_{50}) were −9.8% and 36.1 weeks, respectively. In the model of HbA1c, E_{max} and ET_{50} were −19.6% and 106 weeks, respectively. In addition, the durations for achieving 25%, 50%, 75%, 80%, and 90% E_{max} of L-carnitine on FPG were 13, 36.1, 118, 160, and 390 weeks, respectively. The durations for achieving 25%, 50%, 75%, 80%, and 90% E_{max} of L-carnitine on HbA1c were 38, 106, 334, 449, and 1058 weeks, respectively.

Conclusions: It was the first time to provide valuable quantitative information for efficacy of L-carnitine supplementation on glycemic control in type 2 diabetes mellitus patients.

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KEYWORDS
Quantitative efficacy; L-carnitine supplementation; glycemic control; type 2 diabetes mellitus; fasting plasma glucose; glycated hemoglobin

1. Introduction

L-carnitine, 162 Da of molecule weight, was produced from methionine and lysine in the kidney, liver, and brain. It transported long-chain fatty acids into the mitochondria, inducing adenosine triphosphate production from long-chain fatty acids using beta oxidation, the tricarboxylic acid cycle, and the electron transport chain [1,2]. The main pockets of L-carnitine storage and consumption were the skeletal and cardiac muscles. In general, healthy people could procure L-carnitine via milk, meat, and fish consumption [3,4]. However, patients with inherited metabolic diseases using antibiotics containing a pivoxil group, anticancer drugs, or valproic acid [5–7] and undergoing regular hemodialysis could develop hypocarnitinemia [8,9], indicating the significance of L-carnitine to the human body.

Oxidative stress, mitochondrial dysfunction, and apoptosis were the related events underlining the pathology of numerous diseases such as metabolic disorders [10]. With a critical role in the metabolism of glucose and fatty acids, L-carnitine had the potential to adjust these unfavorable events [10] and had protective effects against these cellular events in several manners including the maintenance of mitochondrial functions and decreasing the production of reactive oxygen species at different points [10]. Many studies had reported that L-carnitine had important pharmacological actions [10–17], among which L-carnitine could treat insulin resistance more effectively with prolonging the medication time [18]. It was important that the administration of L-carnitine in type 2 diabetes mellitus was associated with an improvement in glycemia and plasma lipids [19].

However, the effect of L-carnitine supplementation in type 2 diabetes mellitus patients, especially quantitative efficacy on glycemic control remained unknown. The present study aimed to explore the quantitative efficacy of L-carnitine supplementation on glycemic control in type 2 diabetes mellitus patients using model-based meta-analysis (MBMA).

2. Methods

2.1. Search strategy and data extraction

We conducted a comprehensive and detailed search of the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) with the deadline of January 2020. The terms 'L-carnitine' and 'diabetes' (or diabetic) were used in the present search strategy. Only literatures published in English and clinical studies were searched. The inclusion criteria were as follows: (a) randomized controlled trial (RCT), (b) type 2 diabetes mellitus, (c) reported literatures included fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c), and (d) exact dose and duration of L-carnitine. RCT studies information included

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Article highlights

- It was the first time to provide valuable quantitative information for efficacy of L-carnitine supplementation on glycemic control in type 2 diabetes mellitus patients.
- For the efficacy of L-carnitine on fasting plasma glucose (FPG), 2 g/day L-carnitine was required for at least 36.1 weeks.
- For the efficacy of L-carnitine on glycated hemoglobin (HbA1c), 2 g/day L-carnitine was required for at least 106 weeks.

authors, year, country, groups, sample size, age, dosage and duration of treatment, sex ratio, body mass index (BMI), FPG, and HbA1c.

To eliminate baseline effects, the FPG and HbA1c change rates from baseline were designated as efficacy indicators of L-carnitine supplementation on glycemic control in type 2 diabetes mellitus patients. The changes from baseline of FPG and HbA1c were estimated using Equation (1):

$$E\% = \frac{E_t - E_{baseline}}{E_{baseline}} 100\% \quad (1)$$

Where E_t represents the values of FPG or HbA1c at time t and $E_{baseline}$ represents the values of FPG or HbA1c at baseline.

