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A Review on Therapeutic Effects of L-Carnitine: An Update

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Abstract

Metabolic syndrome and obesity are two major determinants for many noncommunicable diseases, such as non-alcoholic fatty liver disease, diabetes and cancer. Lifestyle modification, dietary interventions and weight loss are found to be efficacious remedies. In alternative medications, many functional foods and nutraceuticals have contributed significantly until now. L-carnitine is one of them, which is gaining importance as an ergogenic aid among athletes for muscle building and energy production. It has supported many medical therapies for the treatment of liver, heart and other diseases. It is available in pharmacological form as well as found naturally in various animal and plant foods.

This review of recent clinical trials was aimed to show the efficacy and safety of carnitine supplements available in medicine form or food sources. The clinical outcome of various studies included for analysis indicated that when L-carnitine tablets (0.5 g-2 g) were given to intervention group patients of various diseases, for about 2-6 months duration, helped in a significant reduction of liver enzymes, blood sugar and bodyweight compared to controls. Furthermore, a few randomized clinical trials in which carnitine-rich low-fat animal foods on the Mediterranean diet were given in their recommended doses to patients, provided therapeutic benefits. The beneficial effects of lysine and methionine-rich foods through the Green Mediterranean diet on vegetarians for endogenous carnitine synthesis have been reported. Large-scale clinical trials, including natural foods that would be cost-effective, long-term and safe for vegetarians, are warranted.

Keywords: *Metabolic syndrome, L-carnitine, Diabetes, Mediterranean diet, non-alcoholic fatty liver disease.*

1. Introduction

A continuum from Obesity to Metabolic syndrome has become one of the major public health challenges in the recent past ascribable to excessive calorie intake, rapid urbanization, lack of physical activity and sedentary lifestyle. People with metabolic syndrome and obesity are susceptible to many diseases such as type-2 diabetes, cardiovascular disease, non-alcoholic fatty liver disease, PCOS, lung disease and cancer. Epidemiological evidence indicates that both non-alcoholic fatty liver disease (NAFLD) and Type 2 Diabetes Mellitus (T2DM) are strongly associated with obesity. Therefore, the new term metabolic-associated fatty liver disease (MAFLD) has been proposed by Eslam et al., 2020. Non-alcoholic fatty liver disease (5-10% liver fat) progresses into inflamed liver called non-alcoholic steatohepatitis which advances to Liver cirrhosis and carcinoma. This occurs due to an imbalance in liver fat's β-oxidation and its disposal in the form of acetyl CoA. Fat and toxins accumulate in the liver, causing the slowdown of metabolism, glycolysis and glycogenolysis resulting in obesity. Available treatment is lifestyle modification, consisting of dietary, herbal, or pharmacological interventions, exercise, and sustained weight loss. Functional foods and Nutraceuticals have contributed significantly to the improvement and management of various lifestyle-related diseases (Palanisamy et al., 2021). Several molecules have been studied as adjuvant therapy, including moringa oleifera, L-carnitine, CoQ_{10}, vitamin E, milk thistle, tea polyphenol and insulin sensitizers such as metformin (Guo et al., 2022). This review of recent clinical studies was aimed to assess the efficacy and safety of carnitine supplementation (medicine or food source) on various diseases.

1.1. L-carnitine

Carnitine (β-hydroxy-γ-N-trimethylammonium butyrate, $C_7H_{15}NO_3$) is a water-soluble amino acid, which is found in many cells of the human body (Almannai et al., 2019). It is mostly synthesized in the kidneys and liver and stored in the heart, brain, skeletal muscles and sperm. It was first discovered in muscle extract by two Russian scientists in 1905. The name carnitine is derived from the Latin word "caro/*carnis*" (meaning flesh/meat). It exists as L-carnitine, acetyl-L-carnitine and propionyl-L-carnitine. L-carnitine is the most popular form, which can be naturally sourced or synthesized by plant and animal cells. It can also be synthesized in a lab from chemicals and is used in medicine for therapeutic benefits. The first primary carnitine-deficient patient was identified in 1973. A healthy human body contains 300mg/kg of L-carnitine and a 70kg person can synthesize 11-34 mg of L-carnitine in a day in the liver, kidney and brain (Dayanand et al., 2011). Muscles and other tissues obtain it from the blood.

