A little history: this is the report that first made me start thinking about carnitine.


Relative carnitine insufficiency in children with type I diabetes mellitus.
Winter SC, Simon M, Zorn EM.
Department of Pediatrics, University of California, San Francisco.
Recognizing the similarity of type I diabetes mellitus to inborn errors of metabolism that have responded to carnitine therapy, we initiated a study of 54 children with type I diabetes mellitus. Examining a fasting blood sample for levels of carnitine, glucose, and glycosylated hemoglobin A1c, and a urine sample for levels of ketones and glucose, we found 13 children were deficient of free carnitine (less than 20 mumol/L) and 30 had elevated acyl carnitine levels (greater than 11 mumol/L). Statistical tests confirmed a significant difference between the diabetic population and normal population for reduced free carnitine, elevated acyl carnitine, and an elevated ratio of acyl carnitine to free carnitine. Also, a significant correlation was found between the levels of urine glucose and ketones and the level of acyl carnitine. Our data indicate that carnitine deficiency and relative insufficiency may be an overlooked component in the management of diabetes.

Flanagan JL, Simmons PA, Vehige J.
ABSTRACT: Carnitine is a conditionally essential nutrient that plays a vital role in energy production and fatty acid metabolism. Vegetarians possess a greater bioavailability than meat eaters. Distinct deficiencies arise either from genetic mutation of carnitine transporters or in association with other disorders such as liver or kidney disease. Carnitine deficiency occurs in aberrations of carnitine regulation in disorders such as diabetes, sepsis, cardiomyopathy, malnutrition, cirrhosis, endocrine disorders and with aging. Nutritional supplementation of L-carnitine, the biologically active form of carnitine, is ameliorative for uremic patients, and can improve nerve conduction, neuropathic pain and immune function in diabetes patients while it is life-saving for patients suffering primary carnitine deficiency. Clinical application of carnitine holds much promise in a range of neural disorders such as Alzheimer's disease, hepatic encephalopathy and other painful neuropathies. Topical application in dry eye offers osmoprotection and modulates immune and inflammatory responses. Carnitine has been recognized as a nutritional supplement in cardiovascular disease and there is increasing evidence that carnitine supplementation may be beneficial in treating obesity, improving glucose intolerance and total energy expenditure.
Inspiratory muscle strength is correlated with carnitine levels in type 2 diabetes. Kilici F, Dökmetas S, Candan F.

INTRODUCTION: Plasma carnitine insufficiency has been known to cause muscle weakness. 

Carnitine levels and pulmonary functions were lower in patients with diabetes. PATIENTS AND METHODS: To determine whether pulmonary functions are correlated with carnitine levels in patients with type 2 diabetes. In this study, we evaluated pulmonary functions and carnitine concentrations in 49 patients with type 2 diabetes and 34 healthy controls. RESULTS: Carnitine levels were lower in type 2 diabetes group than control group (52.56 +/- 12.38 and 78.96 +/- 10.66 hmol/mL, respectively, p < 0.0001). Pulmonary functions were not significantly different between groups. Carnitine levels were not correlated with age, duration of diabetes, fasting blood glucose levels, and glycemic control (HbA1c%) in patients with type 2 diabetes. However, carnitine levels in patient group were correlated with % forced vital capacity (FVC%) (r = 0.35, p = 0.016), % forced expiratory volume in 1 s (FEV1%) (r = 0.318, p= 0.029), FEV1/FVC (r= 0.302, p= 0.039), inspiratory muscle strength (Pimax) (r = 0.407, p = 0.023), and PImax% (r = 0.423, p= 0.018). CONCLUSION: This study suggests that low carnitine levels may be associated with lower PImax and PImax% in type 2 diabetes.


Carnitine and type 2 diabetes. Mynatt RL.

Studies in humans and animals demonstrate that "lipid over supply" causes or worsens insulin resistance via multiple mechanisms involving the accumulation of intracellular lipids in multiple tissues. In particular, the accumulation of fatty acyl CoA derivatives/metabolites in muscle inhibits both insulin signaling and glucose oxidation. Therefore agents that ameliorate the accumulation of fatty acyl CoA derivatives and/or their metabolites would be beneficial in the treatment or prevention of insulin resistance and T2D.

Hyperinsulemic/euglycemic clamp studies in Humans and Carnitine Supplementation studies in rodents provide "proof-of-concept" that carnitine is effective at improving insulin-stimulated glucose utilization and in reversing abnormalities of fuel metabolism associated with T2D. Carefully controlled clinical trials are warranted to determine the efficacy dietary carnitine supplementation as an adjunctive treatment for type 2 diabetes.


Effect of Carnitine and herbal mixture extract on obesity induced by high fat diet in rats. Amin KA, Nagy MA.