2.2. Model development

It was hypothesized that the effects of L-carnitine on FPG and HbA1c would vary with time and reach a plateau. Hence, the effect profiles for L-carnitine on FPG and HbA1c were evaluated using the E_{max} model, in which time was considered as an independent variable, as shown in Equations (2) and (3):

$$E_{L-carnitine,\,k,\,i,\,j} = E_{Intervention,\,k,\,i,\,j} - E_{Control,k,\,i,\,j} \quad (2)$$

$$E_{L-carnitine,\,k,\,i,\,j} = \frac{E_{max,k,i,j} \times Time}{ET_{50,k,i,j} + Time} + \frac{\varepsilon_{k,i,j}}{\sqrt{N_{k,i,j}}} \quad (3)$$

The variabilities of inter-study were described by the exponential error model, as shown in Equations (4) and (5):

$$E_{max,\,k,\,i,\,j} = E_{max,\,k} \times exp\,(\eta_{k,1,i}) \quad (4)$$

$$ET_{50,\,k,\,i,\,j} = ET_{50,\,k} \times exp\,(\eta_{k,2,i}) \quad (5)$$

Where $E_{Intervention,\,k,\,i,\,j}$ was the sum effects of $E_{L\text{-carnitine},\,k,\,i,\,j}$ and $E_{Control,\,k,\,i,\,j}$, among which k represented the effects on FPG or HbA1c, i represented different studies, and j represented the time point of every study. $E_{max,\,k}$ was the maximal effect of L-carnitine on FPG or HbA1c, and $ET_{50,\,k}$ was the treatment duration to reach half of the maximal effects for L-carnitine on FPG or HbA1c. $\eta_{k,1,i}$ and $\eta_{k,2,i}$ were the inter-study variabilities, which when available, would be added to $E_{max,\,k}$ and $ET_{50,\,k}$, respectively. $\eta_{k,1,i}$ and $\eta_{k,2,i}$ were assumed to be normally distributed, with a mean of 0 and variance of $\omega_{k,1,i}^2$ and $\omega_{k,2,i}^{2,}$ respectively. The $\varepsilon_{k,\,i,\,j}$ was the residual error of study i with j time for FPG or HbA1c. $N_{k,\,i,\,j}$ was the sample size in study i with time point j for FPG or HbA1c. $\varepsilon_{k,\,i,\,j}$ was weighted by sample size, assumed to be normally distributed, with a mean of 0 and variance of $\sigma_k 2/N_{k,i,j}$. The model development was carried out with nonlinear mixed effects modeling (NONMEM).

Once the basic model was built up, age, sex ratio, BMI and the baseline values of FPG or HbA1c as covariates were considered for adding into $E_{max,\,k}$. The changes in objective function value (OFV) were calculated using covariate inclusions and a decrease of OFV > 3.84 (χ^2, α = 0.05, d.f. = 1) was considered sufficient for inclusion and an increase of OFV > 6.63 (χ^2, α = 0.01, d.f. = 1) was considered sufficient for significance in the final model.

2.3. Model validation

The accuracy of final models for the effects of L-carnitine on FPG and HbA1c were evaluated using visual inspection of routine diagnostic plots. Monte Carlo simulations were performed 1000 times to predict 95% confidence intervals of the parameters for final models. Prediction-corrected visual predictive check plots were used to evaluate the predictive performance of the final models.

2.4. Model prediction

Based on the final models for the effects of L-carnitine on FPG and HbA1c, the curves of the final models for L-carnitine on FPG and HbA1c were simulated by Monte Carlo method and the time for achieving the desired percentage E_{max} of L-carnitine on FPG and HbA1c were recommended, respectively.

3. Results

3.1. Included studies

The retrieval process is shown in Figure 1 and a total of eight randomized controlled studies [20–27] were eligible for further analysis, including 916 type 2 diabetes mellitus patients, the range of mean age was from 45.0 years to 57.8 years. The dosage of L-carnitine was 2 g/day in the included studies. The duration of these studies was between 12 weeks to 12 months. The details of these included studies are shown in Table 1.

3.2. Modeling and validation

Based on these studies, we established the pharmacodynamic models for effects of L-carnitine on FPG and HbA1c. In the model for FPG, we found that the E_{max} and ET_{50} were −9.8% and 36.1 weeks, respectively. In the model for HbA1c, the E_{max} and ET_{50} were −19.6% and 106 weeks, respectively. Simultaneously, the median and 95% confidence intervals for the parameters of final models from Monte Carlo simulations are shown in Table 2.

