Original papers

L-carnitine treatment of insulin resistance: A systematic review and meta-analysis

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Abstract

Background. L-carnitine has been used for several years as an adjuvant therapy in oxidative stress, blood sugar, high-sensitivity C-reactive protein (CRP), anemia, etc. However, the efficacy of L-carnitine treating insulin resistance (IR) remains controversial. Homeostasis model assessment of Insulin Resistance (HOMA-IR) is widely used in the clinical evaluation of patients with IR.

Objectives. A meta-analysis, including randomized controlled trials (RCTs), was performed to assess the effect of L-carnitine on HOMA-IR patients.

Material and methods. The Cochrane Library, PubMed, and EMBASE databases were systematically searched to identify RCTs which evaluated the effects of L-carnitine on HOMA-IR patients. We screened relevant studies according to predefined inclusion and exclusion criteria. In the selected articles, we extracted the data: study design, sample size, age, L-carnitine dose and regimen, body mass index (BMI) of patients, mode of administration, study duration and study outcomes.

Results. A total of 5 studies were included for the meta-analysis. The result showed L-carnitine was useful in the treatment of IR (WMD −0.724, CI −0.959 −0.488, p < 0.0001). Evaluation at 3, 6, 9, 12 months, the p-values were 0.875, 0.165, 0.031, 0, 007, respectively.

Conclusions. L-carnitine was useful in treating patients with IR. L-carnitine can treat IR more effectively with prolonging the medication time. However, more RCTs with long-term L-carnitine treatment of IR are needed to confirm the viewpoint.

Key words: insulin resistance, meta-analysis, L-carnitine

Many factors can cause insulin resistance (IR), such as infection, acidosis, excessive stress, smoking, exposure to secondhand smoking.[1] IR means the cells require higher concentrations of insulin in order to produce insulin response.[2] Plasma IR, induced by high insulin and high sugar content, can lead to metabolic syndrome, gout and type II diabetes.[3–5]

Homeostasis model assessment of Insulin Resistance (HOMA-IR) was first proposed by Turner of the University of Oxford research group in 1985 and has been widely used in the clinical evaluation of insulin sensitivity.[6] HOMA-IR was calculated as [serum insulin (IU/L) × × Plasma glucose (mmol/L)]/22.5.[6] The HOMA model is used to estimate cell function from fasting plasma insulin and glucose concentrations. A higher score of HOMA-IR indicates more severe IR. HOMA-IR of the normal is less than 2.68.

L-carnitine is an important transporter of long-chain fatty acids which is primary synthesized in the liver and kidney.[7] Its shortage will impair the use of fat as fuel, which will result in an acute metabolic decompensation.[8] Previously, L-carnitine was mainly used to lose weight and to assist in dialyzing kidneys.[9,10] Recently, several studies have reported its use in treating IR.[11,12] However, the real effect of L-carnitine on IR remains unclear. Therefore, we performed this meta-analysis.

Data sources and search strategy

Two investigators (XY and JWJ) independently searched the Cochrane Central Register of Controlled Trials, PubMed, and EMBASE databases from inception to 2014–2010. The search terms were "L-carnitine" and "insulin resistance". If the 2 investigators had disagreements, it would be resolved by a 3rd person (MTL).

Study selection

When selecting studies, we obeyed the following criteria.
Inclusion criteria: Randomized Controlled Trials (RCTs) which evaluated the effects of L-carnitine on HOMA-IR. HOMA-IR as the index in assessing the degree of IR in patients. Treatment time was less than 6 months. Publications written in English.

Exclusion criteria: Non-randomized controlled trials. Results were not evaluated by HOMA-IR. Studies did not offer the detailed data.

Study quality assessment

The Newcastle-Ottawa Scale was used to assess the methodological quality of the included studies based on their selection of participants, comparability of groups and exposure/outcome ascertainment. A total score of 6 or higher (max score, 9) was used to identify higher-quality studies. The quality of these studies was evaluated by 2 authors (XY and JWJ) independently. If 2 investigators had disagreements, it would be resolved by the 3rd person (MTL).

