L-Carnitine and Balanced Diet in Alzheimer’s Disease

Subjects: Pathology

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The prevention or alleviation of neurodegenerative diseases, including Alzheimer’s disease (AD), is a challenge for contemporary health services. For the prevention or alleviation of AD by introducing an appropriate carnitine-rich diet, dietary carnitine supplements and the MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet, it contains elements of the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet. L-carnitine (LC) plays a crucial role in the energetic metabolism of the cell. A properly balanced diet contains a substantial amount of LC as well as essential amino acids and microelements taking part in endogenous carnitine synthesis. In healthy people, carnitine biosynthesis is sufficient to prevent the symptoms of carnitine deficiency.

Keywords: Alzheimer’s disease ; L-carnitine ; carnitine supplementation ; Mediterranean diet

1. Prevention of Alzheimer’s Disease—Mediterranean and MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) Diets

In contemporary medicine, the prevention of neurodegenerative diseases is one of the main objectives for many branches of health services. The appropriate types and quality of food may be important factors for preventing and supporting the treatment of Alzheimer’s disease (AD). The early prevention of AD starts by reducing risk factors: reducing the smoking of cigarettes, preventing hypertension, insuring optimal concentrations of homocysteine, preventing type 2 diabetes, combating insulin resistance and obesity, limiting stress, avoiding toxins, and mental and physical training are important components of AD prevention. Appropriate nutrition is an essential and modifiable factor that plays a key role in preventing and/or delaying the onset of dementia, including AD. It was reported that a reduction in amount of fried meat and an increase in the amounts of other foods (such as fish, cheese, vegetables and vegetable oil) in the diet significantly reduced the incidence of AD [1]. Diets rich in advanced glycation end products (AGEs), which arise during long-lasting food thermal processing (heating, frying and irradiation), significantly accelerate the development of AD [2]. High concentrations of AGEs are contained in (a) products containing sugar (candy, cookies, chocolate biscuits, cakes, fizzy drinks, pastries and sauces); (b) processed meats such as sausages and conserved and preserved meat; (c) processed dairy products; (d) food containing trans fats such as margarine and cream; and (e) highly fried products such as fried potatoes, crisped cakes etc. The lowest amounts of AGEs are found in fresh fruits, vegetables, seafood, products with short thermal processing, and raw and non-processed food. A correctly composed diet rich in polyunsaturated (from the families of omega-3 and omega-6) and monounsaturated fatty acids as well as antioxidative vitamins (E, C and β-carotene) reduces the risk of AD development. It was reported that a decrease in the impairment of cognitive function and dementia risk were connected with a decrease in the consumption of milk and dairy products. The consumption of full-fat dairy products may be connected with worsening cognitive function in older people. It was reported that moderate alcohol consumption may be connected with a decrease in the risk of dementia due to AD [3][4]; however, recently, the Lancet published a statement concerning alcohol, that there is “no safe limit, even one drink a day, increases risk of chronic non infectious diseases” [5].

A large one was demonstrated the association of consuming a Mediterranean diet with a decrease in the incidence of AD, which creates hope for using the Mediterranean diet as a modifiable risk factor in protection against AD [6][7]. A Mediterranean diet rich in vegetables with low starch contents, fruit with low glycemic indices, cereal products, legumes, plant oils (olive, colza, linen and sunflower) and fish (especially sea fish: halibut, herring, mackerel and sardines) and a diet containing moderate amounts of meat and dairy products positively affect health conditions and may decrease the risk of the development of many diseases including neurodegenerative diseases [8][9].

It was reported that people adhering to a Mediterranean diet have a 28% decreased risk of cognitive disturbances and 48% decreased risk of AD in comparison to people who do not consume a Mediterranean diet [10]. It seems that a complex nutritional strategy initiated in the early stages of cognitive impairment is the most pragmatic approach for controlling the progress of AD [11]. Presently, for the elderly and people at risk of AD, nutrition based on the MIND

(Mediterranean-DASH Intervention for Neurodegenerative Delay) diet—composed of DASH (Dietary Approaches to Stop Hypertension) diet and the Mediterranean diet (MD), considered as the healthiest diet on earth, constituting a careful nutritional program—is recommended [12]. In the opinion, the MIND diet should be a very important element of many disease prevention strategies, including those for dementia and AD.