Figure 2 shows the visual evaluation of the models. Figure 2(a–c) is observations *vs*. individual predictions, absolute value of weighted residuals of individual ($|iWRES|$) *vs*. individual predictions, and the individual plots from the

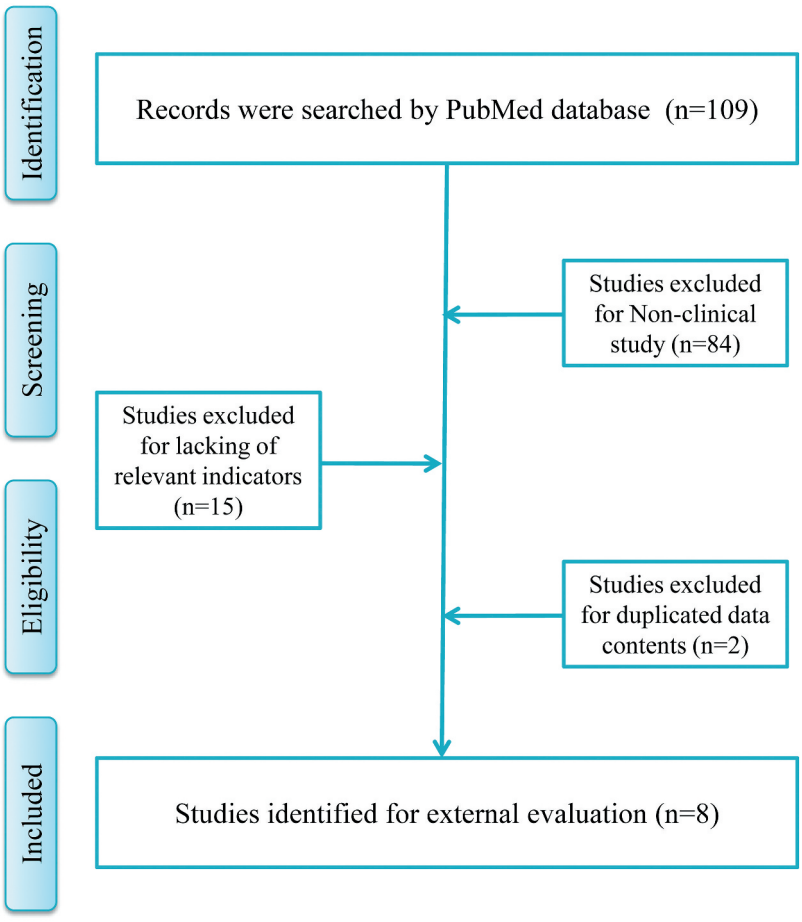

Figure 1. Overview of the strategy for literature review.

pharmacodynamic model of L-carnitine effect on FPG, respectively. Figure 2(d–f) is observations *vs*. individual predictions, absolute value of weighted residuals of individual (|iWRES|) *vs*. individual predictions, and the individual plots from the pharmacodynamic model of L-carnitine effect on HbA1c, respectively. The visual evaluation of the two models indicated that the models were relatively good.

The visual predictive check plots were used to evaluate the predictive performance of the final models. As shown in Figure 2(g,h), in the models for FPG and HbA1c, the most observed data were included in the 95% prediction intervals produced by simulation data, demonstrating the predictive power of the final model.

3.3. Prediction

We also simulated the curves of the final models for effects of L-carnitine on FPG and HbA1c by Monte Carlo method. As shown in Figure 3(a), the time for achieving 25%, 50%, 75%, 80%, and 90% E_{max} for L-carnitine effect on FPG were 13 weeks, 36.1 weeks, 118 weeks, 160 weeks, and 390 weeks, respectively. As shown in Figure 3(b), the time for achieving 25%, 50%, 75%, 80%, and 90% E_{max} for L-carnitine effect on HbA1c were 38 weeks, 106 weeks, 334 weeks, 449 weeks, and 1058 weeks, respectively. In addition, in order to play better curative effects, for the efficacy of L-carnitine on FPG, 2 g/day L-carnitine was required for at least 36.1 weeks. For the efficacy of L-carnitine on HbA1c, 2 g/day L-carnitine was required for at least 106 weeks.

4. Discussion

Type 2 diabetes mellitus, accompanied by insulin resistance, was a chronic disease in which there was an initial early compensatory increase in the insulin level, however, at a later time, pancreatic β cell damage triggered the decrease of insulin secretion [28]. It had been reported that more than 366 million people from all over the world were diabetic patients, and the number would add up to nearly double by 2030 [29]. Type 2 diabetes mellitus was known to be the 4th main cause for death in high-income countries, with a double excess mortality risk [30].

