

Mitochondria & Longevity: Unlocking the Cellular Key to Vitality and Lifespan



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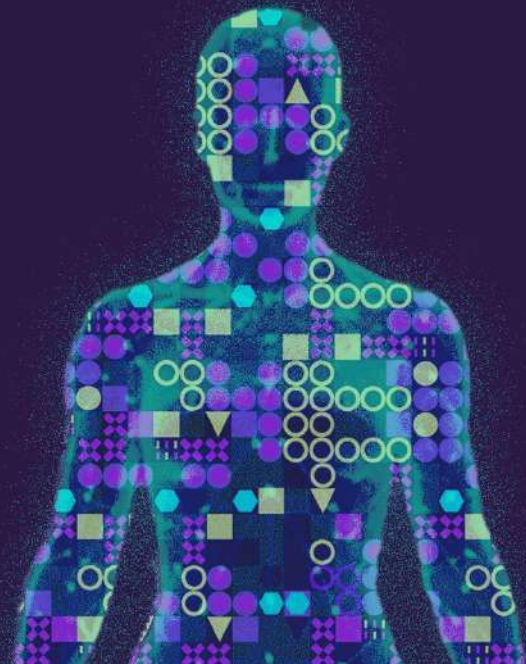


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Learning objectives:

- Review how the (dys)function of mitochondria relates to cellular and physiological health in the context of ageing.
- Explore the strengths and limitations of assessments of mitochondrial in clinical practice.
- Learn how certain dietary patterns and specific nutrients and phytonutrients can be used to optimise mitochondrial function.
- Cover examples of lifestyle medicine-based interventions that have been shown to improve mitochondrial number and/ or function.
- Examine how interventions can be personalised to the individual.



Yang qi theory and ageing

“From a traditional point of view, Yang Qi represents “material energy” or “energy flow”. Yang Qi runs through the meridians and spreads throughout the body to maintain human life activities. It is the root of human growth, development, and reproduction. Coincidentally, mitochondria also represent energy and are closely related to life.”

Phenomics. 2022 Jun 16;2(5):336-348.



Phenomics (2022) 2:336–348
<https://doi.org/10.1007/s44014-022-10000-5>

Review

Mitochondria as the Essence of Yang Qi in the Human Body

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Abstract
 The concept of Yang Qi in Traditional Chinese Medicine (TCM) has many similarities with mitochondria as modern medicine. Both are indispensable to human beings and closely related to life and death. This article discusses the similarities in various aspects between mitochondria and Yang Qi, including body temperature, aging, metabolism, circulation, function, interaction, and mutation. It is well-known that Yang Qi is vital to human health. Interestingly, decreased mitochondrial function is thought to be key to the development of various diseases. Here, we further explore diseases induced by Yang Qi deficiency, such as cancer, chronic fatigue syndrome, sleep disorder, stroke, dementia, and metabolic diseases. From the perspective of mitochondria of function, we aim to establish qualitative and quantitative between two important concepts, and hope our essay can stimulate further discussion and investigation on existing important concepts in western medicine and alternative medicine, especially TCM, and provide unique holistic insights into understanding human health.

Keywords Mitochondria · Yang Qi · Diseases · TCM (Traditional Chinese Medicine)

Abbreviations
 TCM Traditional Chinese Medicine
 mtDNA Mitochondrial DNA
 CNPFBs Oxidative phosphorylation
 mtDNA Mitochondrial DNA
 TCA Tricarbohylic acid
 ETC Electron transport chain
 ATP Adenosine triphosphate
 ROS Reactive oxygen species
 CCP1 Uncoupling protein 1

Introduction
 Mitochondria, as organelles in the cytoplasm, harbor their own genome called mitochondrial DNA (mtDNA), which contains 18,569 base pairs in humans. The mtDNA is a circular double-stranded molecule encoding 37 genes: 13 proteins, 22 transfer RNA, and 2 ribosomal RNA. These 13 proteins constitute the key subunits of the oxidative phosphorylation (OXPHOS) complex I, III, IV, and V (Chen et al. 2016; Filiano and Mazono 2007; Kozhikara et al. 2017). Human mtDNA is maternally inherited, as the paternal mtDNA is rapidly destroyed postfertilization (Chen, Pan, and Saito 2012). Unlike nuclear DNA (nDNA), mtDNA is not protected by histones and does not recombine during meiosis. The mutation rate of mtDNA is about 10–100 times higher than that of nDNA (Harris et al. 2011; Mikkelsen et al. 2007). Mitochondria are vital organelles. The major function of mitochondria is to generate large amounts of energy. As metabolic signaling centers, mitochondria can extract carbohydrate, protein, and fat molecules into CO₂ and water using the tricarbohylic acid (TCA) cycle and electron transport