2. Physiological Properties of L-Carnitine

2.1. Role of L-Carnitine and Acetyl-L-Carnitine in Human Brain Metabolism

L-carnitine is actively transported to the brain through the blood–brain barrier by the organic cation transporter OCTN2 and accumulates in neural cells especially as acetylcarnitine. LC, besides its important role in the metabolism of lipids, is also a potent antioxidant (free radical scavenger) and thus protects brain tissues against oxidative damage [13]. Mitochondria, as the main source of cell energy as well as ROS and antioxidants, play a key role in the production of ATP, regulating apoptosis and detoxication, maintaining membrane potentials and the distributions of ions in appropriate compartments of the cell, etc. Maintaining mitochondrial homeostasis is crucial for the development and proper action of neurons. Dietary supplements applied for maintaining mitochondrial homeostasis include L-carnitine; coenzyme Q_{10}; mitoquinone mesylate; and other mitochondrion-targeted antioxidants such as N-acetylcysteine; vitamins C, E, K_1 and B; sodium pyruvate; and lipoic acid [14].

Even though the brain's basic energetic substrate is glucose, L-carnitine (LC) is important in brain energetic lipid metabolism, taking part in the transport of the long chain fatty acids from the cytoplasm to mitochondria [15] and acetyl groups from mitochondria to the cytoplasm [16]. Maintaining a suitable relationship between cellular acetyl-CoA and CoA, L-carnitine ensures correct energetic cell metabolism [17]. It should be mentioned that connecting acyl and acetyl groups to LC increases LC's hydrophobicity, which facilitates LC's crossing of the blood–brain barrier. After the penetration of brain mitochondria with long chain fatty acids, LC reacts with free coenzyme A (CoASH)—a reaction catalyzed by carnitine palmitoyltransferase II (CPT II)—releasing LC [18].

Therefore, LC improves energetic brain homeostasis by supplying acyl groups to the mitochondria of the brain cells. ALC is an important factor expanding the brain's sources of energy; therefore, treatment with ALC is responsible for a reduction in brain glycolytic flow and the enhancement of the utilization of alternative energy sources, such as fatty acids or ketone bodies [19], that may reduce brain glucose utilization [20]. ALC can provide an acetyl moiety that can be oxidized for energy production; used as a precursor for acetylcholine; or incorporated into glutamate, glutamine and γ-aminobutyric acid, as well as into lipids for myelination and cell growth [21]. ALC also has many other functions in the body. ALC's ability to freely pass the brain–blood barrier could help brain fatty acid transport for oxidation in mitochondria that improves brain energy metabolism. ALC supplementation positively influences the activity of enzymes in the tricarboxylic acid cycle, the electron transport chain and amino acid metabolism [22]. ALC acts neuroprotectively by improving the energetic function of brain mitochondria, the elimination of oxidative products, the stabilization of the cell membranes and neurotrophic factor production (stimulates protein and phospholipid biosynthesis), and it exerts anti-apoptotic functions, as well as modulating the expression of genes coding proteins, and protects neural cells from excitotoxicity [23]. Additionally, ALC provides acetyl groups for the synthesis of acetylcholine [24] and acetylation of nuclear histones [25]. ALC counteracts stressogenic agents by maintaining proper plasma concentrations of β-endorphin and cortisol [26]. ALC stimulates α-secretase activity and physiological amyloid precursor protein (APP) metabolism. In particular, ALC favors the delivery of disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), the most accredited α-secretase, to the post-synaptic compartment and, consequently, positively modulates ADAM10's enzymatic activity toward APP [27]. Palmitoylcarnitine (ester of carnitine with palmitic acid) can stimulate the expression of GAP-43 (also named B-50, neuromodulin, F1, pp45), a protein involved in neural development, neuroplasticity and neurotransmission [28]. ALC increases the concentration of the brain-derived neurotrophic factor (BDNF), that is lowered in AD patients [29][30]. ALC increases astrocytes' glutathione concentrations (an important cellular antioxidant), which are lowered with age [31]. ALC is recommended for delaying the onset and development of Alzheimer's and Parkinson's diseases, and alleviating the symptoms of senile depression and memory disturbances connected with age; it also improves memory [32][33][34]. It was confirmed that the multidirectional positive role of ALC in the dopaminergic system [35] depended on the slowing down of the progressive deterioration of dopaminergic receptors with a simultaneous increase in the concentrations of dopamine (a neurotransmitter responsible for mood, processes of thinking, the coordination of movement and resistance to stress) in neurons [36]. It was reported that the LC supplementation of experimental animals significantly increased their levels of neurotransmitters such as noradrenaline, adrenaline and serotonin, especially in brain regions rich in cholinergic neurons, i.e., the brain cortex, hippocampus and striatum [35][37]. ALC improves dopamine metabolism, prevents degenerative changes in dopamine-producing neurons and reduces the age-dependent process of the destruction of receptors that bind dopamine [38]. Cristofano et al. [39] showed a progressive decrease in ALC and other acyl-carnitines' serum levels in people changing

