Metabolic Effects of L-carnitine on Type 2 Diabetes Mellitus: Systematic Review and Meta-analysis

Abstract

Introduction: Carnitine is an endogenous metabolite and exogenous nutrient with a pivotal role in lipid metabolism. Plasma levels of carnitine are reduced in type 2 Diabetes Mellitus (T2DM). The aim was to evaluate the metabolic effects of the administration of L-carnitine in T2DM.

Method: A systematic review was performed. Relevant randomized, controlled-trials trials were searched in Pubmed, Trip Database and Cochrane Library, and selected when they had enough methodological quality assessed with the Jadad scale. Article search strategy included “Carnitine” OR “L-carnitine” AND “Diabetes Mellitus” OR “Diabetes mellitus, type 2” OR “Noninsulindependent-diabetes mellitus”. Meta-analysis was performed, and the difference of means calculated with a 95 % confidence interval. Heterogeneity was evaluated with the Q statistic.

Results: The systematic review included 4 trials with 284 patients. Oral L-carnitine lowered fasting plasma glucose [−14.3 mg/dl (CI95 % −23.2 to −5.4); p = 0.002], total cholesterol [−7.8 mg/dl (95 % CI −15.5 to −0.1); p = 0.09], low density lipoprotein [−8.8 mg/dl (CI95 % −12.2 to −5.0); p < 0.0001], apolipoprotein-B100 [−7.6 mg/dl (CI95 % −13.6 to −1.6); p = 0.013] and apolipoprotein-A1 [−6.0 mg/dl (CI95 % −10.5 to −1.5); p = 0.523]. There was no significant heterogeneity. The changes in triglycerides, lipoprotein (a) or HbA1c were not significant.

Conclusion: The administration of L-carnitine in type 2 diabetes mellitus is associated with an improvement in glycaemia and plasma lipids.
metabolism measured with hyperinsulinaemic euglycaemic clamp, mainly by a non-oxidative mechanism that results in the accumulation of glycogen [3–5]. In type 2 Diabetes Mellitus (T2DM), carnitine infusion improved glucose oxidation and glycogen storage [6,7]. Among diabetic patients with associated complications, L-carnitine plasma levels are 25% lower than among those without complications, and it has been suggested that carnitine could be a useful treatment in T2DM [8,9].

A systematic review and meta-analysis was performed to test the current evidence about the efficacy of L-carnitine supplementation in the amelioration of metabolic disturbances of T2DM patients.

Methods
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Search strategy and inclusion criteria
A bibliographic search for randomised, controlled trials testing the effects of L-carnitine against a placebo in T2DM was performed in Medline (PubMed), Trip Database, and Central (Cochrane Library) databases. Article search strategy included “Carnitine” OR “L-carnitine” AND “Diabetes Mellitus” OR “Diabetes mellitus, type 2” OR “Noninsulindependent-diabetes mellitus”. The initial eligibility criteria for including studies in the review were the type of assay (randomised, double-blinded, controlled studies), species (humans), and language (English, Spanish). The identified studies were evaluated for inclusion by the reviewers, who were not blinded to authors, institutions or journal at any during the selection process. When several papers from a same study were found, the publication with higher methodological quality was selected. The adequacy of the selected articles was measured using the Jadad scale, which considers if the study is randomised (and the method of randomisation), double blinded (and the method of blindness) and the description of lost patients. A minimal punctuation of 3 was necessary for the inclusion in this review. The quality assessment of each article was independently performed by 2 different reviewers.