The treatment for type 2 diabetes mellitus included therapeutic lifestyle changes, moderate exercise, and pharmacotherapy [31,32]. Many studies had reported that improved long-term glycemic control measured by HbA1c in type 2 diabetes mellitus patients could reduce microvascular and macrovascular complications [29]. Moreover, effective decrease of risk of microvascular complications had also been proved by targeting intensive glycemic control [33]. Anti-diabetic drugs without adverse effects and complications were urgently needed because a drawback of traditional

Table 1. Included randomized controlled studies.

Study	Country	Group		Sample size		Age (years)		Duration
		Intervention	Control	Intervention	Control	Intervention	Control	
El-Sheikh et al. [20]	Egypt	2 g/day L-carnitine+ 4 mg/day glimepiride	4 mg/day glimepiride	31	27	50.9 ± 8.6	50.3 ± 8.8	6 months
Derosa et al. [21]	Italy	2 g/day L-carnitine+ 360 mg/day orlistat	360 mg/day orlistat	132	126	51.0 ± 4.0	53.0 ± 6.0	12 months
Derosa et al. [22]	Italy	2 g/day L-carnitine+ 10 mg/day sibutramine	10 mg/day sibutramine	129	125	54.0 ± 5.0	51.0 ± 4.0	12 months
Malaguarnera et al. [23]	Italy	2 g/day L-carnitine+ 20 mg/day simvastatin	20 mg/day simvastatin	40	40	47.0 ± 13.0	45.0 ± 12.0	12 weeks
Malaguarnera et al. [24]	Italy	2 g/day L-carnitine+ placebo	placebo	41	40	49.0 ± 13.0	48.0 ± 11.0	3 months
Galvano et al. [25]	Italy	2 g/day L-carnitine+ 20 mg/day simvastatin	20 mg/day simvastatin	38	37	52.1 ± 8.1	51.4 ± 7.6	4 months
Morano et al. [27]	Italy	2 g/day L-carnitine+ 50 mg/day sildenafil	50 mg/day sildenafil	8	8	57.8 ± 7.0	54.0 ± 7.4	12 weeks
Derosa et al. [25]	Italy	2 g/day L-carnitine+ placebo	placebo	46	48	52.0 ± 6.0	50.0 ± 7.0	6 months

Study	Male (%)		BMI (kg/m^2)		FPG		HbA1c (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
El-Sheikh et al. [20]	35.5	29.6	34.46 ± 5.3	34.25 ± 5.6	195.42 ± 13.3 (mg/dl)	194.26 ± 28.3 (mg/dl)	9.68 ± 0.9	9.84 ± 1.1
Derosa et al. [21]	49.2	49.2	32.9 ± 2.8	33.1 ± 2.9	140 ± 19 (mg/dl)	136 ± 16 (mg/dl)	8.7 ± 1.6	8.4 ± 1.4
Derosa et al. [22]	50.4	50.4	33.9 ± 3.5	33.4 ± 3.2	146 ± 21 (mg/dl)	144 ± 20 (mg/dl)	8.8 ± 1.6	8.7 ± 1.5
Malaguarnera et al. [23]	65.0	72.5	28.0 ± 2.1	27.7 ± 2.4	7.99 ± 1.1 mmol/L	7.82 ± 1.3 mmol/L	7.1 ± 0.4	7.1 ± 0.5
Malaguarnera et al. [24]	73.2	70.0	27.4 ± 1.7	27.0 ± 1.9	7.04 ± 1.34 mmol/L	7.14 ± 1.40 mmol/L	7.3 ± 0.8	7.0 ± 0.7
Galvano et al. [26]	39.5	40.5	28.2 ± 2.5	27.8 ± 2.4	136 ± 27 (mg/dl)	137 ± 28 (mg/dl)	7.1 ± 0.4	7.1 ± 0.8
Morano et al. [27]	100	100	27.7 ± 3.2	28.2 ± 2.2	189.6 ± 30.2 (mg/dl)	160.4 ± 27 (mg/dl)	7.0 ± 0.7	7.8 ± 1.7
Derosa et al. [25]	52.2	47.9	27.3 ± 2.5	26.8 ± 2.2	135 ± 30 (mg/dl)	141 ± 25 (mg/dl)	7.3 ± 0.6	7.1 ± 0.8

Table 2. Parameter estimates of final model and 95% confidential interval.