from normal to AD and concluded that the decreased serum concentrations of ALC and hence its disturbed functions may predispose to AD and contribute to neurodegeneration. Clinical ones in humans demonstrated positive effects of ALC on brain function, cognition and memory that led to the suggestion that ALC may slow or reverse mild cognitive impairment and the progression of dementia in Alzheimer's disease [40].

ALC supplementation is recommended for improving brain and nervous system action, memory, the speed of learning and memorization, the level of brain energy, psychological conditions and mood, and the effects of therapies for brain neurodegenerative disorders and peripheral neuropathies [13][33].

2.2. Recommendations for L-Carnitine Content in the Diet

LC is an essential nutritional component delivered in food produced from animals, because LC endogenic synthesis is insufficient to cover metabolic needs. Primary carnitine deficiency is rare, but secondary carnitine deficiency is more frequent, being associated with several inborn errors of metabolism and acquired medical or iatrogenic conditions, for example, in patients under valproate and zidovudine treatment. Other chronic conditions such as diabetes mellitus, heart failure and Alzheimer's disease in connection with diseases creating increased catabolism may cause secondary carnitine deficiency [41].

Presently, there are no published recommended carnitine reference values. In the majority, the estimated average daily carnitine requirements for an adult person amount to 20–200 mg, which is covered by diet and endogenous synthesis. Meat, fish and dairy products provide at least 80% of the required LC [42]. Based on rational dietary rules supporting good health, it is important to introduce carnitine-rich food [43][44], including carnitine supplementation. However, it should be taken into consideration that the bioavailability of LC from food is about four times higher than that from dietary supplements. Additionally, it should be taken into consideration that a high-fat, low-carbohydrate diet might be capable of boosting the endogenous synthesis of carnitine and its metabolites [45].

2.3. Supplementation with L-Carnitine and Its Derivatives

In the prevention and treatment of patients with Alzheimer's disease, supplementation with carnitine is essential for complementing intracellular and extracellular carnitine resources. In addition, LC supplementation is intended to facilitate the elimination of toxic metabolites that may interfere with mitochondrial homeostasis, thereby interfering with the production of cellular energy, further leading to increased ROS production in many neurodegenerative diseases.