Data extraction and management

The following data was extracted: study design, sample size, mean age of patients, body mass index (BMI) of patients, L-carnitine dose and regimen, mode of administration, study duration and study outcomes. The data was independently extracted by 2 authors (XY and JWJ) and disagreements were resolved by the 3rd author (MTL).

Data synthesis and statistical analysis

Using the data derived from these RCTs, we used the weighted mean differences (WMDs) to report the continuous outcomes, and 95% confidence intervals (CIs) were also calculated.[13] Subgroup analysis was used to assess the differences at evaluation time of 3, 6, 9, 12 months, respectively. I^2 was used to assess the heterogeneity among the selected studies. The meta-analyses were performed with STATA 12.0 software (copyright 1985–2011 StataCorp LP).

Results

Study selection and characteristic

Searching the database with time limit from the database set up date to October 2014. A total of 581 studies were included in the search and then 314 studies based on animal experiments, theme inconsistent, letters, review and meta-analysis were excluded. After reading the full text content roughly, we excluded the papers which were not randomized controlled trial, not relevant to L-carnitine and not relevant to IR. Then, we further analyzed the rest of the data. We further excluded 22 articles which presented with different indicator of IR and units of IR. Finally, 5 studies were included in the meta-analysis.[11,12,14–16] Details of the study selection process and reasons for study exclusion were presented in Fig. 1.

These 5 studies involved a total of 631 patients, in which 319 were treated with L-carnitine and 312 with placebo. Study duration ranged from 4 weeks to 12 months. The characteristics of included studies were summarized in Table 1. In the 5 articles, the Nos score (95% CI) was 6 ± 2. The detail rules of NOS scoring system are listed in Table 2.

Table 1. Characteristics of the included studies

Study	Study design	Patients L	Patients C	Gender (m/f) L	Gender (m/f) C	BMI L	BMI C	Mean age (years) L	Mean age (years) C	HOMA-IR L	HOMA-IR C	Route of administration	L-carnitine dose	Study duration	Nos score
Alessio Molfino (2010)[12]	RCT	8	8	NR	NR	28.6 ± 6.8	25.8 ± 6.8	69.1 ± 12.6	64.2 ± 14.5	1.1 ± 0.5	1.9 ± 0.7	oral	2 g/day	4 weeks	7
Richard Bloomer (2009)[13]	RCT	14	15	NR	NR	27.8 ± 1.7	32.6 ± 24.4	31 ± 3	35 ± 3	2.9 ± 1.2	3.5 ± 1.6	oral	3 g/day	8 weeks	4
Mariano Malaguarnera (2010)[15]	RCT	36	38	20/26	20/18	26.6 ± 3.7	26.5 ± 3.8	47.9 ± 5.4	47.8 ± 5.8	3.26 ± 0.56	4.03 ± 0.71	oral	2 g/day	24 weeks	7
Pamela Maffioli (2010)[16]	RCT	129	125	21/19	21/18	NR	NR	51 ± 4	53 ± 6	7.0 ± 3.7	7.4 ± 4.1	oral	2 g/day	3, 6, 9, 12 months	8
Giuseppe Derosa (2010)[17]	RCT	132	126	20/23	21/25	32.1 ± 2.6	32.2 ± 2.7	NR	NR	6.1 ± 3.2	6.6 ± 3.4	oral	2 g/day	3, 6, 9, 12 months	8

RCT – Randomized Controlled Trial, L – L-carnitine group, C – control group, NR – not reported, BMI – body mass index, HOMA-IR = fasting insulin (IU/l) × fasting plasma glucose (mmoL/L)/22.5, NOS score – The Newcastle-Ottawa Scale (NOS) for assessing the quality.