ABSTRACT: BACKGROUND: Obesity-associated type 2 diabetes is rapidly increasing throughout the world. It is generally recognized that natural products with a long history of safety can modulate obesity. AIM: To investigate the development of obesity in response to a high fat diet (HFD) and to estimate the effect of L-carnitine and an Egyptian Herbal mixture formulation (HMF) (consisting of T. chebula, Senae, rhubarb, black cumin, aniseed, fennel and licorice) on bodyweight, food intake, lipid profiles, renal, hepatic, cardiac function markers, lipid Peroxidation, and the glucose and insulin levels in blood and liver tissue in rats. METHOD: White male albino rats weighing 80-90 gm, 60 days old. 10 rats were fed a normal basal diet (Cr), 30 rats fed a high-fat diet (HFD) for 14 weeks during the entire study. Rats of the HFD group were equally divided into 3 subgroups each one include 10 rats. The first group received HFD with no supplement (HFD), the 2nd group HFD+L-carnitine and the third group received HFD+HMF. Carnitine and HMF were administered at 10th week (start time for treatments) for 4 weeks. RESULTS: Data showed that feeding HFD diet significantly increased final body weight, triglycerides (TG), total cholesterol, & LDL concentration compared with controls, while significantly decreasing HDL; meanwhile treatment with L-carnitine, or HMF significantly lessened the effect of the HFD. Hyperglycemia,
hyperinsulinemia, and high insulin resistance (IR) significantly increased in HFD in comparison with the control group. The treatment with L-carnitine or HMF improved the condition. HFD elevated hepatic MDA and lipid peroxidation associated with reduction in hepatic GSH and catalase activity; whereas administration of L-carnitine or herbal extract significantly ameliorated these hepatic alterations. CONCLUSION: HFD induced obesity associated with a disturbed lipid profile, defective antioxidant stability, and high values of IR parameters; this may have implications for the progress of obesity related problems. Treatment with L-carnitine, or HMF extract improved obesity and its associated metabolic problems in different degrees. Also HMF has antioxidant, hypolipidaemic insulin sensitizing effects. Moreover HMF might be a safe combination on the organs whose functions were examined, as a way to surmount the obesity state; and it has a distinct anti-obesity effect.

Carnitine insufficiency caused by aging and overnutrition compromises mitochondrial performance and metabolic control. Noland RC, Koves TR, Seiler SE. In addition to its essential role in permitting mitochondrial import and oxidation of long chain fatty acids, carnitine also functions as an acyl group acceptor that facilitates mitochondrial export of excess carbons in the form of acylcarnitines. Recent evidence suggests carnitine requirements increase under conditions of sustained metabolic stress. Accordingly, we hypothesized that carnitine insufficiency might contribute to mitochondrial dysfunction and obesity-related impairments in glucose tolerance. Consistent with this prediction whole body carnitine diminution was identified as a common feature of insulin-resistant states such as advanced age, genetic diabetes, and diet-induced obesity. In rodents fed a lifelong (12 month) high fat diet, compromised carnitine status corresponded with increased skeletal muscle accumulation of acylcarnitine esters and diminished hepatic expression of carnitine biosynthetic genes. Diminished carnitine reserves in muscle of obese rats was accompanied by marked perturbations in mitochondrial fuel metabolism, including low rates of complete fatty acid oxidation, elevated incomplete beta-oxidation, and impaired substrate switching from fatty acid to pyruvate. These mitochondrial abnormalities were reversed by 8 weeks of oral carnitine supplementation, in concert with increased tissue efflux and urinary excretion of acetylcarnitine and improvement of whole body glucose tolerance. Acetylcarnitine is produced by the mitochondrial matrix enzyme, carnitine acetyltransferase (CrAT). A role for this enzyme in combating glucose intolerance was further supported by the finding that CrAT overexpression in primary human skeletal myocytes increased glucose uptake and attenuated lipid-induced suppression of glucose oxidation. These results implicate carnitine insufficiency and reduced CrAT activity as reversible components of the metabolic syndrome.

Overexpression of carnitine palmitoyltransferase-1 in skeletal muscle is sufficient to enhance fatty acid oxidation and improve high-fat diet-induced insulin resistance. Bruce CR, Hoy AJ, Turner N. OBJECTIVE: Skeletal muscle insulin resistance is associated with lipid accumulation, but whether insulin resistance is due to reduced or enhanced flux of long-chain fatty acids into the mitochondria is both controversial and unclear. We hypothesized that skeletal muscle-specific overexpression of the muscle isoform of carnitine palmitoyltransferase 1 (CPT1), the enzyme that controls the entry of long-chain fatty acyl CoA into mitochondria, would enhance rates of fatty acid oxidation and improve insulin action in muscle in high-fat diet insulin-resistant rats. RESEARCH DESIGN AND METHODS: Rats were fed a standard (chow) or high-fat diet for 4 weeks. After 3 weeks, in vivo electrotransfer was used to overexpress the muscle isoform of CPT1 in the distal hindlimb muscles (tibialis anterior and extensor digitorum longus [EDL]). Skeletal muscle insulin action was examined in vivo during a hyperinsulinemic-euglycemic clamp. RESULTS: In vivo electrotransfer produced a physiologically relevant increase of approximately 20% in enzyme activity; and although the high-fat diet produced insulin resistance in the sham-treated muscle, insulin action was improved in the CPT1-overexpressing muscle. This improvement was associated with a reduction in triacylglycerol content, the membrane-to-cytosolic ratio of diacylglycerol, and protein kinase C
theta activity. Importantly, overexpression of CPT1 did not affect markers of mitochondrial capacity or function, nor did it alter skeletal muscle acylcarnitine profiles irrespective of diet. **CONCLUSIONS:** Our data provide clear evidence that a physiological increase in the capacity of long-chain fatty acyl CoA entry into mitochondria is sufficient to ameliorate lipid-induced insulin resistance in muscle.