LC in the form of powder, fluid, tablets or capsules has been approved by the American Food and Drug Administration (FDA) for the treatment of primary and secondary carnitine deficiency. Experimental data obtained in in vitro and in vivo research did not demonstrate toxicity of LC. No side effects (including allergic reactions) were observed after the oral administration of LC in humans. However, some people using LC showed symptoms of alimentary tract intolerance (periodical nausea, diarrhea and tummy ache). People using large doses of LC may emit a fish body odor caused by the trimethylamine produced in the gut from LC by intestinal bacteria [46]. There were no published of LC intoxication. For the LC supplementation of the healthy adults, there were administered 250 mg to 2.0 g (highest safe dose) of LC daily, in several doses [47]. Daily LC doses greater than 2.0 g appeared to offer no advantage, since the gut mucosal absorption of carnitine appears to be saturated at about a 2.0 g daily dose [48]. A meta-analysis of 21 double-blind, randomized, placebo-controlled ones lasting from three months to one year showed that ALC either improved cognitive deficits or delayed the progression of cognitive decline. Improved cognitive function and delayed progression of cognitive decline were both statistically and clinically significant, with the magnitude of the effects increasing over time. Most used daily doses of LC of 1.5–2.0 g, which were well tolerated [49]. The treatment of ALC with doses of 2.25–3.0 g/day in patients with mild (initial) dementia caused by AD and vascular dementia (VD) led to a significant clinical improvement in patients with AD compared to in VD patients and placebo-treated patients [50]. In another one, 11 patients suffering from senile dementia of the Alzheimer's type were treated intravenously with ALC at 30 mg/kg for 10 days, and 1.5 g/day per os for 50 days, in three daily doses. It was concluded that the intravenous and oral administration of multiple doses of ALC increases ALC plasma and CSF concentrations in patients suffering from AD, which suggests that ALC easily crosses the blood–brain barrier [51]. The bioavailability of LC in food supplements depends on the applied doses [45][52]. As a general guideline, the average therapeutic ALC dose is 1.0 g, given two to three times daily for a total of 2.0–3.0 g. No advantage appears to exist in giving an oral dose greater than 2.0 g of ALC at one time, since absorption ones was indicated the saturation of GI receptors (receptors coupled with proteins G) at this dose [45]. The reported side effects of LC (especially at high doses) include agitation, headaches, diarrhea, nausea, vomiting, anorexia and abdominal discomfort, mostly of mild or moderate severity [53].

2.4. Choosing Proper Form of Carnitine Supplements

LC and its derivatives have been proposed as drugs or as adjuncts to conventional medicine for many conditions, including stable angina, intermittent claudication, diabetic neuropathy, kidney disease and dialysis, hyperthyroidism, male infertility, erectile dysfunction, chronic fatigue syndrome, AD and memory impairment [53]. Many specimens containing LC differing only in form (powder, liquid, tablets or capsules) are available on the market. Free or in combination with organic acids, e.g., citric, fumaric or orotic acids, LC given as a dietary supplement is perfectly bioavailable. A combination of LC and arginine facilitates the release of ammonia as an end product of protein and amino acid metabolism. It was reported that for epileptics, exceptionally beneficial is a combination of LC with taurine because taurine acts as a modulator of membrane excitability in the central nervous system by inhibiting the release of other neurotransmitters and decreasing the mitochondrial release of calcium [54]. When administering organic salts of LC, it should be taken into consideration that a given free carnitine content corresponds to a higher weight of drug [45][52]. However, healthy people should avoid the oral intake of LC at amounts higher than 1.0–2.0 g/day in 3–4 doses [55]. The bioavailability of LC from foods is 54–87% of the LC content and is dependent on the amount of LC in the meal. The absorption of LC from dietary supplements (0.5–6.0 g/day) is primarily passive, and the bioavailability is 14–18% of LC in the dose. LC that is unabsorbed in the gastrointestinal tract is mostly degraded by microorganisms in the large intestine [40].

2.4.1. Pure L-Carnitine (LC)

A prevalent and the most economical form of L-carnitine supplementation is orally administered LC powder or solution. LC powder or solution is recommended for people taking care of their appearance and pursuing a reduction in or maintaining the proper level of their body weight. LC is also recommended for supporting the circulatory system by reducing the risk of ischemic heart disease and other circulatory disorders [56]. LC, as an organic osmoprotectant, has been proven to have protective roles against the production of proinflammatory mediators and apoptosis in primary human corneal epithelial cells exposed to hyperosmotic media, as well as in dry-eye patients [57][58]. It was reported that LC supplementation improved the depression state in patients undergoing hemodialysis [59]. A deficiency of carnitines in terminally ill HIV/AIDS patients requires supplementation. Significant reductions in serum lactate after LC supplementation may have clinical significance in patients taking certain antiretroviral drugs [60]. L-carnitine plays an important role in energy metabolism. Skeletal muscles store about 95% of the total of 20 g carnitine contained in the adult human body, but high-intensity physical exercise decreases the muscle's carnitine content. It has been proven that L-carnitine supplementation may enhance athletic performance when coupled with physical exercise itself [61].