Model	Parameter	Estimate	Shrinkage (%)	Simulation (n = 1000)	
				Median	95% Confidence interval
For FPG	E_{max}, %	−9.8	24.8	−9.8	[−9.8, −9.8]
	ET_{50}, week	36.1	99.7	33.6	[10.5, 52.0]
	ω_{Emax}, %	90.1	1.7	88.4	[9.9, 128.0]
	ω_{ET50}, %	0.3	99.7	0.4	[0.3, 181.0]
	Ɛ, %	14.8	15.1	14.4	[3.9, 19.9]
For HbA1c	E_{max}, %	−19.6	15.9	−19.6	[−19.6, −6.0]
	ET_{50}, week	106	52.0	85.8	[39.0, 370.9]
	ω_{Emax}, %	102.5	16.5	92.1	[0.3, 239.8]
	ω_{ET50}, %	60.1	54.9	0.6	[0.3, 134.5]
	Ɛ, %	17.5	13.1	17.4	[10.3, 22.1]

95% confidential interval was displayed as the 2.5th, 97.5th percentile of Monte Carlo simulations. FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; E_{max}, the maximal effects of L-carnitine on FPG or HbA1c; ET_{50}, the treatment duration to reach half of the the maximal effects for L-carnitine on FPG or HbA1c; ω_{Emax}, inter-study variability of E_{max}; ω_{ET50}, inter-study variability of ET_{50}; Ɛ, residual error.

medicines was that they could induce hypoglycemia, either directly or indirectly [34].

Fortunately, Fathizadeh et al. reported that L-Carnitine supplementation had positive influences on glycemic control [35], where L-carnitine could be absorbed by healthy people through food, which was relatively safe. However, the effect of L-carnitine supplementation in type 2 diabetes mellitus patients, especially the quantitative efficacy on glycemic control remained unknown. The present study aimed to explore the quantitative efficacy of L-carnitine supplementation on glycemic control in type 2 diabetes mellitus patients using MBMA.

MBMA was an important tool to make quantitative decisions for quantifying drug dose-effect and time-effect relationships [36,37]. Ota et al. reported a model-based comparative meta-analysis of the efficacy of dolutegravir-based and efavirenz-based regimens in HIV-infected patients [38]. Xu et al. reported quantitative efficacy of topical administration of tranexamic acid on postoperative bleeding in total knee arthroplasty [39]. Li et al. reported quantitative efficacy of soy isoflavones on menopausal hot flashes [40]. Wu et al. reported quantitative analysis of efficacy and associated factors of calcium intake on bone mineral density in postmenopausal