**Effect of propionyl-L-carnitine, L-arginine and nicotinic acid on the efficacy of vardenafil in the treatment of erectile dysfunction in diabetes.**

**OBJECTIVE:** The association of diabetes-related vascular damage and the role of metabolic factors in erectile dysfunction are well known in the literature. The compounds propionyl-L-carnitine (PLC), L-arginine (L-Arg) and nicotinic acid have numerous metabolic actions which have been reported to improve endothelial function. This study investigated the administration of the combination of these three compounds alone and in association with an inhibitor of 5-phosphodiesterase (5PDE), vardenafil, on endothelial function in diabetic patients with erectile dysfunction. **METHODS:** A total of 40 patients aged between 50 and 60 years with insulin-dependent diabetes (IDDM) for 3-4 years were selected from 509 patients presenting with erectile dysfunction. The patients were randomly subdivided into four groups of ten to be treated for 12 weeks. Group A was administered one sachet each day of test formulation containing PLC, L-Arg and nicotinic acid (Ezerex); group B with one 20 mg capsule of vardenafil (Levitra) twice a week; group C was treated with one sachet each day of the test formulation plus vardenafil 20 mg twice a week. Group D was administered placebo capsules twice weekly. Endothelial function was evaluated by examining flow-mediated dilation (FMD) and erectile function was estimated with the International Index of Erectile Function (IIEF5) questionnaire in all subjects. **RESULTS:** At the end of treatment group A showed an increment of 2 points in the IIEF5; group B showed an increment of 4 points; group C, the group which was administered all the treatments, showed an increment of 5 points, and group D, treated with placebo, showed no increment in the IIEF5. **CONCLUSION:** Although there was a small number of subjects in this study the data suggest that the test formulation may improve the endothelial situation in diabetes. The test formulation together with vardenafil was better than the 5PDE inhibitor alone, but further studies are needed to confirm these findings.


**Ameliorating hypertension and insulin resistance in subjects at increased cardiovascular risk: effects of acetyl-L-carnitine therapy.**

**Ruggenenti P, Cattaneo D, Loriga G.**

Insulin resistance, a key component of the metabolic syndrome, is a risk factor for diabetes mellitus and cardiovascular disease. Acetyl-L-carnitine infusion acutely ameliorated insulin sensitivity in type 2 diabetics with insulin resistance. In this sequential off-on-off pilot study, we prospectively evaluated the effects of 24-week oral acetyl-L-carnitine (1 g twice daily) therapy on the glucose disposal rate (GDR), assessed by hyperinsulinemic euglycemic clamps, and components of the metabolic syndrome in nondiabetic subjects at increased cardiovascular risk a priori segregated into 2 groups with GDR < or =7.9 (n=16) or >7.9 (n=16) mg/kg per minute, respectively. Baseline GDR and systolic blood pressure were negatively correlated (n=32; P=0.001; r=-0.545), and patients with GDR < or =7.9 mg/kg per minute had higher systolic/diastolic blood pressure than those with higher GDR. Acetyl-L-carnitine increased GDR from 4.89+/−1.47 to 6.72+/−3.12 mg/kg per minute (P=0.003, Bonferroni-adjusted) and improved glucose tolerance in patients with GDR < or =7.9 mg/kg per minute, whereas it had no effects in those with higher GDRs. Changes in GDR were significantly different between groups (P=0.017, ANCOVA). Systolic blood pressure decreased from 144.0+/−13.6 to 135.1+/−8.4 mm Hg and from 130.8+/−12.4 to 123.8+/−10.8 mm Hg in the lower and higher GDR groups, respectively (P<0.05 for both; P<0.001 overall) and progressively recovered toward baseline over 8 weeks posttreatment. Total and high molecular weight adiponectin levels followed specular trends. Diastolic blood pressure significantly decreased only in those with higher GDRs. Treatment was well
tolerated in all of the patients. **Acetyl-L-carnitine safely ameliorated arterial hypertension, insulin resistance, impaired glucose tolerance, and hypoadiponectinemia in subjects at increased cardiovascular risk. Whether these effects may translate into long-term cardioprotection is worth investigating.**

**Expert Opin Pharmacother.** 2009 Aug;10(12):1875-82.

**Effects of simvastatin and carnitine versus simvastatin on lipoprotein(a) and apoprotein(a) in type 2 diabetes mellitus.**

Galvano F, Li Volti G, Malaguarnera M.

AIM: The aim of the present study was to compare the effects of simvastatin and L-carnitine coadministration versus simvastatin monotherapy on lipid profile, lipoprotein(a) (Lp(a)) and apoprotein(a) (Apo(a)) levels in type II diabetic patients. PATIENTS/METHODS: In this double-blind, randomized clinical trial, 75 patients were assigned to one of two treatment groups for 4 months. Group A received simvastatin monotherapy; group B received L-carnitine and simvastatin. The following variables were assessed at baseline, after washout and at 1, 2, 3 and 4 months of treatment: body mass index, fasting plasma glucose, glycated hemoglobin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, Apolipoprotein A1, Apo B, lipoprotein(a) and apoprotein(a).