Outcome measures
The investigators independently extracted the following data, using a common form for this purpose: a) Glucose metabolism: fasting plasma glucose (FPG), postprandial glucose (PPG), HbA1c, and insulin levels. b) Lipid metabolism: total cholesterol (TC), HDL-cholesterol, LDL-cholesterol, triglycerides, apolipoprotein-A1, apolipoprotein-B100 and lipoprotein (a). c) Body weight and HDL-cholesterol, LDL-cholesterol, triglycerides, apolipoprotein- and insulin levels. b) Lipid metabolism: total cholesterol (TC), fasting plasma glucose (FPG), postprandial glucose (PPG), HbA 1c using a common form for this purpose: a) Glucose metabolism: fasting plasma glucose (FPG), postprandial glucose (PPG), HbA1c, and insulin levels.
Effects on glucose metabolism
The changes in FPG were evaluated in the 4 studies (Fig. 2). When the meta-analysis was performed, a MD of $-14.3$ mg/dL ($95\%$CI $-23.2 \text{ to } -5.4$; $p=0.002$) favoured the group treated with L-carnitine, without evidence of heterogeneity ($\chi^2=3.19$, $p=0.363$). HbA1c, was evaluated in 3 of the included studies, and no significant effect was found after aggregating the results: $MD=0.1\% \ (95\%CI \ -0.7 \ \text{ to } 0.9$; $p=0.892$), without associated heterogeneity ($\chi^2=1.58$; $p=0.454$). The study by Derosa et al. did not obtain significant differences between the L-carnitine and placebo groups regarding postprandial glycaemia and insulinaemia [9].

Effects on lipid metabolism
All studies included data about total cholesterol, HDL, LDL and triglycerides. The analysis of aggregated data showed a significant reduction in total cholesterol ($MD=-7.8$ mg/dL ($95\%$CI $-15.5 \text{ to } -0.1$; $p=0.09$; without heterogeneity: $\chi^2=3.25$, $p=0.280$)) and LDL ($MD=-8.8$ mg/dL ($95\%$CI $-12.2 \text{ to } -8.5$; $p<0.0001$; heterogeneity: $\chi^2=2.78$, $p=0.425$) associated with the administration of L-carnitine (Fig. 3, 4). There was no significant changes in the concentration of HDL ($MD=1.9$ mg/dL ($95\%$CI $-1.2 \text{ to } 5.1$; $p=0.212$; without heterogeneity: $\chi^2=3.41$, $p=0.332$). There was also no significant effect on triglycerides with the pooling of the 4 studies ($MD=-2.5$ mg/dL ($95\%$CI $-12.6 \text{ to } 7.6$; $p=0.622$; without associated heterogeneity: $\chi^2=4.77$, $p=0.190$).

The effect of treatment on apolipoprotein AI was evaluated in 3 studies, and on apolipoprotein B100 and lipoprotein(a) in 2 studies. The use of L-carnitine was associated with a significant lowering of apolipoprotein AI ($MD=-6.0$ mg/dL ($95\%$CI $-10.5 \text{ to } -1.5$; $p=0.008$) and B100 ($MD=-7.6$ mg/dL ($95\%$CI $-13.6 \text{ to } -1.6$; $p=0.013$). There was no significant changes in the concentration of lipoprotein(a) ($MD=-2.3$ mg/dL ($95\%$CI $-9.5 \text{ to } 4.8$; $p=0.523$). There was no heterogeneity among the reviewed studies.

The trial by Rahbar et al., which used a higher dose of L-carnitine (3 g/day vs. 2 g/day), found significant increases in triglycerides, apoAI and apol100 [10]. When this study was not included in the meta-analysis, the aggregated effects of 2 g/day of L-carnitine remained not significant ($MD=-4.4$ mg/dL ($95\%$CI $-13.3 \text{ to } 4.6$); $p=0.334$; without associated heterogeneity: $\chi^2=3.47$, $p=0.309$]. Santo et al. found that in the carnitine-supplemented group the time for oxidation of LDL particles was significantly prolonged when compared with the placebo group (1.61 vs. 0.91 h) [11]. On the other hand, in the study by Malaguarnera et al. the concentration of oxidised-LDL particles was significantly lower in patients who received L-carnitine (43.1 vs. 55.0 U/L; $p<0.001$) [12].

Effects on weight
3 studies evaluated the evolution of weight by means of BMI. After the aggregation of the results, there was no significant difference associated with the administration of L-carnitine ($MD=-0.3$ kg/m² ($95\%$CI $-2.4 \text{ to } 1.7$; $p=0.751$; without heterogeneity: $\chi^2=1.39$, $p=0.499$).