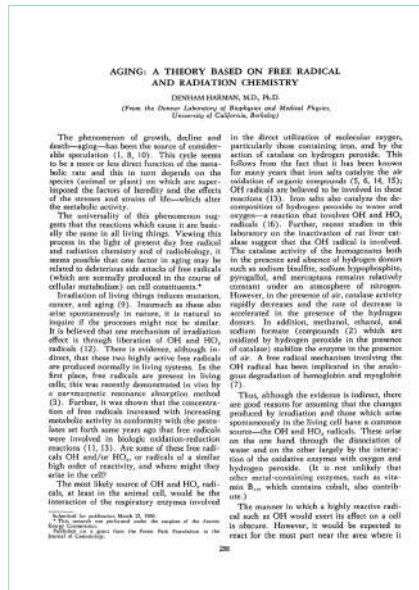
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 1 Beijing Advanced Innovation Center for Protein Research and Frontiers Health, Key Laboratory of Protein Science and Health, Chinese Academy of Sciences, Beijing 100191, China
 2 State Key Laboratory of Genetic Engineering, Collaborative Innovation Center for Genetic and Developmental and Human Genome Science, Fudan University, Shanghai 200035, China
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Free radical theory and ageing

The initial free radical theory of aging proposed that energy metabolism in the electron transport chain produce intracellular reactive oxygen species that elicit cellular damage and eventually cellular dysfunction.

J Gerontol. 1956 Jul;11(3):298-300.



Mitochondrial theory and ageing

“The importance of mitochondrial biology as a trait d’union between the basic biology of aging and the pathogenesis of age-related diseases is stronger than ever, although the emphasis has moved from reactive oxygen species production to other aspects of mitochondrial physiology, including mitochondrial biogenesis and turnover, energy sensing, apoptosis, and calcium dynamics.”

J Gerontol A Biol Sci Med Sci. 2015 Nov;70(11):1334-42.



Triage theory and ageing

“Triage theory posits that when a micronutrient is inadequate, nature selects for a rebalancing of metabolism (e.g., by selection for micronutrient binding constants) that ensures survival of the organism at the expense of metabolism whose lack has only longer-term consequences, which I propose include chronic diseases of aging.”

Mech Ageing Dev. 2010 Jul-Aug;131(7-8):473-9.

