

Can L-carnitine replace tumor necrosis factor-alpha blockers? a systematic review and dose–response meta- analysis

Farnaz Naeimzadeh ^{1,2}, Amirreza Naseri ¹, Sarvin Sanaie ³, Seiedhadi Saghaleini ⁴, and Afshin Gharekhani ^{2*}

¹ *Student Research Committee, Tabriz University of Medical Sciences, Iran*

² *Department of Clinical Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran*

³ *Research Center for Integrative Medicine in Ageing, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran*

⁴ *Clinical Research Development Unit, Sina Educational, Research and Treatment Center, Tabriz University of Medical Sciences, Tabriz, Iran*

Corresponding Author: Afshin Gharekhani, Pharm.D., PhD, Associate Professor of Clinical Pharmacy, Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

Email: anqarekhani@yahoo.com, Tel: +984133341315, Fax: +984133344798.

Table S1. Summary of included randomized controlled studies

Author (Publication year)	Country	Study design	Sample size (male: female)	Age (Intervention: Placebo) [mean ± SD]	BMI (Intervention: Placebo) [mean ± SD]	Underlying condition	L-Carnitine dose, route of administration and duration	control	Amount (pre) [mean ± SD]	Amount (post) [mean ± SD]	Amount (pre) [mean ± SD]	Amount (post) [mean ± SD]	Final conclusion
Badrasawi ³⁴ (2016)	Malaysia	Double-blind RCT	50 (23: 27)	(68.2 ± 6.3): (68.8±6.5)		Pre-frail older adults	L-carnitine 1.5 g/day (PO) for 10 weeks	Placebo (N/M)	5.9 ± 2.0	5.9 ± 4.9	6.2±2.1	5.9 ± 2.0	No significant change in TNF-α
Derosa ¹⁵ (2011)	Italy	Double-blind RCT	254 (129:125)	(54 ± 5):(51 ± 4)	Baseline: 33.9 ± 3.5: 33.4 ± 3.2 3 M: 32.6 ± 2.9: 33.0 ± 3.0 6 M: 32.1 ± 2.6: 32.2 ± 2.7 9 M: 30.8 ± 2.0: 30.9 ± 2.1 12 M: 30.1 ± 1.8: 30.3 ± 1.9	obese uncontrolled diabetic patients	Sibutramine 10 mg plus, L-carnitine 2 g (PO) for 12 months	sibutramine 10 mg (PO)	4.8 ± 2.1	3 M: 4.2 ± 1.6 6 M: 3.5 ± 1.2 9 M: 3.0 ± 1.0 12 M: 2.6 ± 0.9	4.9 ± 2.2	3 M: 4.3 ± 1.7 6 M: 4.2 ± 1.6 9 M: 3.7 ± 1.3 12 M: 3.2 ± 1.1	TNF-α reduced significantly

Lee³² (2015)	Taiwan	single-blind RCT	39 (39:0)	(71.9±10.6):(72.7 ± 10.1)	(24.8± 2.6):(26.0± 2.4)	Coronary artery disease patients	L-carnitine 1000 mg/day (PO) for 12 weeks	Placebo (Starch)	2.1±1.3	1.8±0.8	1.9±1.9	2.4±2.1	TNF- α reduced significantly
Jirillo¹⁷ (1991)	Italy	Double-blind RCT	20 (10:10)	49±17	N/M	Active pulmonary tuberculosis	L-carnitine 2 g/day (PO) for 30 days	Placebo (N/M)	9±4	13±8	10+6	15+10	No significant change in TNF- α
Shakeri¹⁸ (2010)	Iran	Unblinded RCT	36 (23:13)	(54.5 ± 19.0)	(23 ± 4): (23 ± 3)	hemodialysis patients with Lp (a) hyperlipoproteinemia	L-carnitine 1000 mg/day (PO) for 12 weeks		3.2 ± 1.4	2.8 ± 0.5	3.7 ± 2.4	2.9 ± 1.6	No significant change in TNF- α
Malaguarnera (14) (2010)	Italy	Double-blind RCT	74 (40:34)	(47.9 ± 5.4): (47.8 ± 5.8)	(26.6± 3.7): (26.5± 3.8)	patients with a clinical and pathologic diagnosis of nonalcoholic	Diet + L -carnitine 2 g per day divided into two equal doses (PO) for 24 weeks	Diet + placebo	1.44 ± 0.28	1.08 ± 0.15	1.38 ± 0.22	1.30 ± 0.21	TNF- α reduced significantly