Effects on OS
2 studies evaluated OS, but they followed different methodologies. In the study by Santo et al., the use of L-carnitine was associated with significant reductions in malondialdehyde, 4-hydroxynonal and the nitrate/nitrate ratio, while in the study by Malaguarnera et al. L-carnitine administration was associated with lower concentrations of TBARS and conjugated dienes. The data could not be aggregated for meta-analysis.

Discussion
Carnitine is a nutrient that plays a key role in the metabolism of FA. It is well known that in the pathogenesis of T2DM disturbances of glucose and lipid metabolism (glucotoxicity and lipo-toxicity, respectively) interact, as well as an increase in oxidative stress. Carnitine appears therefore as a potential therapeutic agent for this disease. This review verifies that few studies with adequate methodological quality to assess the efficacy of carnitine have been published. The results of this meta-analysis support a favourable

<table>
<thead>
<tr>
<th>Study</th>
<th>Carnitine Mean</th>
<th>SD</th>
<th>n</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>n</th>
<th>Weight</th>
<th>MD</th>
<th>CI95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahbar</td>
<td>130</td>
<td>33</td>
<td>19</td>
<td>164</td>
<td>47</td>
<td>16</td>
<td>8.2%</td>
<td>-34</td>
<td>[-61.4, -6.6]</td>
</tr>
<tr>
<td>Derosa</td>
<td>126</td>
<td>26</td>
<td>46</td>
<td>135</td>
<td>20</td>
<td>48</td>
<td>26.7%</td>
<td>-9</td>
<td>[-18.4, 0.4]</td>
</tr>
<tr>
<td>Malaguarnera</td>
<td>114</td>
<td>21</td>
<td>41</td>
<td>120</td>
<td>21</td>
<td>40</td>
<td>27.2%</td>
<td>-6</td>
<td>[-15.6, 2.6]</td>
</tr>
<tr>
<td>Santo</td>
<td>145</td>
<td>3</td>
<td>37</td>
<td>164</td>
<td>3</td>
<td>37</td>
<td>37.8%</td>
<td>-19</td>
<td>[-20.6, -18.0]</td>
</tr>
<tr>
<td>Total</td>
<td>143</td>
<td></td>
<td></td>
<td>141</td>
<td></td>
<td></td>
<td>100%</td>
<td>-14.3</td>
<td>[-23.2, -5.4]</td>
</tr>
</tbody>
</table>

**Fig. 2** Forest plot of studies that evaluated the effect of L-carnitine supplementation on fasting plasma glucose (circles represent effect size; extended lines show 95% confidence intervals).
effect on fasting glucose that did not result in a significant improvement in glycaemic control, as measured by HbA1c. The changes in fasting glucose were moderate, and the study that assessed postprandial glucose did not find significant effects with the administration of L-carnitine, thus it is possible that the improvement of glucose metabolism was insufficient to reach changes in glycated hemoglobin. Some animal and human studies have suggested that carnitine deficiency impairs insulin-sensitivity and can produce elevations of fasting glucose. Carnitine can improve glucose metabolism by means of several mechanisms. First, the enhancement of mitochondrial oxidation of long chain-AcylCoA, which accumulation produces insulin-resistance in muscle and heart. Second, inducing changes in glycolitic and gluconeogenic enzymes. Third, modifying the expression of genes related to the insulin signaling cascade. And finally, improving the glucose utilization by heart [14]. These mechanisms were not evaluated in any of the collected studies of this systematic review.