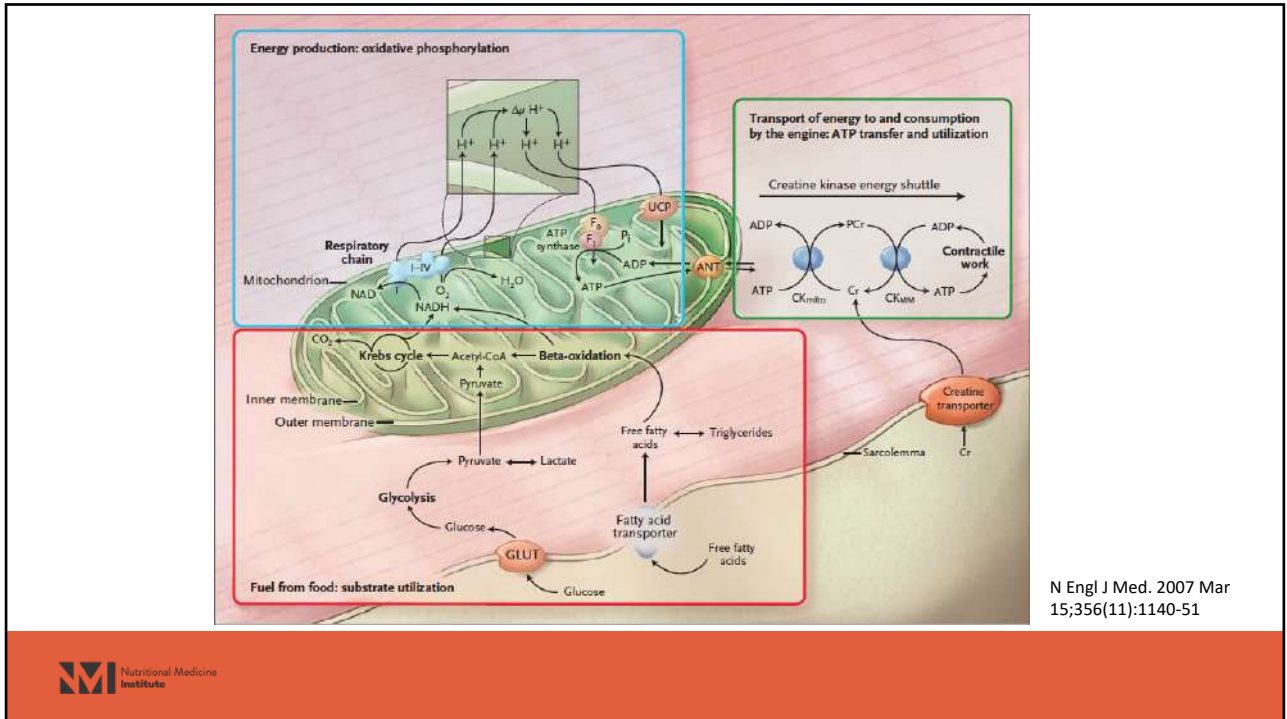


Mitochondrial nutrients

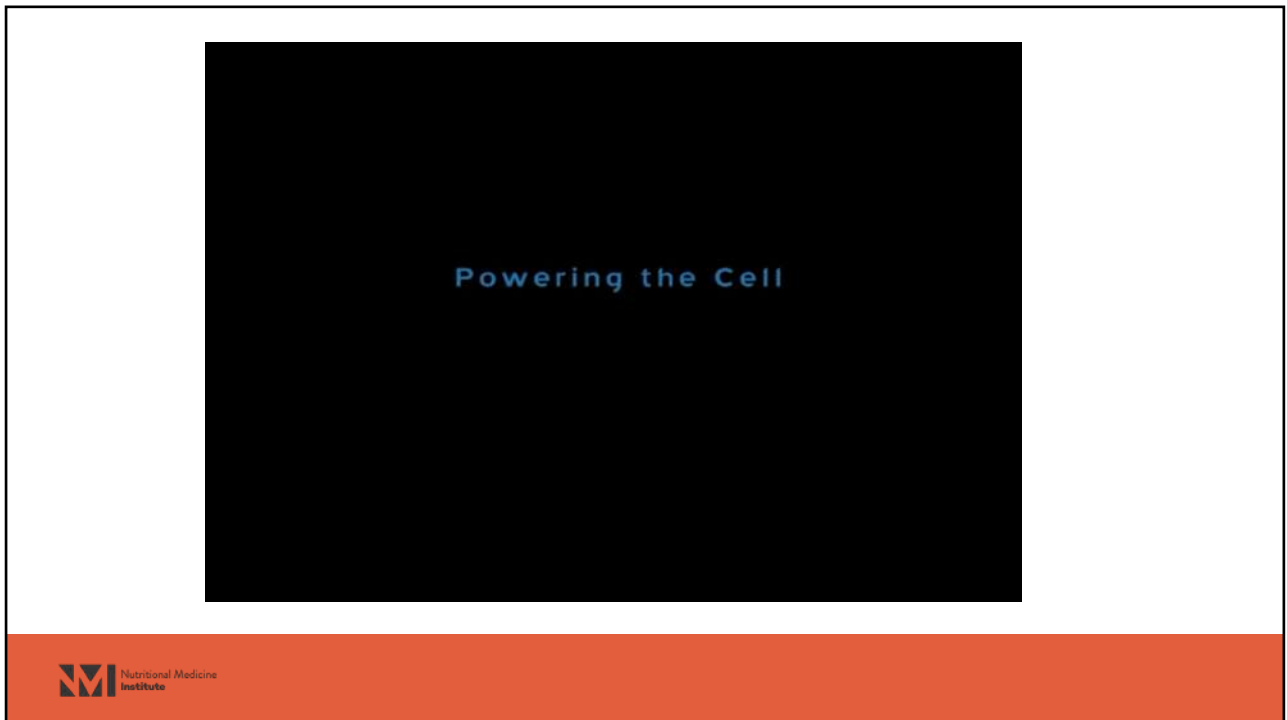
“Mitochondrial nutrients have been defined as nutritional compounds that (1) enter the cells and mitochondria following exogenous administration, (2) protect the mitochondria from oxidative damage, and (3) improve mitochondrial function.”

Altern Ther Health Med. 2014 Jan-Feb;20(1):29-40.