RESULTS: At the end of treatment in the carnitine and simvastatin combined group compared with the simvastatin alone group, we observed a significant decrease in glycemia (p < 0.001), triglycerides (p < 0.001), Apo B (p < 0.05), Lp(a) (p < 0.05), apo(a) (p < 0.05), while HDL significantly increased (p < 0.05).

CONCLUSIONS: The coadministration of carnitine and simvastatin resulted in a significant reduction in Lp(a) and apo(a) and may represent a new therapeutic option in reducing plasma Lp(a) levels, LDL cholesterol and Apo B100.

**Metabolism.** 2009 Nov;58(11):1618-23.

**Effect of L-carnitine on the size of low-density lipoprotein particles in type 2 diabetes mellitus patients treated with simvastatin.**

Malaguarnera M, Vacante M, Motta M.

Therapeutic modulation of low-density lipoprotein (LDL) size could be of benefit in reducing the risk of cardiovascular events in diabetic patients. This study evaluated the efficacy of L-carnitine on the size of LDL particles in type 2 diabetes mellitus patients treated with simvastatin. Eighty diabetic patients were randomly assigned to 1 of 2 treatment groups for 3 months. The 2 groups received either simvastatin monotherapy 20 mg (n = 40) or L-carnitine 2 g/d and simvastatin 20 mg (n = 40). The following variables were assessed at baseline; after washout; and at 1, 2, and 3 months of treatment: body mass index, fasting plasma glucose, glycated hemoglobin, total cholesterol, LDL cholesterol, LDL subclasses, LDL size, high-density lipoprotein cholesterol, triglycerides, apolipoprotein A-1, and apolipoprotein B-100. After 12 weeks, comparing the 2 groups, we observed a decrease in fasting plasma glucose (1.45 vs 0.61 mmol/L, P < .001) and an increase in glycosylated hemoglobin (0.2% vs 0.4%, P < .05). Moreover, there was a decrease in total cholesterol (2.07 vs 1.45 mmol/L, P < .001), LDL (1.65 vs 1.29 mmol/L, P < .001), triglycerides (1.36 vs 0.41 mmol/L, P < .001), apo B-100 (49 vs 9 g/L, P < .001), and small-sized LDL proportion (10.8% vs 4.9%, P < .001), whereas LDL particle size increased (6 vs 3 A, P < .001) and HDL increased (0.2 vs 0.11 mmol/L, P < .001). **We observed that patients treated with carnitine and simvastatin showed a reduction in small-sized LDL proportion and an increase in LDL particle size.**


**L-Carnitine supplementation reduces oxidized LDL cholesterol in patients with diabetes.** Malaguarnera M, Vacante M, Avitabile T.

BACKGROUND: Patients with type 2 diabetes are under high oxidative stress, and levels of hyperglycemia correlate strongly with levels of LDL oxidation. Carnitine favorably modulates oxidative stress. OBJECTIVE: This objective of this study was to evaluate the efficacy of L-carnitine on the reduction of oxidized LDL cholesterol in patients
with type 2 diabetes. DESIGN: Eighty-one patients with diabetes were randomly assigned to 1 of 2 treatment groups for 3 mo. The 2 groups received either 2 g L-carnitine once daily (n = 41) or placebo (n = 40). The following variables were assessed at baseline, after washout, and at 1, 2, and 3 mo of treatment: body mass index, fasting plasma glucose, glycosylated hemoglobin, total cholesterol, LDL cholesterol, triglycerides, apolipoprotein A1, apolipoprotein B-100, oxidized LDL cholesterol, thiobarbituric acid-reactive substances, and conjugated dienes. RESULTS: At the end of the study period, the L-carnitine-treated patients showed significant improvements compared with the placebo group in the following markers: oxidized LDL levels decreased by 15.1 compared with 3.0 U/L (P < 0.001); LDL cholesterol decreased by 0.45 compared with 0.16 mmol/L (P < 0.05); triglycerides decreased by 1.02 compared with 0.09 mmol/L (P < 0.001); apolipoprotein A1 concentrations decreased by 0.12 compared with 0.03 mg/dL (P < 0.05); apolipoprotein B-100 concentrations decreased by 0.13 compared with 0.04 mg/dL (P < 0.05); thiobarbituric acid-reactive substance concentrations decreased by 1.92 compared with 0.05 (P < 0.001), and conjugated diene concentrations decreased by 0.72 compared with 0.11 in the placebo group (P < 0.001).

CONCLUSION: Our study indicates that oral administration of L-carnitine reduces oxidized LDL cholesterol levels in patients with type 2 diabetes.