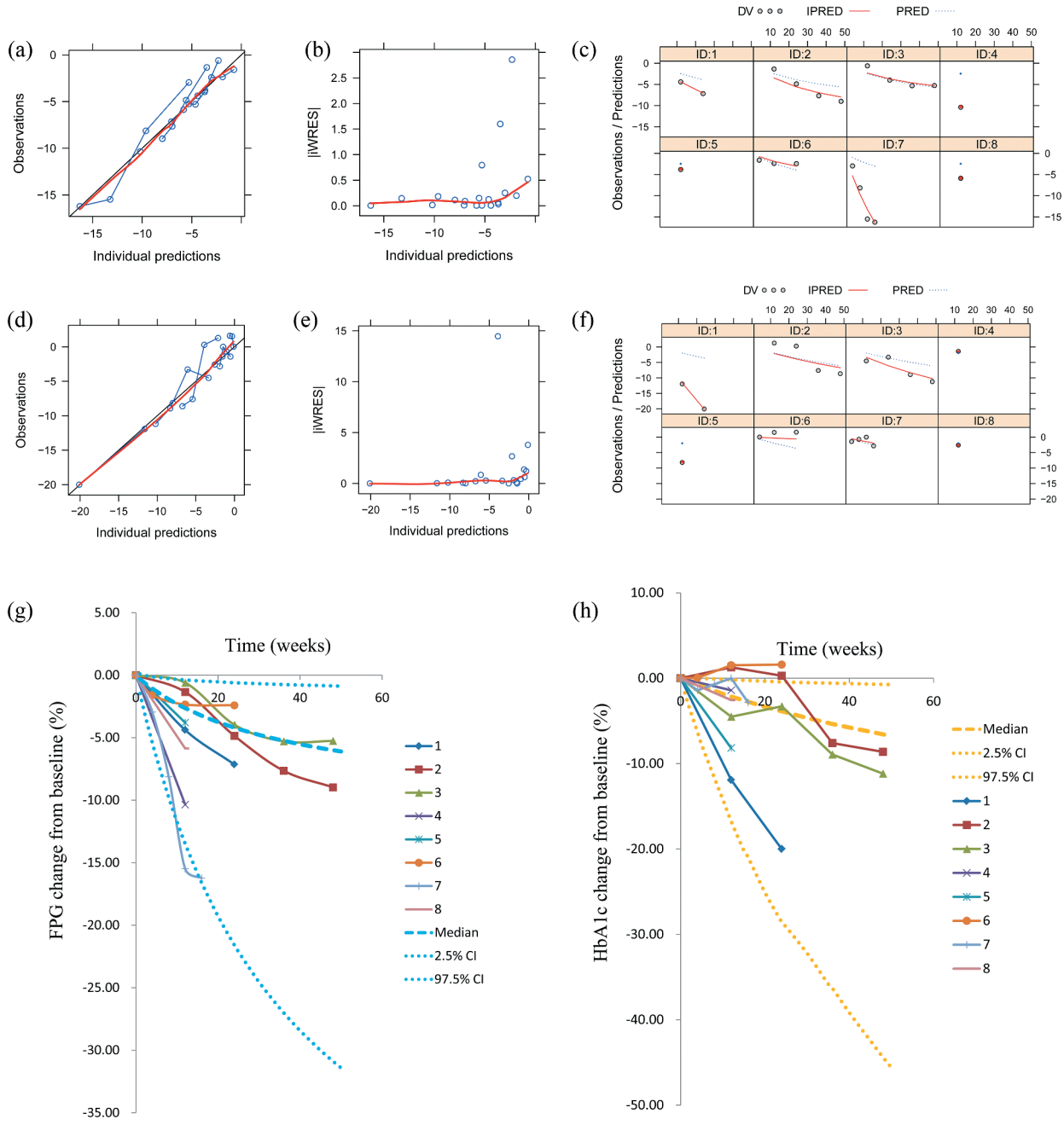

Figure 2. Model evaluation.

(a) observations *vs.* individual predictions for model from L-carnitine effects on FPG. (b) absolute value of weighted residuals of individual (|iWRES|) *vs.* individual predictions for model from L-carnitine effects on FPG. (c) individual plots for model from L-carnitine effects on FPG. (d) observations *vs.* individual predictions for model from L-carnitine effects on HbA1c. (e) absolute value of weighted residuals of individual (|iWRES|) *vs.* individual predictions for model from L-carnitine effects on HbA1c. (f) individual plots for model from L-carnitine effects on HbA1c. (g) visual predictive check of model from L-carnitine effects on FPG. (h) visual predictive check of model from L-carnitine effects on HbA1c. Median, 2.5% CI and 97.5% CI were simulated by Monte Carlo (n = 1000); CI, confidence interval; From 1 to 8 were studies come form El-Sheikh et al. (2019) [20], Derosa et al. (2011) [21], Derosa et al. (2010) [22], Malaguarnera et al. (2009) [23], Malaguarnera et al. (2009) [24], Derosa et al. (2003) [25], Galvano et al. (2009) [26], Morano et al. (2007) [27], respectively.

women [36]. In our study, the aim was to explore quantitative efficacy of L-carnitine supplementation on FPG and HbA1c in type 2 diabetes mellitus patients.

In the present study, we established the pharmacodynamic models for effects of L-carnitine on FPG and HbA1c. To eliminate baseline effects, the FPG and HbA1c change rates from baseline were designated as efficacy indicators of L-carnitine supplementation on glycemic control in type 2 diabetes mellitus patients. For covariates, we inspected age, sex ratio, BMI and the baseline values of FPG or HbA1c. however, none of these potential covariates were included in the final model. In the model for FPG, we found that the E_{max} and ET_{50} were −9.8% and 36.1 weeks, respectively. In the model for HbA1c, the E_{max} and ET_{50} were −19.6% and 106 weeks, respectively. In addition, the time for achieving 25%, 50%, 75%, 80%, and 90% E_{max} for L-carnitine effect on FPG were 13 weeks, 36.1 weeks, 118 weeks, 160 weeks, and 390 weeks, respectively. The time for achieving 25%, 50%, 75%, 80%, and 90% E_{max} for L-carnitine effect on HbA1c were 38 weeks, 106 weeks, 334 weeks, 449 weeks, and 1058 weeks, respectively. For the efficacy of L-carnitine on FPG,