2.4.2. Acetyl L-Carnitine (ALC)

L-carnitine acetylation increases L-carnitine's hydrophobicity, which permits ALC's crossing of the blood–brain barrier. ALC shows neuroprotective action on nervous cells, supports energetic metabolism and the regeneration of nerve cell structures, and alleviates mitochondrial dysfunction and apoptosis [62], improving memory and creativity. It has been suggested a beneficial effect of ALC on cognition and behavior in aging and AD subjects [32]. In AD patients, ALC improves clinical and cognitive functions in the short and medium term (3 and 6 months) in varied doses (1.5–3.0 g/day). Additionally, with 12 month treatment at a dose of 2.0 g/day, ALC slows down the deterioration of cognitive function in AD patients [63]. Other experimental data confirm the effectiveness of ALC supplementation in protecting against brain damage, for example, the application of 100 mg/kg body weight of ALC reduced the volume of brain injury and improved victims' behavior after traumatic brain injury. Additionally, ALC reduces oxidative stress and improves the function of mitochondrial membranes provoked by neurotoxic glutamate action [64]. The efficacy, safety and tolerability of ALC were learned during a double-blind, placebo-controlled, 12-week trial in patients with initial dementia caused by AD and vascular dementia (VD). The trial ended with the conclusion that ALC (carnicetine) can be recommended at doses of 2.25–3.0 g/day for the treatment of the early stages of AD and VD. ALC was well-tolerated [50]. Recently, the unique pharmacological properties of ALC have been confirmed, which allowed to look at this molecule as a representative of the next generation of antidepressants with a safe profile, especially for older people [65].

2.4.3. Propionyl L-Carnitine (PLCAR)

Propionyl-L-carnitine (PLCAR), or L-carnitine esterified with propionic acid, is more stable and bioavailable than free carnitine, with significantly stronger action than free L-carnitine, especially in the circulatory system and cardiac muscle. PLCAR was recommended for the treatment of diseases of the peripheral arteries and other disturbances of the cardiovascular system [56][66]. According to some data, PLCAR increases the concentration of L-carnitine in muscles independently of insulin levels, which is beneficial during the application of low carbohydrate diets. It was proven that PLCAR prevents the peripheral neuropathy connected with diabetes or toxic chemotherapy, improving nervous conductivity and blood flow in peripheral nerves [33].

2.4.4. Acetyl L-Carnitine Arginate (ALCA)

Damaged mitochondria are associated with decreased ATP production and increased reactive oxygen species production, both of which characterize AD patients. Arginine is a substrate for nitric oxide (NO) synthesis that improves the extension of blood vessel walls and improves blood circulation in the organism [67]. Acetyl L-Carnitine Arginate is an assistant to mitochondrial function, that helps to promote cell growth and cellular differentiation and may even play a role in the slowing the aging process. ALCA helps to boost mitochondrial energy production and promotes targeted benefits for the brain, heart and central nervous system. Supplementation with ALCA results in an increase in resting nitrate/nitrite levels in pre-diabetics, without any statistically significant changes in other substances connected with metabolic or oxidative stress (malondialdehyde, xanthine oxidase activity and hydrogen peroxide) [68]. Alpha-lipoic acid (ALA) (an eight-carbon saturated fatty acid)—a compound with strong antioxidative action, required by the pyruvate dehydrogenase complex for starting the tricarboxylic acids cycle—is frequently added to ALC. An important function of ALA in organisms is a redirection of anaerobic to aerobic metabolism in cells, preventing the acidification of the organism and enabling the generation of much more energy than can be generated by anaerobic metabolism [69]. It was reported that old rats that were fed with ALC and ALA significantly reduced their numbers of severely damaged mitochondria and increased the numbers of intact mitochondria in the hippocampus. The above results suggest that feeding ALC with ALA may also ameliorate age-associated mitochondrial ultrastructural decay in humans [69].