Effect of oral acetyl L-carnitine arginate on resting and postprandial blood biomarkers in pre-diabetics. Bloomer RJ, Fisher-Wellman KH, Tucker PS. ABSTRACT:

BACKGROUND: Resting and postprandial oxidative stress is elevated in those with metabolic disorders such as diabetes. Antioxidant supplementation may attenuate the rise in oxidative stress following feeding. Therefore we sought to determine the effects of acetyl L-carnitine arginate (ALCA) on resting and postprandial biomarkers of glucose and lipid metabolism, as well as oxidative stress. METHODS: Twenty-nine pre-diabetic men and women were randomly assigned to either 3 g.day-1 of ALCA (n = 14; 31 +/- 3 yrs) or placebo (n = 15; 35 +/- 3 yrs) in a double-blind design, to consume for eight weeks. Fasting blood samples were taken from subjects both pre and post intervention. After each fasting sample was obtained, subjects consumed a high fat, high carbohydrate meal and additional blood samples were taken at 1, 2, 4, and 6 hours post meal. Samples were analyzed for a variety of metabolic variables (e.g., glucose, HbA1c, lipid panel, C-reactive protein, nitrate/nitrite, and several markers of oxidative stress). Area under the curve (AUC) was calculated for each variable measured post meal, both pre and post intervention. RESULTS: ALCA, but not placebo, resulted in an increase in nitrate/nitrite (25.4 +/- 1.9 to 30.1 +/- 2.8 mumol.L-1) from pre to post intervention, with post intervention values greater compared to placebo (p = 0.01). No other changes of statistical significance were noted (p > 0.05), although ALCA resulted in slight improvements in glucose (109 +/- 5 to 103 +/- 5 mg.dL-1), HbA1c (6.6 +/- 1.1 to 6.2 +/- 1.2%), and HOMA-IR (3.3 +/- 1.3 to 2.9 +/- 1.2). AUC postprandial data were not statistically different between ALCA and placebo for any variable (p > 0.05). However, nitrate/nitrite demonstrated a moderate effect size (r = 0.35) for increase from pre (139.50 +/- 18.35 mumol.L-1.6 hr-1) to post (172.40 +/- 21.75 mumol.L-1.6 hr-1) intervention with ALCA, and the magnitude of decrease following feeding was not as pronounced as with placebo.

CONCLUSION: Supplementation with ALCA results in an increase in resting nitrate/nitrite in pre-diabetics, without any statistically significant change in other metabolic or oxidative stress variables measured at rest or post meal.


Effect of short term treatment of L-carnitine on tissue ACE activity in streptozotocin-induced diabetic rats. Sharifi AM, Zare B, Keshavarz M. Diabetes is commonly related to the both microvascular as well as macrovascular complications. It appears that both metabolic and hemodynamic factors interact to create these problems. In this study the effects of orally administered L-carnitine, a natural amino acid, on ACE activity in streptozotocin (STZ)-induced diabetic rats were investigated. Streptozotocin (60mg/kg body weight) was given intraperitoneally. Fifty male Sprague-Dawley rats were divided into four groups: untreated normal (C), L-carnitine treated normal (CT), untreated diabetics (D), L-carnitine-treated diabetics (DT). CT and DT received daily L-carnitine 1g/kg orally for 3 weeks after inducing diabetes. The ACE activities in aorta, heart
and kidney homogenates was measured at the end of 3 weeks. They were significantly increased in D compared to C group (P<0.05) and significantly decreased in aorta, heart and kidney in DT compared to D group. In conclusion, L-carnitine can reduce tissue ACE activity in aorta, heart and kidney in streptozotocin diabetic rats, which may be due to higher NO production.


Plasma acylcarnitine profiles suggest incomplete long-chain fatty acid beta-oxidation and altered tricarboxylic acid cycle activity in type 2 diabetic African-American women. Adams SH, Hoppel CL, Lok KH. Inefficient muscle long-chain fatty acid (LCFA) combustion is associated with insulin resistance, but molecular links between mitochondrial fat catabolism and insulin action remain controversial. We hypothesized that plasma acylcarnitine profiling would identify distinct metabolite patterns reflective of muscle fat catabolism when comparing individuals bearing a missense G304A uncoupling protein 3 (UCP3 g/a) polymorphism to controls, because UCP3 is predominantly expressed in skeletal muscle and g/a individuals have reduced whole-body fat oxidation. MS analyses of 42 carnitine moieties in plasma samples from fasting type 2 diabetics (n = 44) and nondiabetics (n = 12) with or without the UCP3 g/a polymorphism (n = 28/genotype: 22 diabetic, 6 nondiabetic/genotype) were conducted. Contrary to our hypothesis, genotype had a negligible impact on plasma metabolite patterns. However, a comparison of nondiabetics vs. type 2 diabetics revealed a striking increase in the concentrations of fatty acylcarnitines reflective of incomplete LCFA beta-oxidation in the latter (i.e. summed C10- to C14-carnitine concentrations were approximately 300% of controls; P = 0.004). Across all volunteers (n = 56), acetylcaritnine rose and propionylcarnitine decreased with increasing hemoglobin A1c (r = 0.544, P < 0.0001; and r = -0.308, P < 0.05, respectively) and with increasing total plasma acylcarnitine concentration. In proof-of-concept studies, we made the novel observation that C12-C14 acylcarnitines significantly stimulated nuclear factor kappa-B activity (up to 200% of controls) in RAW264.7 cells. These results are consistent with the working hypothesis that inefficient tissue LCFA beta-oxidation, due in part to a relatively low tricarboxylic acid cycle capacity, increases tissue accumulation of acetyl-CoA and generates chain-shortened acylcarnitine molecules that activate proinflammatory pathways implicated in insulin resistance.