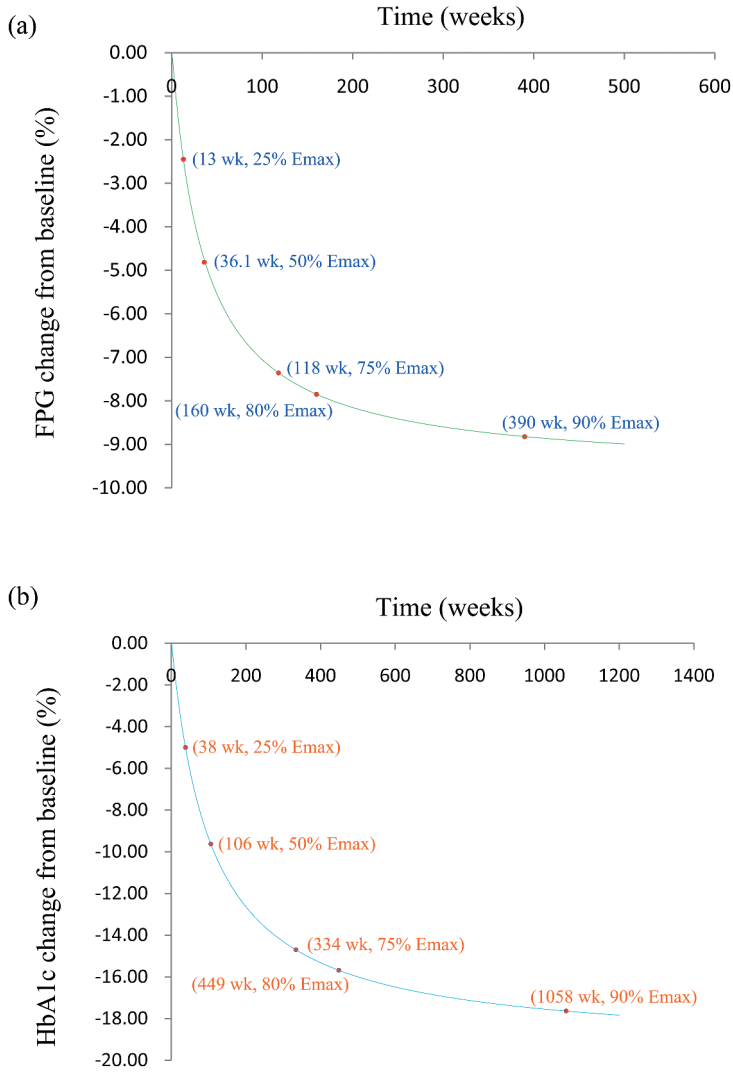

Figure 3. Model prediction.

(a) Model prediction for L-carnitine effects on FPG. (b) model prediction for L-carnitine effects on HbA1c. wk, weeks.

2 g/day L-carnitine was required for at least 36.1 weeks. For the efficacy of L-carnitine on HbA1c, 2 g/day L-carnitine was required for at least 106 weeks.

As we all know, L-carnitine could treat insulin resistance more effectively with prolonging the medication time [18] and was associated with an improvement in glycemia and plasma lipids [19]. In addition, receiving the L-carnitine resulted in weight loss [41] and improving blood sugar regulation. Therefore, the possible metabolic mechanisms underlying the observed effects of L-carnitine in type 2 diabetes mellitus patients may involve these two aspects. Among the eight included studies, six studies showed that the intervention was L-carnitine combined with other different drugs. At present, no studies have clearly shown that L-carnitine interacts with these drug. In the present study, L-carnitine was just added as the supplementation.

Of course, there were limitations to this study. Among the eight included studies, seven studies implemented in Italy. Therefore, more type 2 diabetes mellitus patients in other countries or regions need to be validated.

5. Conclusion

It was the first time to provide valuable quantitative information for efficacy of L-carnitine supplementation on glycemic control in type 2 diabetes mellitus patients.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with

the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Authors contributions

D. Wang and X. Chen conceived and designed the study. D. Wang, Y. Mao, S. He, Y. Yang and X. Chen collected and analyzed data. D. Wang wrote the paper. X. Chen reviewed and edited the manuscript. All authors read and approved the final manuscript.

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