Table 2. The Newcastle-Ottawa Scale (NOS) tool

| NOS assessment	Alessio Molfino (2010)	Richard Bloomer (2009)	Mariano Malaguarnera (2010)	Giuseppe Derosa (2010)	Pamela Maffioli (2010)
Selection (0~4 scores)					
Definition adequate? (1 score)	1	1	1	1	1
Representativeness of the cases? (1 score)	1	1	1	1	1
Selection of controls? (1 score)	1	1	1	1	1
Definition of controls? (1 score)	1	0	1	1	1
Comparability (0~2 scores)					
Select the most important factor? (1 score)	0	0	1	1	1
Any additional factor? (1 score)	1	0	0	0	1
Exposure (0~3 scores)					
Ascertainment of exposure? (1 score)	1	1	1	1	1
Same method of ascertainment for cases and controls? (1 score)	1	0	1	1	1
Non-response rate (1 score)	0	0	0	1	0
Total	7	4	7	8	8
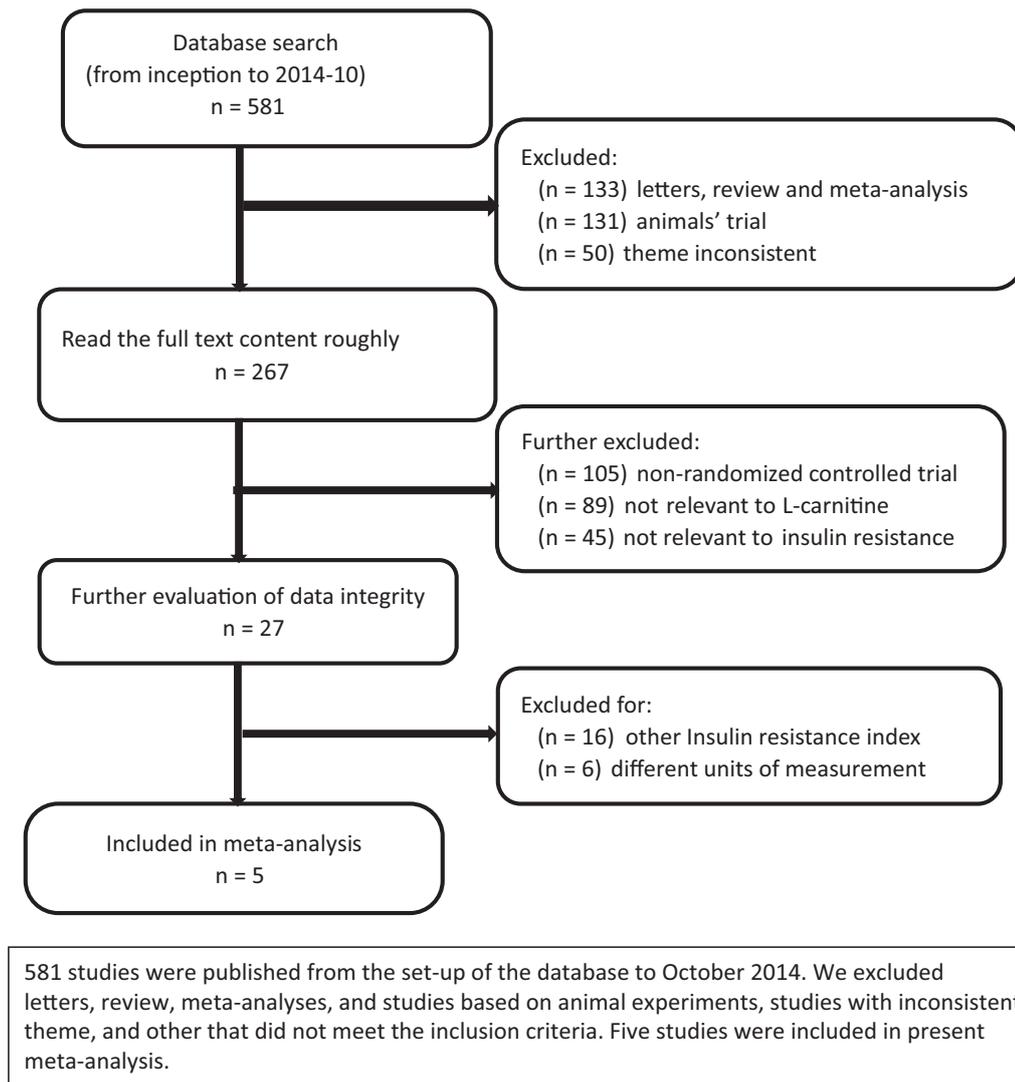
Fig. 1. Flow diagram of literature searching and selecting