						steatohepatitis							
Amiri-Moghadam¹⁴ (2015)	Iran	Double-blind RCT	68 (N/M)	(41.6 ± 8.8):(45.3±12.1)	(31.9±5.3):(30.1±3.7)	nonalcoholic steatohepatitis	L -carnitine 2 gr (PO) per day for 12 weeks	Placebo (N/M)	91.10±16.4	43.77±6.22	99.00±30.84	70.80±23.41	TNF-α reduced significantly
Simone²⁷ (1993)	Italy	RCT Blinding (N/M)	28 (28:0)	36±2.4	N/M	AIDS patients	L -carnitine 6 gr (PO) per day for two weeks	Placebo (N/M)	21.3+17	13±4	21.8±10	22±9	TNF-α reduced significantly in patients exhibiting highly elevated levels
Mahdavi²⁵ (2017)	Iran	Double-blind RCT	69 (0:69)	51.63 ± 5.69): (52.44 ± 6.56)	N/M	Women with knee osteoarthritis	L-carnitine 750 mg/day (PO) for 8 weeks	Placebo (N/M)	10.2 ± 7.9	9.1 ± 4.9	9.2 ± 6.9	10.4 ± 5.4	TNF-α reduced significantly
Mazdeh²⁶ (2022)	Iran	Double-blind RCT	69 (32:37)	(65:24 ± 12:89): (70:37 ± 13:58)	(24:25 ± 2:96): (25:29 ± 3:31)	patients with acute ischemic stroke	Acetyl-L-carnitine 1000 mg three times per day (PO) for three consecutive days	Placebo (N/M)	3:50 ± 1:05	2:58 ± 0:89	16:50 ± 15:19	15:85 ± 13:88	TNF-α reduced significantly

Fu ¹⁶ (2010)	China	open label RCT	40 (22:18)	53.5±7.1	N/M	maintenance hemodialysis patients	L-carnitine 1 g/day (IV) after each hemodialysis session for 3 months	No Placebo	12.11±3.30	10.93±2.70	11.79±3.10	12.34±3.20	TNF- α level did not change significantly
Volek ³⁶ 2008	United States	Double-blind RCT	30 (16:14)	30 ± 8	24.1 ± 4.3	Healthy Young Adults	l-Carnitine l-Tartrate 2 g/day (PO) for 3 weeks	Placebo (powdered cellulose)	Fasting: 0.99 ± 0.39	3 Hours: 0.95 ± 0.31	Fasting: 1.06 ± 0.49	3 Hours: 1.03 ± 0.42	There were no significant postprandial changes or supplement effects for TNF- α level
Sawicka ³⁵ (2018)	Poland	Double-blind RCT	22 (0:22)	(67.8 ± 2.3): (66.4 ± 1.3)	(27.5 ± 4.5):(26.5 ± 4.4)	Older Women	L-carnitine-L-tartrate 1500 mg (PO) for 24 weeks	Placebo (isonitrogenous placebo)	0.58 ± 0.32	24.58±6.5.27	0.56± 0.26	14.56±29.4	TNF- α level did not change significantly
Delogu ²⁸ (1993)	Italy	RCT Uncertain Blanding method	20 (N/M)	(47 ± 9):(45 ± 13)	(N/M)	patients were admitted for	Neurolept anaesthesia plus L-carnitine 8 g at the end	Neurolept anaesthesia	6±2	After 2 hours: 30±5	5±2	After 2 hours: 40±2	TNF- α reduced significantly.

						surgery	of surgery (IV) and 24 h afterwards.			After 24 hours: 15 ±4		After 24 hours: 68±8	
										After 48 hour: 22±9		After 48 hours: 62±7	
El-sheikh ³³ (2019)	Egypt	RCT Uncertain Blanding method	58 (19:39)	(50.9 ± 8.6) : (50.3 ± 8.8)	(34.46 ± 5.3):(34.25 ± 5.6)	asymptomatic HIV-infected subjects with advanced immunod efficiency	glimepiride 2 mg twice daily plus L-carnitine 1 g twice daily (PO) for 6 months	glimepiride alone 2 mg twice daily	4.57±1.3	After 3 months: 4.81±1.3 After 6 months: 5.44±1.2	4.74±1.4	After 3 months: 3.32±1.1 After 6 months: 2.48±0.79	TNF-α reduced significantly
Derosa ³⁰ (2011)	Italy	Double-blind RCT	258 (127:131)	(51 ± 4):(53 ± 6)	(32.9 ± 2.8):(33.1 ± 2.9)	obese diabetic patients	Orlistat 120 mg three times a day plus L-carnitine 2 g daily (PO) for 12 months	orlistat 120 mg three times a day	4.8 ± 2.1	3 M: 4.3 ± 1.7 6 M: 3.4 ± 1.1 9 M: 3.1 ± 0.9 12 M: 2.8 ± 0.7b	4.4 ± 1.8	3 M: 4.0 ± 1.5 6 M: 3.8 ± 1.3 9 M: 3.7 ± 1.2 12 M: 3.3 ± 1.0	TNF-α reduced significantly
Chi ³¹ (2021)	China	RCT	50 (29:21)	(71.08 ± 9.18): (71.20 ± 6.31)	N/M	elderly patients on	High-flux hemodialysis + L-	High-flux	42.87±4.01	24.03±2.64	42.65±3.63	29.45±2.35	The results of the

		Single blind				maintenan ce hemodialy sis	carnitine 1 g/day (IV) 3 times a week at the end of dialysis for one month	hemodia lysis					compariso n of the two groups have not been explicitly reported.
--	--	-----------------	--	--	--	-------------------------------------	--	------------------	--	--	--	--	---