The effects on lipid metabolism focused on reductions in total cholesterol, LDL and B100, all of them atherogenic particles, but the levels of apo AI were also decreased. The last lipoprotein is a constituent of HDL particles, and it is therefore potentially antatherogenic. On the other hand, triglyceride levels were not affected, a surprising result given the role of L-carnitine in the metabolism of FA. The fact that all lipid analysis were performed whilst in a fasting state, and that in T2DM patients postprandial concentrations of triglycerides and FA may be increased, means that it is possible that the beneficial effects on these parameters have not been properly evaluated [15]. Furthermore, these lipid abnormalities may be related to the phenomena of insulin resistance and lipotoxicity, the mechanisms by which carnitine could improve glucose metabolism. A dose-dependent effect should be considered as well, as beneficial effects could be observed using 2 g/day of L-carnitine, but doses of 3 g/day were related to increases in triglycerides concentrations in the study by Rahbar et al. [11]. The results for oxidative stress are incom-

<table>
<thead>
<tr>
<th>Study</th>
<th>Carnitine Mean SD n</th>
<th>Placebo Mean SD n</th>
<th>Weight</th>
<th>MD</th>
<th>CI95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahbar</td>
<td>175 35 19</td>
<td>197 39 16</td>
<td>12.1%</td>
<td>-22</td>
<td>[-46.4, 2.4]</td>
</tr>
<tr>
<td>Santo</td>
<td>207 34 37</td>
<td>200 48 37</td>
<td>18.9%</td>
<td>7</td>
<td>[-11.7, 26.1]</td>
</tr>
<tr>
<td>Malaguarnera</td>
<td>230 31 41</td>
<td>239 32 40</td>
<td>31.1%</td>
<td>-9</td>
<td>[-23.4, 4.1]</td>
</tr>
<tr>
<td>Derosa</td>
<td>225 28 46</td>
<td>234 31 48</td>
<td>37.8%</td>
<td>-9</td>
<td>[-20.9, 2.9]</td>
</tr>
<tr>
<td>Total</td>
<td>143 141</td>
<td>141 100%</td>
<td>-7.8</td>
<td>-15.5, -0.1</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.25 (p = 0.291)

**Fig. 3** Forest plot of studies that evaluated the effect of L-carnitine supplementation on total cholesterol (circles represent effect size; extended lines show 95% confidence intervals).

<table>
<thead>
<tr>
<th>Study</th>
<th>Carnitine Mean SD n</th>
<th>Placebo Mean SD n</th>
<th>Weight</th>
<th>MD</th>
<th>CI95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahbar</td>
<td>87 39 19</td>
<td>88 28 16</td>
<td>2.3%</td>
<td>1</td>
<td>[-23.0, 21.5]</td>
</tr>
<tr>
<td>Derosa</td>
<td>158 20 46</td>
<td>160 25 48</td>
<td>11.9%</td>
<td>-2</td>
<td>[-11.1, -8.7]</td>
</tr>
<tr>
<td>Malaguarnera</td>
<td>136 19 41</td>
<td>145 20 40</td>
<td>13.4%</td>
<td>-9</td>
<td>[-17.4, 0.1]</td>
</tr>
<tr>
<td>Santo</td>
<td>112 437</td>
<td>122 48 37</td>
<td>72.4%</td>
<td>-10</td>
<td>[-11.7, -8.7]</td>
</tr>
<tr>
<td>Total</td>
<td>143 141</td>
<td>141 100%</td>
<td>-8.8</td>
<td>-12.2, -8.5</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.78 (p = 0.425)

**Fig. 4** Forest plot of studies that evaluated the effect of L-carnitine supplementation on LDL-cholesterol (circles represent effect size; extended lines show 95% confidence intervals).
plete, as is the case with other antioxidants studied in T2DM [16,17]. Finally, we did not find heterogeneity among the included studies, although the Q test may underestimate it when few studies are included for meta-analysis.

In conclusion, administration of oral L-carnitine at doses of 2-3 g/day in type 2 Diabetes Mellitus patients is associated with improvements in fasting glucose and decreases in total cholesterol, LDL, and apolipoproteins B100 and AI. Further trials should clarify the effects of L-carnitine on insulin resistance and postprandial lipid dysmetabolism.

Authorship: AVC and LMLP performed the search of articles. All the authors assessed the articles, extracted the data and revised the manuscript. AVC performed the statistical analysis.

Competing interest: Vegenat S.A. (Badajoz, Spain) has provided financial support to this project. The authors have no conflicts of interest to declare.

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References