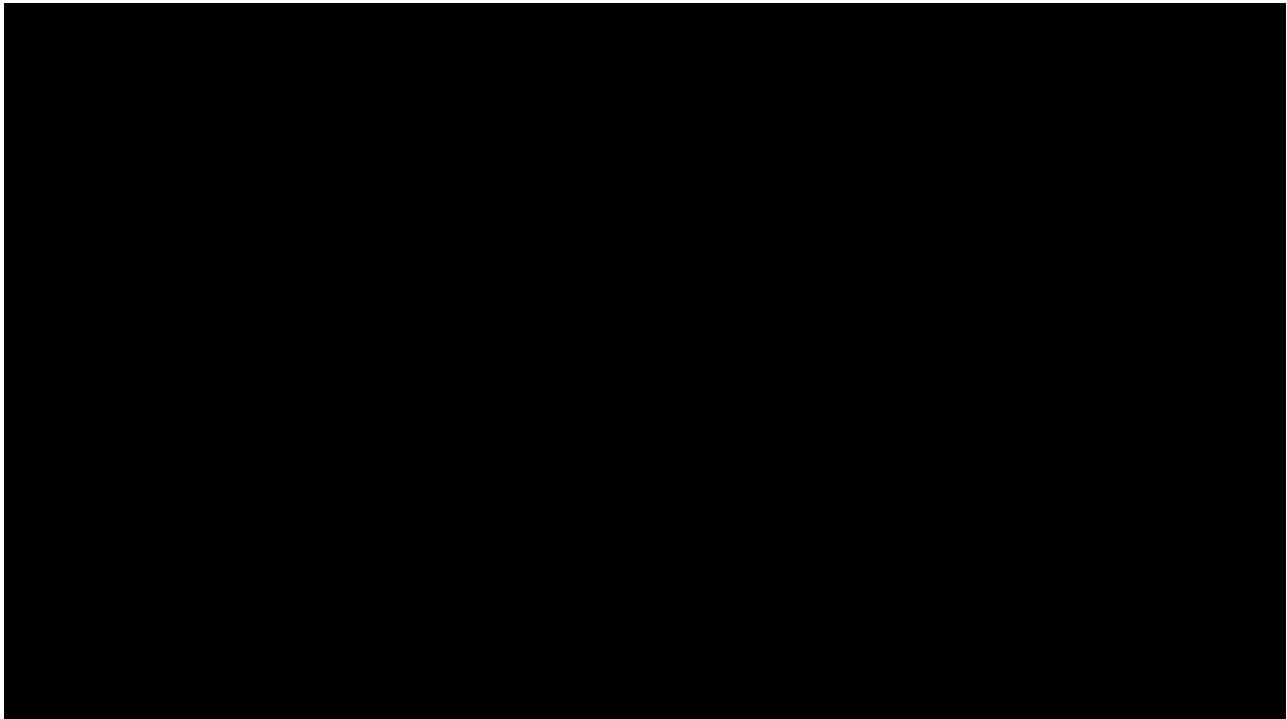




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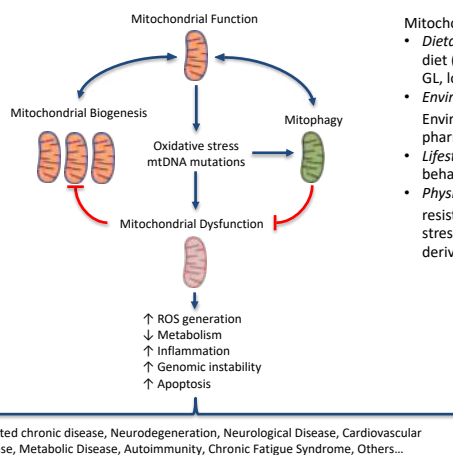


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Mitochondrial (dys)function, mitophagy and lifestyle medicine

Mitochondrial function

- **Dietary characteristics:** Caloric balance, intermittent fasting, low-glycemic load (GL), low-saturated fat, high omega-3, high phytonutrient density, organic.
- **Co-factors:** B-group vitamins, ascorbic acid, vitamin D, calcium, iron, magnesium, manganese, iodine, zinc, CoQ10, carnitine, n-acetylcysteine, taurine, ribose, lipoic acid.
- **Trophic-factors:** EPA/ DHA, phospholipids, resveratrol, curcumin, ginkgo, quercetin, spermidine, urolithin A, pyrroloquinoline quinone.
- **Lifestyle factors:** Exercise, relaxation.

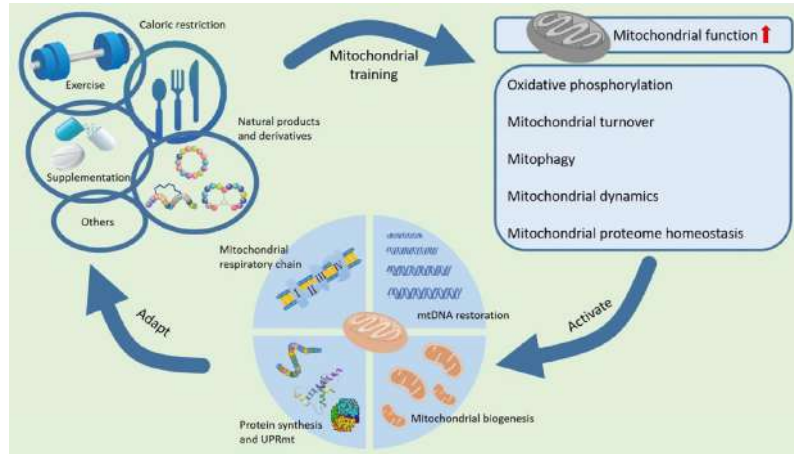


Mitochondrial dysfunction

- **Dietary characteristics:** Western diet (energy dense, high-fat, high-GL, low-nutrient density)
- **Environmental factors:** Environmental pollutants, pharmaceutical drugs.
- **Lifestyle factors:** Sedentary behavior, psychological stress.
- **Physiological factors:** insulin resistance, obesity, oxidative stress, inflammation, infection, gut-derived endotoxin exposure.