1.2. Role of L-Carnitine in metabolism of Fat

L-carnitine helps the body turn *Fat into Energy*. L-carnitine in the presence of carnitine palmitoyl transferase (CPT-1 and CPT-2) enzymes, transfers long-chain fatty acids from the cytosol into the mitochondria for β-oxidation and TCA cycle (generation of energy) (Longo et al., 2016). To prevent accumulation of Acetyl-CoA derivatives in mitochondria it exports excess ones for Lipogenesis. Savic et al., 2020, suggested that a deficiency of L-carnitine causes incomplete fatty acid oxidation and accumulation of triglyceride in the Liver and adipose tissues, resulting in NAFLD, obesity, muscle weakness and cardiomyopathy.

1.3 Endogenous Synthesis of L-carnitine

L-carnitine is synthesized in the body from the two amino acids Lysine and Methionine where ascorbic acid, iron, vitamin B6 and niacin act as catalysts (Bremer et al., 1983). Due to adequate synthesis of Carnitine in the body under good health and growth conditions, the US Food

and Nutrition Board of the National Research Council declared it as a 'conditionally essential nutrient'.

However, the rate of synthesis declines with age, obesity and many chronic and metabolic diseases or prolonged use of steroids and antibiotics. If deficiency occurs then the person should take carnitine supplement or eat carnitine-rich foods. According to Li and Zhao (2021) total creatine stored in the body is 300 mg/kg (~20 g), 75 % of the daily carnitine requirement comes from meat, fish and dairy products and 25 % from endogenous synthesis. Therefore, one should consume >150 mg of carnitine from the food and get ~50mg from endogenous synthesis if the diet is rich in precursors of L-carnitine.

The objectives of this study are:

1) Evaluation of the studies in which carnitine was given to patients, in the form of supplement (drug or food sources) for therapeutic benefits.

2) To assess the clinical outcomes obtained after carnitine supplementation.

3)Possible adverse effects of L-carnitine drug-based supplements if taken for a longer duration.

Recent original randomized controlled clinical trials, and published various databases were analyzed and included in this review study. The following **Inclusion criteria** were applied: 1) only secondary carnitine deficient patients, 2) vivo clinical trials- a) animals, fed on high fat diet, b) human subjects, Obese with or without NAFLD, Type-2 Diabetes, CKD, CVD, fertility issues, 3) intervention-patients received carnitine drug or lysine drug or carnitine/lysine and methionine rich food items in the recommended doses, while the control group received placebo, 4) results- minimum two test results out of many (e.g. liver function test, lipid profile, BMI, CRP, etc.) to prove the efficacy of carnitine, 5) studies were not restricted in terms of geographical setting.

Exclusion criteria were: 1) primary carnitine deficiency patients, 2) studies with insufficient data and duplicate studies.

The studies were reviewed and assessed for their quality and biasness if any, by the two authors independently.

2. Results

Initially identified 180 studies from different databases on the topic then after the screening process, tabulated 17 relevant research studies.

Table-1: Recently published studies to date, evaluating the effects of L-carnitine in tablet form