Carnitine and type 2 diabetes. Mynatt RL. Studies in humans and animals demonstrate that "lipid over supply" causes or worsens insulin resistance via multiple mechanisms involving the accumulation of intracellular lipids in multiple tissues. In particular, the accumulation of fatty acyl CoA derivatives/metabolites in muscle inhibits both insulin signaling and glucose oxidation. Therefore agents that ameliorate the accumulation of fatty acyl CoA derivatives and/or their metabolites would be beneficial in the treatment or prevention of insulin resistance and T2D. Hyperinsulemic/euglycemic clamp studies in humans and carnitine supplementation studies in rodents provide "proof-of-concept" that carnitine is effective at improving insulin-stimulated glucose utilization and in reversing abnormalities of fuel metabolism associated with T2D. Carefully controlled clinical trials are warranted to determine the efficacy dietary carnitine supplementation as an adjunctive treatment for type 2 diabetes.


Effects of L-carnitine on obesity, diabetes, and as an ergogenic aid. Cha YS. Data on the functionalities of L-carnitine on obesity, diabetes, and as an ergogenic aid are summarized as follows: Obesity: Total lipid, triglyceride, and total protein increased during the 3T3-L1 cell differentiation. However, nonesterified carnitine (NEC), acid-soluble acylcarnitine (ASAC), and acid-insoluble acylcarnitine (AIAC) concentrations were lower in the differentiated 3T3-L1 cells. In addition, the exogenously added carnitine inhibited the increases in triglyceride and total lipid levels. In an animal study, L-carnitine supplementation reduced serum leptin and abdominal fat weight caused by high-fat diet in C57BL/6J mice. Diabetes: In an animal study, streptozotocin-induced diabetic rats had markedly lower
IGFBP-3 than normal rats, and IGFBP-3 was increased by L-carnitine treatment, demonstrating that L-carnitine treatment of diabetic rats modulates the IGFs/IGFBPs axis. A study of Korean diabetics indicated that there is a remarkable abnormality in lipid and carnitine metabolism in Korean diabetic patients. Ergogenic aids: We investigated the separate and combined effects of L-carnitine and antioxidant supplementation on carnitine and lipid concentrations in trained and non-trained animal and humans. 

**Supplementation of L-carnitine and antioxidants improve lipid profiles and exercise ability in exercise-trained rats.** Also, both exercise training and supplementation of carnitine and antioxidants improved lipid profiles and carnitine metabolism in humans, suggesting that carnitine and antioxidant supplementation may improve exercise performance.


**Role of acetyl-L-carnitine in the treatment of diabetic peripheral neuropathy.** Evans JD, Jacobs TF, Evans EW. **OBJECTIVE**: To examine the role of acetyl-L-carnitine (ALC) in the treatment of diabetic peripheral neuropathy (DPN). **DATA SOURCES**: A MEDLINE search (1966-April 2008) of the English-language literature was performed using the search terms carnitine, diabetes, nerve, and neuropathy. Studies identified were then cross-referenced for their citations. **STUDY SELECTION AND DATA EXTRACTION**: The search was limited to clinical trials, meta-analyses, and reviews addressing the use of ALC for the treatment of DPN. Studies that included other disease states that could cause peripheral neuropathy were excluded. Two large clinical studies that used ALC for the treatment of DPN were identified. No case studies were identified. **DATA SYNTHESIS**: The results from 2 published clinical trials involving 1679 subjects were included. Subjects who received at least 2 g daily of ALC showed decreases in pain scores. One study showed improvements in electrophysiologic factors such as nerve conduction velocities, while the other did not. Patients who had neuropathic pain reported reductions in pain using a visual analog scale. Nerve regeneration was documented in one trial. The supplement was well tolerated. A proprietary form of ALC was used in both studies. **CONCLUSIONS**: Data on treatment of DPN with ALC support its use. It should be recommended to patients early in the disease process to provide maximal benefit. Further studies should be conducted to determine the effectiveness of ALC in the treatment and prevention of the worsening symptoms of DPN.


**Thioctic acid and acetyl-L-carnitine in the treatment of sciatic pain caused by a herniated disc: a randomized, double-blind, comparative study.** Memeo A, Loiero M. **BACKGROUND AND OBJECTIVE**: Sciatica is a painful condition characterized by radiating leg pain that most commonly originates from a herniated disc in the lumbar or sacral spine. Although sciatic pain is typically self-limiting, pharmacological analgesic therapy forms the mainstay of treatment. Acetyl-L-carnitine (levacecarnine; ALC) is a naturally occurring substance that promotes peripheral nerve regeneration and has been shown to have analgesic effects in patients with peripheral neuropathies of diabetic, HIV-related or chemotherapeutic origin. Thioctic acid, a key compound in oxidative metabolism, has antioxidant properties that may help the recovery of nerve functionality and decrease neuropathic pain. This study aimed to compare, for the first time, the efficacy of oral treatment with ALC or thioctic acid in patients with peripheral neuropathic (sciatic) pain associated with a herniated disc. **METHODS**: This was a randomized, double-blind trial conducted in a hospital setting. A total of 64 consecutive patients (mean age 61 years; range 29-85) with acute backache and moderate sciatica were recruited. Patients in group 1 (n = 33) received ALC 1180 mg/day; patients in group 2 (n = 31) received thioctic acid 600 mg/day. The study period was 60 days. The primary efficacy endpoint was change in clinical signs and symptoms of sciatica, as measured on the Neuropathy Impairment Score in the Lower Limbs (NIS-LL) questionnaire, the Neuropathy Symptoms and Change in the Lower Limbs (NSC-LL) questionnaire, and the Total Symptom Score (TSS) questionnaire. The secondary efficacy endpoint was improvement in neurological deficit (as measured by electromyography) compared with baseline.
RESULTS: Both treatments produced significant improvements from baseline in neuropathy on electromyography at day 60, and greater mean improvements were observed with thioctic acid (-0.19 +/- 0.29 vs baseline) than with ALC (-0.09 +/- 0.40 vs baseline), although the between-group difference was not statistically significant. Thioctic acid produced significantly greater mean improvements than ALC from baseline for NIS-LL (-2.52 +/- 1.50 vs -1.48 +/- 1.37, respectively), NSC-LL (-2.16 +/- 1.37 vs 1.42 +/- 1.37, respectively) and TSS (-1.90 +/- 1.08 vs 1.18 +/- 1.01, respectively) scores (p < 0.05 for all comparisons). More patients receiving thioctic acid than ALC reported a decreased need for analgesia (71.0% vs 45.5%, respectively; p < 0.05) and neither treatment impacted significantly on sleep quality.