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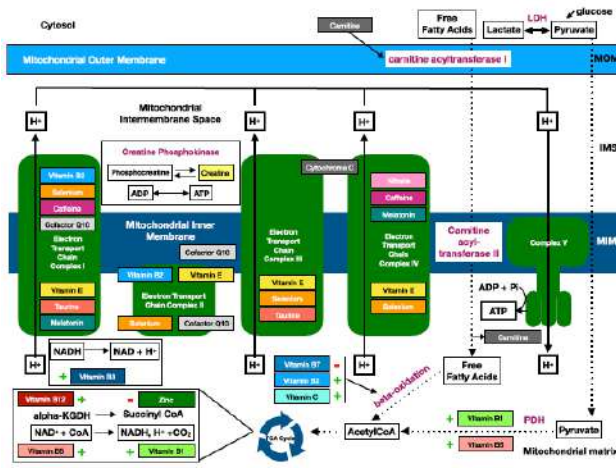
An opportunity for personalised lifestyle medicine



Journal of Holistic Integrative Pharmacy.
Volume 6, Issue 2, June 2025, Pages 159-174.



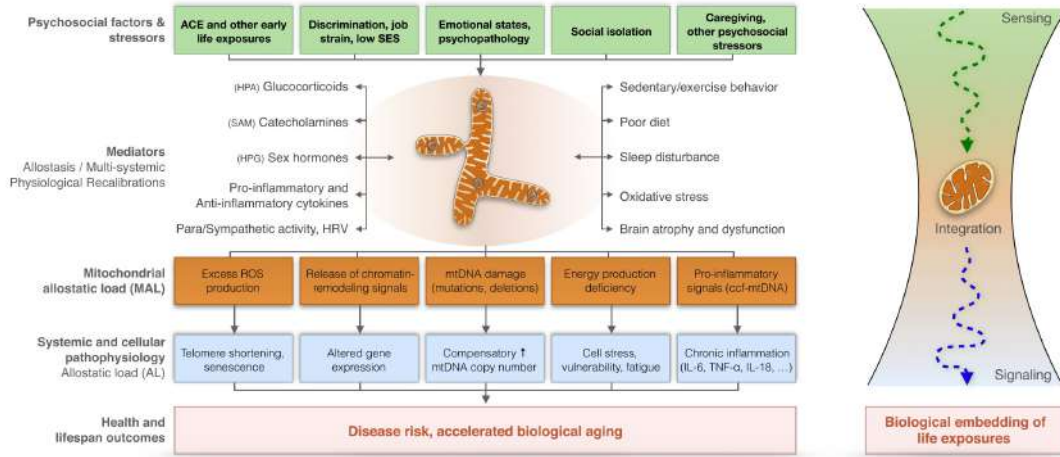
An opportunity for personalised nutrition



Clin Nutr. 2019 Jun;38(3):982-995.



An opportunity for mind-body medicine



Picard and McEwen. Psychosom Med. 2018 Feb/Mar;80(2):126-140.



Acetyl-L-carnitine



Carnitine deficiency and frailty

Frailty status (criteria; involuntary weight loss, exhaustion, muscle weakness, slow gait speed and sedentary behaviour) **is associated with carnitine deficiency**. In frail elderly subjects (3 or more criteria) mean serum concentrations of total and free carnitine were lower compared to both prefrail (1 or 2 criteria) and robust subjects (0 criteria).

Nutrients. 2020 Dec 19;12(12):3887.