S N	References	Year of Pub.	Type of Study	Sample Size, M/F	Duration (m/week)	Intervention Group (Dose in mg)	Disease (diagnosis)	Outcomes
1	Savic et al.	2020	Review Study RCT, placebo	30-80 patients	1-3 months	500 mg-3000 mg	NAFLD, DM-2, NASH	Significant reduction in Liver enzymes and insulin sensitivity
2	Hazzan et al.	2022	Randomized double blind	22 patients	4 months	2g L-carnitine+150mg magnesium tablet	NAFLD	Significant reduction in Liver enzymes
3	Abbasnezhad, et al.	2020	6 RCTs, Syst. Review	234 humans	> 2 months	2000mg/day carnitine	NAFLD, NASH, Hept C	Reduced Liver inflammation-CRP Reduced liver enzymes, TG, TC, LDL
4	Karalis et al.	2022	Randomized controlled trial	181 patients (M 84/F 97)	6 months	Med Diet + 2g/d Carnitine	Type-2 DM	Significant reduction in HbA1c, FBS, TG, tiredness, insomnia, mental activity
5	Nachvak et al.	2020	Randomized Placebo T	75 humans	3 months	75mg per day	CVD	significant reduction in (MPO), myeloperoxidase, nitrotyrosine, CRP levels
6	Chen et al.	2014	31 RCTs Syst. Review	1734 subjects	6 months	L-carnitine 2g/day	Dialysis	Reduced C-reactive Protein CRP, LDL cholesterol but not Triglyserides
7	Wang et al.	2021	10 RCTs	1239 humans	3-6 months	L-carnitine 2-3g/day	Obese + DM-2	Significant reduction in BMI of intervention group compare to control
8	Askarpour et al.	2020	16 RCTs Syst. Review	1025 subjects	3-6 months	L-carnitine 2g/day	NAFLD	Significant reduction in ALT, AST and GGT
9	Kalpana & Aruna	2012	Randomized Placebo Trial	600 subjects	1 month	1000 mg/day	Obese + Overweight	Reduction in body Fat and BMI was more in experimental group
10	Micic et al.	2019	Randomized double blind	175 Men (19-44 yrs)	6 months	1g L-carnitine, o.5g ALC in Proxeed plus tablet	Male fertility	beneficial effects of carnitine derivatives on progressive motility (10%)
11	Kitano et al.	2018	In Vivo st udy	214 Females	2 months, 22 days	IVF-ET+ L-carnitine 2g/d	Female Fertility	L- carnitine supplementation followed by IVF-ET healthy neonates were born
12	Samimi et al.	2018	R double blind placebo CT	60 females overweight	3 months	L-carnitine 250mg	PCOS	Significant reduction in weight, BMI, FBS, WC, HC, serum insulin level
13	Mielgo-Ayuso et al.	2021	11 RCTs	203 subjects 18-46 yrs	9 weeks to 6 months	3g L-carnitine ingested 60-90 min before exercise	Physical activity	Improved performance in high intensity exercises

Table-2: Carnitine supplementation in the form of Mediterranean diet

S N	References	Year of Pub.	Type of Study	Sample size M/F, Ani/Hum	Duration (months)	Intervention Group (Dose in mg)	Disease (diagnosis)	Outcomes
1	Gelli et al	2017	Randomized controlled trial	46 patients	6 months	Med Diet	NAFLD	Significant Reduction in ALT (67% to 11%), AST, GGT, BMI, weight, WC, W/H ratio
2	Khazaei et al.	2023	Case control Study	243 patients	6 months	Med Diet vs Green MED	NAFLD	Plant protein group showed better result than meat group
3	Ristic-medic et al	2020	RCT	24 Obese patients	3 months	Med Diet vs Low fat group	NAFLD	Significant weight loss, liver enzymes, insulin levels in Med group compare to Low-fat group
4	Tsaban et al.	2020	RCT	294 Obese patients	6 months	Med Diet vs Green Med	CVD	Significant reduction in weight, WC, LDL, BP.Increase in HDL
5	Li et al.	2023	Case Control study	400 case+ 400 controls, Humans	9 months	1700mg lysine,750mg threonine, 950mg valine from food	NAFLD	20% reduction of NAFLD risk in 65+ people
6	Chiarioni et al.	2021	Pilot study	26 patients	6 months	Vegan diet (15-1800 kcal)	NAFLD	BMI (26.8 to25.2), ALT (99 to36 U/L), AST(54to 27 U/L), GGT (160 to 55 U/L)
7	Haigh et al.,	2021	26 RCT	3037 patients	9-12month	MED diet (14-1600 kcal)	NASH	Reduction in AST,ALT, liver stiffness, NASH

(NASH=Non-alcoholic steatohepatitis, DM-2=Type-2 diabetes mellitus, AST=aspartate transaminase, CVD=cardiovascular disease, TG=triglyceride, ALT=alanine aminotransferase, CRP=C-reactive protein, MED=Mediterranean, IVF-ET=In vitro fertilization embryo transplant, WC=waist circumference, W/H=waist to hip ratio, FBS=fasting blood sugar, BMI=body mass index, BP=blood pressure), GGT=gamma glutamyl transferase, LDL=low density lipoprotein.