Effects of L-carnitine treatment on HOMA-IR

The results showed that L-carnitine could treat HOMA-IR compared to the placebos (WMD -0.724, CI -0.959 TO -0.488, $p < 0.0001$) Fig. 2. Little heterogeneity existed in the analysis ($I^2 = 0\%$). The results of comparisons among different evaluation time indicated that the treatment of L-carnitine became more and more effective with time elapsed (3, 6, 9, 12 months: $p = 0.875$, 0.165, 0.031, 0.007, respectively) Table 3.

Table 3. Different evaluation time comparison chart

Treatment time	WMD [95%CI]	I^2	p-value
3 months	-0.062 (-0.762 to 0.638)	0.0%	0.875
6 months	-0.459 (-1.099 to 0.181)	0.0%	0.165
9 months	-0.201 (-0.385 to -0.018)	0.0%	0.031
12 months	-0.257 (-0.443 to -0.071)	0.0%	0.007

More detailed comparative analysis was conducted, based on 2 of the 5 enrolled literatures, which had longer experimental time. The analysis results showed that the longer the treatment time, the smaller p-value, indicating that with the extension of treatment time, the effect of L-carnitine is more significant.

Discussion

IR is a state in which a given concentration of insulin produces a less-than-expected biological effect.[17] IR widely exists in a variety of diseases not just in diabetes.[8,18] IR makes up a broad clinical spectrum including obesity, glucose intolerance, diabetes, and the metabolic syndrome which will impair the patients' quality of life,

lower their survival rate and produce a heavy economic burden on society.[9,15,19,20] However, no therapy has been found to treat IR effectively. Recently, several studies researched the use of L-carnitine in treating IR.[21]

L-carnitine is an important transporter of long-chain fatty acids that can be synthesized endogenously from lysine and methionine or obtained from the diet.[16] L-carnitine is widely used in the maintenance of hemodialysis to
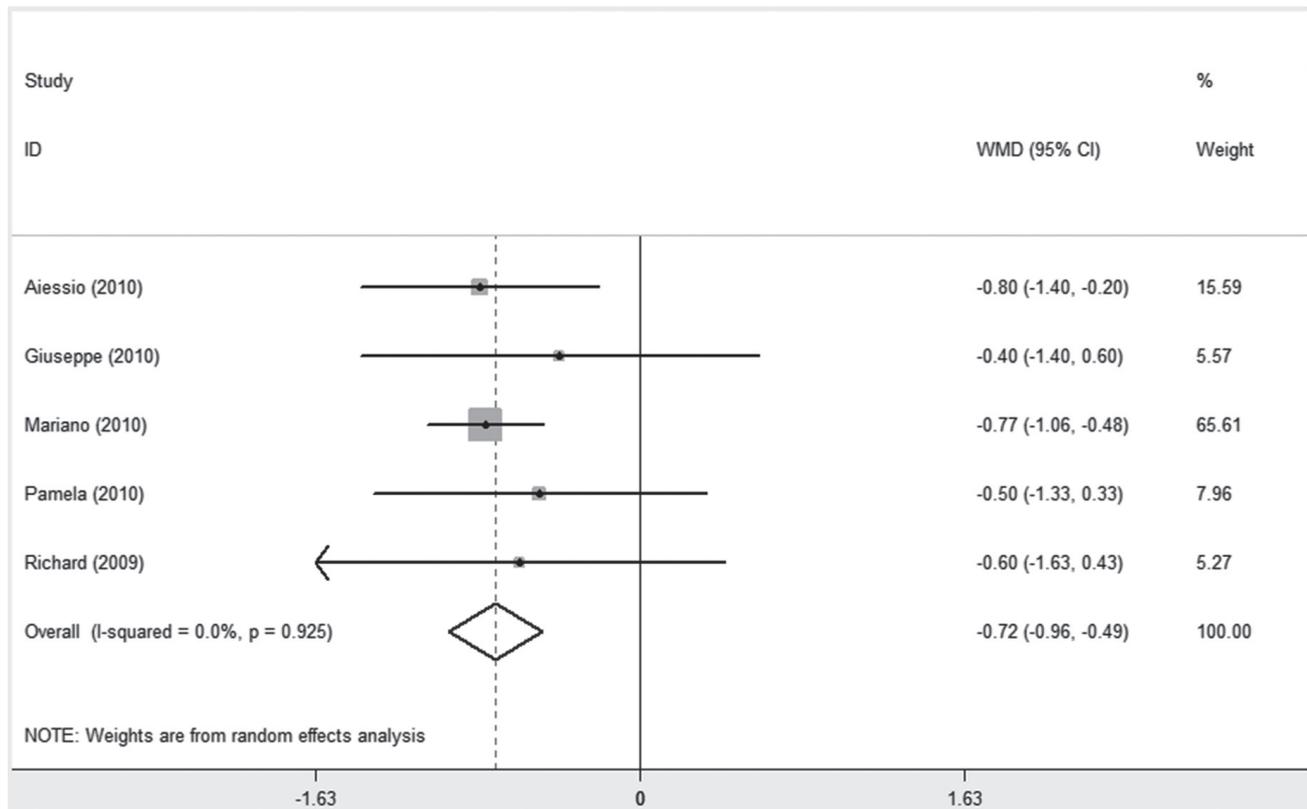
Fig. 2. Forest plot of meta-analysis of L-carnitine on the HOMA-IR in patients