Carnitine Serum Levels in Frail Older Subjects

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Abstract: Frailty is an expression that encompasses and condenses loss of autonomy, both physical and cognitive decline and a wide spectrum of adverse outcomes due to aging. The decrease in physical and cognitive activity is associated with altered mitochondrial function, and energy loss and consequently muscle and mental. In this cross-sectional study we evaluated the carnitine levels in frailty status. The mean serum concentrations of total carnitine (TC) were lower in frail elderly subjects than in prefrail ones ($p < 0.0005$), higher in frail vs. robust subjects ($p < 0.0001$), and higher in prefrail vs. robust subjects ($p < 0.0001$). The mean serum concentrations of free carnitine (FC) were lower in frail elderly subjects than in prefrail ones ($p < 0.0001$), lower in frail vs. robust subjects ($p < 0.0001$) and lower in prefrail vs. robust subjects ($p < 0.0001$). The mean serum concentrations of acylcarnitine (AC) were higher in frail elderly subjects than in prefrail ones ($p = 0.004$) and were higher in prefrail vs. robust subjects ($p = 0.0023$). The mean serum concentrations of PC were lower in frail elderly subjects than in prefrail ones ($p < 0.001$) and lower in frail vs. robust subjects ($p < 0.001$). The mean serum concentrations of free carnitine were lower in frail elderly vs. robust subjects ($p < 0.001$). The mean serum concentrations of acyl carnitine were lower in frail elderly subjects than those in frail prefrail ($p < 0.0001$) and robust subjects ($p < 0.0001$). Conclusion: High levels of carnitine may have a beneficial effect on the functional status and may treat the frailty status in older subjects.

Keywords: carnitine; frailty; biomarkers; physical activity; cognitive function; fatigue; metabolism; mitochondria

1. Introduction

Frailty is a geriatric syndrome characterized by a multidimensional, transitional state of increased vulnerability and loss of ability to adapt to age-associated challenges [1]. The prevalence of frailty ranges from 10% to 20% [2], but due to the aging of the population, this percentage will increase, resulting in high rates of hospitalization. As a consequence, it will considerably increase the public health care costs [3]. Multiple factors that contribute to frailty include cardiovascular dysfunction, endocrine dysregulation, immune dysfunction, abnormalities in energy metabolism and central nervous system injury in older people [4–7]. The decline in the functional capabilities is multifactorial, and the dysregulated mitochondrial metabolism may be a root of age-related frailty. Mitochondria are involved in a variety of critical cell functions including oxidative energy production, programmed cell death, growth and tumor signaling. Several reports have shown that the loss of carnitine may have an impact on mitochondrial biogenesis. In previous studies, we observed that

Version: 1006 (21 Nov 2020 08:33 PM) to 123047 www.mdpi.com/journal/nutrients



Delaying mitochondrial aging

“Feeding R-alpha-lipoic acid plus acetyl-L-carnitine (LA/ALC) to old rats partially restored age-associated mitochondrial dysfunction to the levels of the young rats. These results indicate that oxidative mitochondrial decay plays an important role in brain aging and that a combination of nutrients targeting mitochondria, such as LA/ALC, could ameliorate mitochondrial decay through preventing mitochondrial oxidative damage.”

Neurochem Res. 2009 Apr;34(4):755-63.

Neurochem Res (2009) 34:755–763
 DOI 10.1007/s10945-009-0193-2

ORIGINAL PAPER

Mitochondrial Decay in the Brains of Old Rats: Ameliorating Effect of Alpha-Lipoic Acid and Acetyl-L-carnitine

Jiangping Liang · Tang Cao · Lijiang Tong · Carl W. Cotman · Bruce N. Ames · Jianchang Liu

Accepted: 7 September 2008 / Published online: 18 October 2008
 © Springer Science+Business Media B.V. 2008

Abstract: To investigate the mitochondrial decay and oxidative damage resulting from aging, the acetyl-L-carnitine (ALC) and alpha-lipoic acid (ALA) were administered to the brains of young and old rats as well as old rats fed ALA + ALC and also acetyl-L-carnitine (ALC) alone. The brain mitochondria of old rats, compared with young rats, had significantly decreased mitochondrial membrane and respiratory chain enzyme activity, more oxidative damage to lipids and proteins, and decreased activities of complex I, IV and V. Complex I showed a decrease in binding affinity (increase in K_m) for substrate. Feeding LA/ALC to old rats partially restored age-associated mitochondrial dysfunction to the levels of the young rats. These results indicate that oxidative mitochondrial decay plays an important role in brain aging and that a combination of nutrients targeting mitochondria, such as LA/ALC, could ameliorate mitochondrial decay through preventing mitochondrial oxidative damage.

Keywords: Binding affinity (K_m); Brain mitochondria; Mitochondrial complex activity; Energy intake; Oxidative damage

Introduction

Increasing evidence demonstrates that aging is closely associated with mitochondrial degeneration [1]. Mitochondria are the primary energy generating organelles in the cell. The final step of electron transport energy generating process involves adding four electrons to oxygen to form water. Approximately 1–2% of the oxygen accepts a single electron to form reactive oxidant by-products. These oxidants attack mitochondrial membrane proteins, lipids and nucleic acids, resulting in lower efficiency in electron transfer. In turn, the damaged electron respiratory chain increases the production of oxidants, leading to a cycle of increasing oxidant production and mitochondrial damage with age [2].