CONCLUSIONS: Thioctic acid 600 mg/day appears to be at least as effective as ALC in the treatment of sciatic pain caused by a herniated disc and may be associated with an improvement in symptom scores and reduced need for analgesia. However, because of the limited number of patients evaluated and the lack of a placebo control in this trial, further studies are warranted in order to provide more definitive results.


L-carnitine treatment partially restores urinary bladder function of streptozotocin diabetic rats. Gur S, Irat AM. INTRODUCTION: Diabetes mellitus is associated with urinary bladder dysfunction. This study determined whether or not detrusor responses were altered and reversed by L-carnitine treatment in the urinary bladders of diabetic rats. MATERIALS AND METHODS: Three groups of animals were used: streptozotocin-treated (45 mg x kg(-1) i.p., 8 weeks), parallel L-carnitine-treated (0.6 g x kg(-1) x day(-1) i.p.), and control rats. Contractile and relaxant responses were measured using isolated bath techniques. RESULTS: Serum glucose levels in diabetic rats were partially reversed after L-carnitine treatment. Detrusor strips from diabetic rats exhibited an increase in response to electrical field stimulation (EFS; 0.5-32 Hz). Treatment with L-carnitine restored the hyperreactivity to EFS-induced contractility. The response to direct activation of the smooth muscle with carbachol and KCl remained unaltered. In relaxation studies, the urinary bladders of diabetic rats displayed a diminished response to isoprenaline, an unchanged response to ATP, and an increased response to adenosine of the ATP metabolite. L-carnitine treatment restored the hyporesponsiveness of isoprenaline and the hyperresponsiveness of adenosine-elicited relaxation. CONCLUSIONS: These findings show that carnitine can be implicated in the contractile response of noradrenergic noncholinergic nerve stimulation and the relaxation response of isoprenaline and adenosine. Hence, L-carnitine deficiency can contribute to voiding deficiency in diabetic patients.

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Carnitine in metabolic disease: potential for pharmacological intervention. Arduini A, Bonomini M, Savica V. L-carnitine (LC) deficiency is commonly observed in chronic hemodialysis (HD) patients. As a result of this and other causes of secondary LC deficiencies, LC has been described as a "conditionally essential nutrient" or "conditional vitamin". Although a large number of clinical trials regarding the beneficial effects of LC administration in HD patients have been published, some controversy about its use in this indication persists. In this article, we will review the use of LC in dialysis patients, by focussing mainly on those experimental and clinical data supporting the notion that supra-physiological concentrations of LC in plasma and target organs may exert beneficial effects on several metabolic parameters that have derangements of a common origin (e.g. insulin resistance, type 2 diabetes, dyslipidemia) and which are frequently present in end-stage renal disease (ESRD).

Effect of oral L-carnitine administration on insulin sensitivity and lipid profile in type 2 diabetes mellitus patients. González-Ortiz M, Hernández-González SO, Hernández-Salazar E. AIM: It was the aim of this study to evaluate the effect of oral L-carnitine administration on insulin sensitivity and lipid profile in subjects with type 2 diabetes mellitus. SUBJECTS AND METHODS: A randomized, double-blind, placebo-controlled clinical trial was carried out in 12 subjects with type 2 diabetes. Six subjects received L-carnitine 1 g orally 3 times a day before meals for a period of 4 weeks. Six other individuals took a placebo for the same period of time, as the control group. Before and after the intervention, insulin sensitivity and the lipid profile were estimated. To assess insulin sensitivity, the euglycemic-hyperinsulinemic clamp technique was performed. Wilcoxon's signed rank and the Mann-Whitney U test were used for the statistical analyses. RESULTS: There were no significant differences in basal clinical characteristics between the 2 groups. Insulin sensitivity and the basal lipid profile were similar. There were no significant changes in either group after the intervention in insulin sensitivity (3.2 +/- 1.2 vs. 4.5 +/- 1.7 mg/kg/min, p = 0.115, and 3.5 +/- 0.6 vs. 3.5 +/- 0.4 mg/kg/min, p = 0.917, for the placebo and L-carnitine groups, respectively) and in lipid profile. CONCLUSION: L-Carnitine orally administered for a period of 4 weeks did not modify insulin sensitivity or the lipid profile.