Note: TNF- α : Tumor Necrosis Factor alpha, RCT: Randomized controlled clinical trial, PO: Per Os, IV: Intravenous, N/M: Not Mentioned, M: Months,
AIDS: Acquired Immunodeficiency Syndrome, HIV: Human Immunodeficiency Virus

17 December 2023

PubMed:

("Tumor Necrosis Factor" OR TNF OR "Tumor Necrosis Factor-alpha"[Mesh] OR Cachectin) AND ("Carnitine"[Mesh] OR carnitine OR L-carnitine OR Levocarnitine OR "Vit BT" OR "Vitamin BT" OR Acetyl-L-Carnitine OR L-Carnitine-L-Tartrate OR "Glycine Propionyl-L-Carnitine" OR L-3-hydroxytrimethylamminobutanoate)

374

Scopus:

TITLE-ABS-KEY (("Tumor Necrosis Factor" OR tnf OR cachectin) AND (carnitine OR l-carnitine OR levocarnitine OR "Vit BT" OR "Vitamin BT" OR acetyl-l-carnitine OR l-carnitine-l-tartrate OR "Glycine Propionyl-L-Carnitine" OR l-3-hydroxytrimethylamminobutanoate))

1288

Embase:

('tumor necrosis factor' OR tnf OR cachectin) AND (carnitine OR 'l carnitine' OR levocarnitine OR 'vit bt' OR 'vitamin bt' OR 'acetyl l carnitine' OR 'l carnitine l tartrate' OR 'glycine propionyl-l-carnitine' OR 'l 3 hydroxytrimethylamminobutanoate')

1522

Web of Science

("Tumor Necrosis Factor" OR tnf OR cachectin) AND (carnitine OR l-carnitine OR levocarnitine OR "Vit BT" OR "Vitamin BT" OR acetyl-l-carnitine OR l-carnitine-l-tartrate OR "Glycine Propionyl-L-Carnitine" OR l-3-hydroxytrimethylamminobutanoate) (All Fields)

459

Table S2. The results of subgroup analysis based on the country for both intravenous and oral L-carnitine administration

Group	No. of studies	Cohen's d	[95% conf. interval]		p-value	df	Q	P>Q	tau2	%I2	H2
China	2	-1.605	-3.063	-0.148	0.031*	1	9.03	0.003	0.984	88.92	9.03
Egypt	2	2.822	1.161	4.483	0.001*	1	9.89	0.002	1.293	89.89	9.89
Iran	4	-0.382	-1.027	0.263	0.245	3	16.93	0.001	0.359	83.41	6.03
Italy	11	-0.575	-0.864	-0.287	0*	10	60.24	0	0.197	89.35	9.39
Malaysia	1	0.129	-0.426	0.685	0.648	0	0	.	0	.	.
Taiwan	1	-0.75	-1.4	-0.1	0.024	0	0	.	0	.	.

Table S3. The results of subgroup analysis based on the country oral L-carnitine administration

Only PO, Groups	No. of studies	Cohen's d	[95% conf. interval]		p-value	df	Q	P>Q	tau2	%I2	H2
China	0	-	-	-	-	-	-	-	-	-	-
Egypt	2	2.822	1.161	4.483	0.001*	1	9.89	0.002	1.293	89.89	9.89
Iran	4	-0.382	-1.027	0.263	0.245	3	16.93	0.001	0.359	83.41	6.03
Italy	11	-0.575	-0.864	-0.287	0*	10	60.24	0	0.197	89.35	9.39
Malaysia	1	0.129	-0.426	0.685	0.648	0	0	.	0	.	.
Taiwan	1	-0.75	-1.4	-0.1	0.024*	0	0	.	0	.	.

Note: PO: Per Os, IV: Intravenous, $P < 0.05$ was considered significant. * $p < 0.05$

Table S4. The results of subgroup analysis based on the route of administration of L-carnitine

Route of administration	No. of studies	Cohen's d	[95% conf. interval]		p-value	df	Q	P>Q	tau2	%I2	H2
IV	2	-1.605	-3.063	-0.148	0.031*	1	9.03	0.003	0.984	88.92	9.03
PO	19	-0.188	-0.709	0.334	0.481	18	227.7	0	1.275	97.39	38.28

Note: PO: Per Os, IV: Intravenous, $P < 0.05$ was considered significant. * $p < 0.05$

Table S5. The results of tests of group differences based on the country, sex, dose (grams/day), and duration of administration (in weeks)

	df	Q_b	P> Q_b
Country	4	20.48	0*
Sex	2	4.41	0.11
Dose (g/day)	5	13.21	0.022*
Duration in weeks	8	16.49	0.036*

P < 0.05 was considered significant. **p* < 0.05

Table S6. The results of Random-effects meta-regression based on dose (grams/day), and duration of administration (in weeks)

_meta_es	Coefficient	Std. err.	z	P>z	[95% conf.interval]	
L- carnitine gr/day	-0.26024	0.276643	-0.94	0.347	-0.80245	0.281972
Duration of administration in weeks	-0.00769	0.019952	-0.39	0.7	-0.0468	0.031415
_cons	0.496168	0.792051	0.63	0.531	-1.05622	2.04856