The oxidative modification of proteins is implicated in the etiology or progression of a number of the degenerative diseases of aging [3]. One consequence of protein oxidation is the deterioration of enzymes causing loss of binding affinity (increased K_m) for substrates and substrates with age [2]. Oxidative damage of enzymes contributes to the mitochondrial degeneration of aging [2]. Mitochondrial complex I, III, and IV show activity and function in significantly higher in K_m and decrease in V_{max} with aging, which is accompanied by an increase in oxidants [4]. In old rats, low energy state, mitochondrial membrane potential, cardiolipin level, respiratory control ratio and cellular O_2 uptake are lower; mitochondrial, serum BDNF/BDNF ratio, and synaptic mitochondria from lipid peroxidation are higher [7, 8].



Restoring brain energy in older age

Two mildly depressed, non-demented male subjects 70 and 80 years old were treated with acetyl-L-carnitine at a dose of 3 g daily for 12 weeks. **Acetyl-L-carnitine increased brain prefrontal phosphocreatine levels which directly correlated with an improvement in depressive symptoms.**

Bipolar Disord. 2002 Feb;4(1):61-6.

Brief Report

³¹P-MRS study of acetyl-L-carnitine treatment in geriatric depression: preliminary results

Polgrew JW, Levin J, Gordon S, Siegel JA, Soren-Schneider EJ, Panchalingam K, McSweeney RT. ³¹P-MRS study of acetyl-L-carnitine treatment in geriatric depression: preliminary results. *Bipolar Disord* 2002; 4: 61-66. © Munksgaard, 2002

Objective: The 12-week study of two elderly, depressed subjects investigated the effect of acetyl-L-carnitine (ALCAR) treatment on the Hamilton Depression Rating Scale (HDRS) and on expression of high-energy phosphate and membrane phospholipid metabolites.

Methods: Two mildly depressed (HDRS 15, 20), non-demented male subjects 70 and 80 years old were compared with six non-demented controls (all male, mean age of 73.5 ± 5.6 years). High-energy and membrane phospholipid metabolites were measured by phosphorus magnetic resonance spectroscopy (³¹P-MRS) analysis. HDRS and ³¹P-MRS measurements were taken at entry, 6 and 12 weeks for the depressed subjects.

Results: ³¹P-MRS analysis revealed elevated levels of phosphocreatine (PME) (~3) in the prefrontal region of these mildly depressed subjects, which decreased with ALCAR treatment and showed a trend for normalization of the PME (~1) levels with HDRS. ALCAR treatment also resulted in increasing levels of the prefrontal phosphocholine (PCr), which correlated with HDRS.

Conclusions: In the prefrontal region, the mildly depressed subjects compared with controls had elevated PME (~3) levels which normalized after 12 weeks of ALCAR and increased PCr levels after ALCAR treatment. These preliminary findings suggest further studies are warranted.

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Key words: acetyl-L-carnitine, geriatric depression, magnetic resonance spectroscopy, phosphocreatine, phosphocholine

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The clinical response to antidepressant treatment in later life follows a variable temporal response, with a median time to remission of 12 weeks (1). Never antidepressant still demonstrate a disturbing side-effect profile in this fragile patient population (2, 3). Thus, there is a need for the development of newer antidepressants. One such candidate is acetyl-L-carnitine (ALCAR), a molecule that is naturally present in human brain (4) demonstrating both low side effects (5).

Seven parallel, double-blind, placebo-controlled studies have assessed ALCAR efficacy in various forms of geriatric depression (6). RCT (7). Phosphorus magnetic resonance spectroscopy (³¹P-MRS) directly provides information on membrane phospholipid and high-energy phosphate metabolites in defined, localized brain regions.

Although in vivo ³¹P-MRS studies in major depression are limited, there is evidence of altered high-energy phosphate and membrane phospholipid metabolites in the prefrontal and basal ganglia regions (for review, see Refs 8, 9). In a recent study, increased levels of prefrontal membrane phospholipid, i.e. increased phosphocholine (PME) levels, in the frontal lobe of major depressed subjects compared with controls was reported (9). Kato and colleagues (10) also observed higher PME levels in bipolar subjects in their depression phase compared with the euthymic state. In terms of high-energy phosphate, reduced levels of adenosine triphosphate (ATP) have been observed in both the frontal and basal ganglia of major depressed subjects (9). The level of the high-energy phosphate buffer, phosphocreatine (PCr),