Alzheimer's disease, amnestic mild cognitive impairment, and age-associated memory impairment: current understanding and progress toward integrative prevention. Kidd PM. Alzheimer's disease, AD, is the most common form of dementia. AD initially targets memory and progressively destroys the mind. The brain atrophies as the neocortex suffers neuronal, synaptic, and dendritic losses, and the hallmark amyloid plaques and neurofibrillary tangles proliferate. Pharmacological management, at best, is palliative and transiently effective, with marked adverse effects. Certain nutrients intrinsic to human biochemistry (orthomolecules) match or exceed pharmacological drug benefits in double-blind, randomized, controlled trials, with superior safety. Early intervention is feasible because its heritability is typically minimal and pathological deterioration is detectable years prior to diagnosis. The syndrome amnestic mild cognitive impairment exhibits AD pathology and to date has frustrated attempts at intervention. The condition age-associated memory impairment is a nonpathological extreme of normal brain aging, but with less severe cognitive impairment than amnestic mild cognitive impairment. Age-associated memory impairment is a feasible target for early intervention against AD, beginning with the modifiable AD risk factors - smoking, hypertension, homocysteine, type 2 diabetes, insulin resistance, and obesity. Stress reduction, avoidance of toxins, and mental and physical exercise are important aspects of prevention. The diet should emphasize omega-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid; flavonoids and other antioxidant nutrients; and B vitamins, especially folate, B6 and B12. Dietary supplementation is best focused on those proven from randomized, controlled trials: the phospholipids phosphatidylserine and glycerophosphocholine, the energy nutrient acetyl-L-carnitine, vitamins C and E, and other antioxidants. A comprehensive integrative strategy initiated early in cognitive decline is the most pragmatic approach to controlling progression to Alzheimer's disease.


Preventive effect of acetyl-L-carnitine on the thermal hypoalgesia in streptozotocin-induced diabetic mice. Ohsawa M, Miyata S, Carlsson A, Kamei J. Hypoalgesia is one of the serious complications in diabetes. Since there are few therapeutic treatments for this diabetic hypoalgesia, the present study was designed to examine the effect of acetyl-L-carnitine (ALC) on the changes of nociceptive threshold in diabetic mice. For prophylactic study, ALC was administered once daily from
1 day after the streptozotocin treatment. Diabetic mice showed shorter tail-flick latency at 1-4 weeks after the streptozotocin treatment and longer tail-flick latency at 6-9 weeks after the streptozotocin treatment. The shortened tail-flick latency in early stage of diabetic mice was not affected by prophylactic treatment with ALC. On the other hand, ALC dose-dependently improved the hypoalgesia in diabetic mice. For therapeutic study, ALC was administered once daily from 7 weeks after the streptozotocin treatment, when tail-flick latency was already prolonged. The therapeutic treatment with ALC also ameliorated the prolonged tail-flick latency in diabetic mice. Both prophylactic and therapeutic treatment with ALC did not affect the tail-flick latency in non-diabetic mice, indicating ALC did not affect the general nociceptive transmission. These results provide evidence of the prophylactic and therapeutic potential of ALC on the progressive diabetic neuropathy.


Carnitine revisited: potential use as adjunctive treatment in diabetes.
Power RA, Hulver MW, Zhang JY. AIMS/HYPOTHESIS: This study examined the efficacy of supplemental L-carnitine as an adjunctive diabetes therapy in mouse models of metabolic disease. We hypothesised that carnitine would facilitate fatty acid export from tissues in the form of acyl-carnitines, thereby alleviating lipid-induced insulin resistance. MATERIALS AND METHODS: Obese mice with genetic or diet-induced forms of insulin resistance were fed rodent chow +/- 0.5% L-carnitine for a period of 1-8 weeks. Metabolic outcomes included insulin tolerance tests, indirect calorimetry and mass spectrometry-based profiling of acyl-carnitine esters in tissues and plasma. RESULTS: Carnitine supplementation improved insulin-stimulated glucose disposal in genetically diabetic mice and wild-type mice fed a high-fat diet, without altering body weight or food intake. In severely diabetic mice, carnitine supplementation increased average daily respiratory exchange ratio from 0.886 +/- 0.01 to 0.914 +/- 0.01 (p < 0.01), reflecting a marked increase in systemic carbohydrate oxidation. Similarly, under insulin-stimulated conditions, carbohydrate oxidation was higher and total energy expenditure increased from 172 +/- 10 to 210 +/- 9 kJ kg fat-free mass(-1) h(-1) in the carnitine-supplemented compared with control animals. These metabolic improvements corresponded with a 2.3-fold rise in circulating levels of acetyl-carnitine, which accounts for 86 and 88% of the total acyl-carnitine pool in plasma and skeletal muscle, respectively. Carnitine supplementation also increased several medium- and long-chain acyl-carnitine species in both plasma and tissues. CONCLUSIONS/INTERPRETATION: These findings suggest that carnitine supplementation relieves lipid overload and glucose intolerance in obese rodents by enhancing mitochondrial efflux of excess acyl groups from insulin-responsive tissues. Carefully controlled clinical trials should be considered.