2.1. Therapeutic effect of Carnitine: Pharmacological supplementation

In Liver disease supplementation of L-carnitine might be a potential treatment for NAFLD as it promotes fat oxidation, removes excess acetyl-CoA and is beneficial on carbohydrate metabolism (Savic et al., 2020). A double-blinded, randomized controlled trial by Hazzan et al., 2022, testedthe efficacy of 2g L-carnitine in combination with 150mg magnesium, and was given for 2 months to 22 patients with NAFLD. Significant improvement was observed in AST and ALT levels (decreased by 25% and 20% respectively) in the intervention group compared to placebo. Another meta-analysis and systematic reviewby Askarpour et al., 2020, which included 16 RCTs (1025 participants) indicated that L-carnitine supplementation significantly decreased ALT, AST and GGT in NAFLD patients. L-carnitine can improve glucose metabolism, insulin resistanceand prevent diabetic complications such as fatigue, insomnia and mental activity.

In a study where 2g/day of L-carnitine tablet was given to 181 Greek Type-2 diabetic patients for 6-months along with a Mediterranean diet showed a statistically significant reduction in HbA1c (mean reduction 0.62), fasting sugar (mean reduction 17.5) and triglyceride (-31.39) (Karalis et al., 2020). Carnitine is found to be cardioprotective because it reduces oxidative stress and inflammatory damage. A double-blind placebo-controlled study conducted on 75 patients of coronary artery disease (CAD)supplemented with 1000 mg/day of carnitine, showed a significant reduction in myeloperoxidase and CRP levels (1.18 to 0.51mg/dl) after 3 months (Nachvak et al 2023). Patients of end-stage renal disease (ESRD) undergoing hemodialysis, suffer from L-carnitine deficiency firstly because of impaired synthesis by the kidneys, and secondly its loss into the dialysate. Therefore, the US Food and Drug Administration (FDA) approved the use of a specific intravenous formulation of L-carnitine (10-20 mg/kg body weight) in CKD and dialysis patients. In a meta-analysis of 31 randomized controlled trials, 1734 patients having ESRD treated with L- carnitine (oral or intravenously) found significant reductionsin CRP and LDL cholesterol (Chenetal., 2014).

As L-carnitine converts fat into energy, it is very popular among bodybuilders and athletes as a weight loss supplement. A review study of 10 RCTs including 1239 type-2 diabetic patients, reported that 2-3 g/day of L-carnitine was required for at least 12 weeks to reduce body mass index significantly (Wang et al., 2021). A comparative study by Kalpana and Aruna (2012), concluded that L-carnitine (1g/day) with a carnitine-rich diet and exercise helped obese adults in the intervention group to lose weight significantly compared to the placebo group.

At present in India, carnitine supplements are prescribed by medical practitioners to treat only fertility issues. L-carnitine is concentrated in the male reproductive organ, testis and epididymis. One placebo-controlled, double-blind trial on 175 men (19-44 years) with fertility issues, found that Proxeed Plus (supplementation with L-carnitine), improved sperm quality after 3 months (Micic et al., 2019). L-carnitine has immense capability to regulate the oxidative and metabolic status of female reproductive systems too. 214 patients failed to conceive even after receiving multiple in vitro fertilization-embryo transfers (IVF-ET) but after administration of carnitine for 82 days followed by IVF-ET, the quality of embryos was improved between day 3 and 5 (after insemination) and healthy neonates were born (Kitano et al., 2018). A study by Samimi et al. (2016) showed that 12 weeks of carnitine administration in polycystic ovarian syndrome (PCOS) women resulted in significant reductions in weight, BMI, waist and hip circumferences and fasting blood glucose compared with placebo; however, it did not affect lipid profile. A systematic review by Mielgo-Ayuso et al. (2021), found that 3-4 g of L-carnitine 60 or 90 min before exercise improves the lactate threshold and has positive effects on high-intensity exercise performance, muscle injury and recovery. Recently it has become popular as an ergogenicaid among athletes and bodybuilders in India too. Compared to other fitness supplements (BCAA and CLA), it encourages the body to produce energy from the fat.

2.2. Therapeutic effects of Carnitine: Supplementation in the form of Natural foods

As per the previous research, absorption of carnitine from oral medicine is only 5–25% while from food it is approx. 54–86% (Virmani et al., 2022). Therefore supplementation of L-carnitine through Food sources could be more effective in lowering liver enzymes and insulin levels. Research by Gelli et al., 2017 evaluated the effect of the Mediterranean Diet given to 46 obese and diabetic patients. After 6 months, Fatty liver grade >2 reduced from 93% to 48%, and mean AST, GGT, ALT decreased significantly and body weight reduced by 7%.