replenish carnitine depletion and has several important proven physiological functions, such as offering nutrition, remedying anemia, adjusting dyslipidemia, curing hyperparathyroidism, developing cognitive functions and enhancing the quality of life in patients.[12,22]

HOMA-IR is a useful index in evaluating IR and is widely used in the evaluation of IR. Several studies showed that HOMA-IR and euglycemic hyperinsulinemic glucose clamps (the IR's gold standard).[23]

Therefore, we performed the meta-analysis to evaluate the effect of L-carnitine on HOMA-IR. Five papers of L-carnitine treating in IR were included in the meta-analysis. The results showed that L-carnitine was useful in reducing the HOMA-IR. Little heterogeneity existed in the analysis. Two of the selected articles included the evaluation time separately at 3, 6, 9, 12 months, then we made a further analysis. The results showed that the treatment of L-carnitine became more and more effective with time elapsed.

The meta-analysis had several advantages. Firstly, the heterogeneity among the included studies was insignificant. Secondly, all of the articles included in the meta-analysis were randomized controlled trials. Thirdly, the articles included in the meta-analysis have high quality by using NOS score tool which has high validity and reliability. Lastly, the paper assessed the efficacy of L-carnitine in 3, 6, 9, 12 months separately.

However, this meta-analysis had some limitations. Firstly, the use of mean ± SD of HOMA-IR was probably unsuitable as it is unlikely to be normally distributed and quartile range seemed to be more suitable. However, all the results in the included studies were expressed as mean ± SD, then we contacted authors to raw data but didn't get a response. Secondly, the experimental time was not long enough in the included studies, and the treatment period did not have uniform criteria. Thirdly, uncontrollable factors may exist in the included 2 groups, such as lifestyle, eating habits and the effects of these factors, which can impact the results significantly. Fourthly, the sample size was small, as only 631 patients were included. This may not represent all the patients well. Lastly, only 2 articles included the evaluation time of 3, 6, 9, and 12 months studies separately and the result may not be persuasive.

Taking all the above into consideration, we need more RCTs with longer treatment time and better control of the interference factors to further research the efficiency of L-carnitine, which could guide clinical practice and provide sound advice for patients more efficiently.

Conclusion

L-carnitine was valid in HOMA-IR. The longer is the treatment duration, the more significant is the treatment effect. However, more RCTs with an adequate sample size and hard endpoints are needed to define the effect of L-carnitine on patients.

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