2.4.5. Glycine-Propionyl- L-carnitine (GPLC)

Glycine improves the gut absorption and transfer through the intestinal walls of L-carnitine and facilitates the reaching of the circulation by L-carnitine. The combination of L-carnitine with glycine and propionic acid (GPLC) significantly improves the absorption and utilization of L-carnitine by cells. GPLC supports the production of nitric oxide (NO), an important substance facilitating blood circulation during physical training [70]. By stimulating NO synthesis, GPLC induced the distension of blood vessels, lowering pressure on the blood vessel walls. GPLC facilitates the faster and more efficient transport of fats to muscle cells (an important source of energy during prolonged physical exercise, when glycogen stores are exhausted) and facilitates the elimination of metabolic waste products. GPLC exhibits strong antioxidative properties that protect cells against the action of free radicals of oxygen and nitrogen. It was reported that GPLC significantly increases glutathione levels and decreases the levels of markers reflecting an increased speed of protein and lipid oxidation in humans [71]. GPLC increases the effectivity of citric acid cycle and inhibits lactate synthesis, prolonging the time of effective physical activity [72]. It was showed that GPLC significantly blocked D-galactosamine-induced pro-inflammatory cytokine (TNF-α and IL-6) production and, at the same time, inhibited the expression of α-smooth muscle actin, collagen-I and transforming growth factor-β. It has been demonstrated that GPLC has hepatoprotective effects against fulminant hepatic failure and chronic liver injury induced by D-galactosamine. Blommer et al. [73] determined the effect of GPLC on oxidative stress biomarkers at rest and on reactive hyperemia during the exercise of trained men. They found a decrease in lipid peroxidation with the oral intake of GPLC at rest, and in previously sedentary subjects. Whereas short-term ischemia–reperfusion in trained men results in a modest and transient increase in blood oxidative stress biomarkers, oral GPLC supplementation during short-term ischemia–reperfusion in trained men does not attenuate the increase in oxidative stress biomarkers.

2.4.6. L-Carnitine-L-Tartate (LCLT)

L-carnitine-L-tartate (LCLT) contains L-tartate coupled with L-carnitine. L-tartate intensifies L-carnitine's action by decreasing glucose absorption from the gastro-intestinal tract and decreasing the deposition of spare fats. LCLT is recommended for persons desiring to reduce fat tissue and improve efficiency and muscle force during training. Some research has shown that LCLT supplementation beneficially affects markers of hypoxic stress following resistance exercise. Muscle oxygenation was reduced by LCLT in the trial upper arm occlusion and following each set of resistance exercise. Despite reduced oxygenation, plasma malondialdehyde, a marker of membrane damage, was attenuated during the LCLT trial. The hypoxic stress was attenuated with LCLT supplementation [74]. The use of LCLT relieved the damage caused by metabolic stress and the hypoxic chain of events leading to muscle damage after exercise (reduced post-exercise serum levels of hypoxanthine, xanthine oxidase and myoglobin and perceived muscle soreness) [75]. In addition, a positive effect of LCLT on the endocrine system has been demonstrated. The supplementation of LCLT increased androgen receptor content in the muscle, which may result in increased testosterone uptake and thus enhanced luteinizing hormone secretion via feedback mechanisms, which may promote recovery post resistance exercise [76]. Chronic LCLT supplementation increased carbohydrate oxidation during exercise [77]. The influence of LCLT on markers of purine catabolism (hypoxanthine, xanthine oxidase and serum uric acid), circulating cytosolic proteins (myoglobin, fatty acid-binding protein and creatine kinase), free radical formation, and muscle tissue disruption after squat exercise was examined. Exercise-induced increases in plasma malondialdehyde (a lipid peroxidation product) returned to resting values

sooner with LCLT supplementation than with a placebo. The above data indicate that LCLT supplementation is effective in assisting recovery from high-repetition squat exercise [78].

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