According to Kalpana and Aruna, 2012, 75% of L-carnitine can be obtained from the diet and 25% from the de-novosynthesis. The kidneys reabsorb carnitine through active transport when the dietary intake of carnitine decreases. L-carnitine is found in higher concentrations in animal products such as Red meat, beef (143 mg/100 g), pork, lamb (190 mg/100 g), chicken (13 mg/100 g), fish, eggs and milk. Some of these animal sources of L-carnitine are high in *Saturated Fat*. Dietary carnitine through red meat may accelerate atherosclerosis via gut microbiota metabolites (Johri et al., 2014). Such fatty foods might again increase carnitine depletion due to overconsumption.Therefore 'Mediterranean Diet' based on lean meat, lamb, fish, low-fat milk, nuts & fruits, is found to be effective. A case-control study by Khazaei et al., 2023, found a significant reduction in liver enzymes of the case group NAFLD subjects, after consuming a Green Mediterranean diet, more plant proteins (soy, nuts, vegetables and grains) and less animal protein. A community-based case-control study in China by Li et al., 2020, reported that higher intakes of lysine (1700 mg/day), threonine (750 mg/day) and valine (950 mg/day) through milk, eggs and deep-sea fish, in the case group (400 NAFLD obese), resulted in 20% reduction in liver enzymes compared to 400 healthy controls after 9months. Another pilot study on 26 NAFLD patients aged ±50 years, were treated with Vegan diet for 6 months reported a significant loss in liver enzymes (mean ALT-36 u/l, SD±21), mean AST 27 u/l SD±10) with ≥ 5% weight loss (Chiarioni et al, 2021) Since obesity is a known risk factor for NAFLD and NASH, Ristic-Medic et al. 2020, observed that >9% weight reduction helped in decreased levels of total cholesterol, triglycerides, glucose, hs-CRP and liver enzymes in patients who had Mediterranean diet, rich in lean meats, omega 3 and 6 fatty acids. Thegreen Mediterranean group had green tea, walnuts, less of poultry, and showed maximum decrease in waist circumference (−8.6 cm) than Healthy Diet Guidance (−4.3 cm) and the Mediterranean groups (−6.8 cm)after 6 months. Reduction in LDL, CRP and blood pressure was also maximum inthe green MED group (Tsaban et al., 2021). 26 studies (3037 participants) including calorie- restricted interventions and a Mediterranean diet reduced ALT, AST, hepatic steatosis and liver stiffness. If body weight is reduced by∼5% in NAFLD and ≥7% in NASH then it is beneficial withmoderate physical activity (Haigh et al., 2022).

Non-vegetarians can easily get >2000 mg of carnitine/day, while vegetarians get <100 mg from their regular diet. Vegetarians can include low-fat animal milk and milk products in their daily diet while vegans can consume soya milk, almond milk, or coconut milk. The bioavailability of carnitine is higher in vegetarians than in people who eat meat (Alhasaniah et al., 2023). For vegetarians, a significant portion of L-carnitine comes from endogenous synthesis. Therefore, their daily diet should be adequate in foods rich in lysine and methionine, iron, ascorbate, niacin and pyridoxine. A diet based on nuts, amaranth seeds, sesame seeds, green gram, moringa, pulses, whole grains, soybean, fruits, green tea, and tempeh with mushrooms, is found to be effective in the treatment of various diseases.

3. Conclusion

In conclusion, this review paper has tried to update the therapeutic and nutritional health benefits of L-carnitine in the treatment of various diseases in patients. But prolonged or higher doses (>4 g/day) of carnitine in pill or liquid form, is atherogenic and leads to heart failure in men (Zhao et al., 2022). Higher doses may also cause nausea, vomiting, abdominal cramps, diarrhea, muscle weakness, seizures, and cardiovascular disease. As natural foods provide a variety of macro and micronutrients

nutritional needs should be met primarily through them or fortified foods. Therefore, we make the argument for the need for a safe and cost-effective L-carnitine-rich natural food-based supplement, good for long-term use, which could replace the available expensive L-carnitine drug.

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