Restoring brain energy in older age

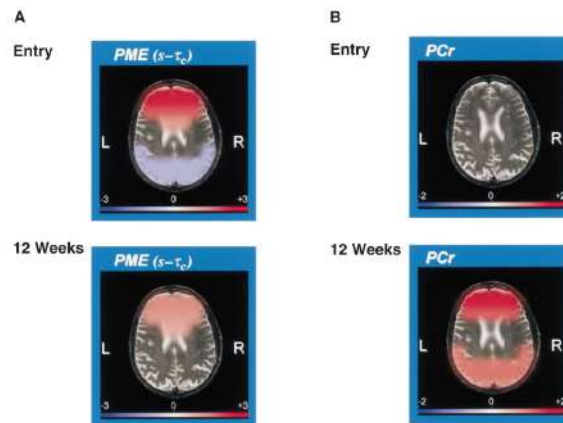


Fig. 3. Z-scores indicated by a color scale of the two mildly depressed subjects compared with controls at entry and 12 weeks for (A) PME($t - t_0$) and (B) PCr metabolite levels for those regions with Z-scores greater than 1. The intensity of the colour is scaled to the z-score (mean difference/SD) given on the scale below the image. Z-scores for PME($t - t_0$) and PCr levels in the frontal region exceed 3.0 and 2.0, respectively.

Bipolar Disord. 2002 Feb;4(1):61-6.

Age related depression

“Twelve RCTs (11 of which were ALC monotherapy) with a total of 791 participants were included. Pooled data across nine RCTs (231 treated with ALC versus 216 treated with placebo and 20 no intervention) showed that **ALC significantly reduced depressive symptoms**. In three RCTs comparing ALC versus antidepressants (162 for each group), **ALC demonstrated similar effectiveness compared with established antidepressants** in reducing depressive symptoms. In these latter RCTs, **the incidence of adverse effects was significantly lower in the ALC group than in the antidepressant group**. Subgroup analyses suggested that **ALC was most efficacious in older adults.**”

Psychosom Med. 2018 Feb/Mar;80(2):154-159.

SYSTEMATIC REVIEW/META-ANALYSIS

Acetyl-L-Carnitine Supplementation and the Treatment of Depressive Symptoms: A Systematic Review and Meta-Analysis

Nicola Veronesi, MD, Brandon Stubbs, PhD, Marco Salini, MD, Olufemi Ajayokun, PhD, Andrea Catalano, MD, and Stefania Nigam, MD

OBJECTIVE: Deficiency of acetyl-L-carnitine (ALC) seems to play a role in the risk of developing depression, indicating a hypothesis of fatty acid transport across the blood-membrane interface. However, data about ALC supplementation in humans are limited. We thus conducted a systematic review and meta-analysis investigating the effect of ALC on depressive symptoms across randomized-controlled trials (RCTs).

DESIGN: A literature search in major databases, without language restriction, was conducted from search until 31 December 2016. Eligible studies were RCTs of ALC alone or in combination with antidepressant medication, with a control group taking placebo, no treatment or antidepressant. Standardized mean differences (SMDs) and 95% confidence intervals (CI) were used for summarizing outcomes with a random-effect model.

RESULTS: Twelve RCTs (11 of which were ALC monotherapy) with a total of 791 participants (mean age = 54 years, 56 female - 45%) were included. Pooled data across nine RCTs (231 treated with ALC versus 216 treated with placebo and 20 no intervention) showed that ALC significantly reduced depressive symptoms (SMD = -1.03, 95% CI = -1.08 to -0.97, $P < 0.001$). In three RCTs comparing ALC versus antidepressants (162 for each group), ALC demonstrated similar effectiveness compared with established antidepressants in reducing depressive symptoms (SMD = -0.95, 95% CI = -1.22 to -0.67, $P = 0.15$). In three other RCTs, the incidence of adverse effects was significantly lower in the ALC group than in the antidepressant group. Subgroup analyses suggested that ALC was most efficacious in older adults.

CONCLUSIONS: ALC supplementation significantly decreases depressive symptoms compared with placebo or intervention, while offering a comparable effect with that of established antidepressants across with these adverse effects. Future large-scale trials are required to investigate these findings.

KEY WORDS: acetyl-L-carnitine, depression, meta-analysis.

INTRODUCTION

Depression is common, affecting an estimated 100 million people worldwide, and it was the second leading cause of global disability in 2010 according to the recent global burden of disease survey (1). Depression is also associated with greatly reduced quality of life, heightened physical comorbidity (2,3), and increased mortality (4). Unfortunately, the prevention and management of depression is a global priority (5). Moreover, depression is pervasive across both sexes and the age spectrum, and is often comorbid with physical health conditions such as diabetes (6), fibromyalgia (7), and dementia (8).

Several studies have been conducted on the elevated risk of depression. Neuroimaging has suggested that alterations of fatty acids and lipid metabolism, important cofactors of neuroplasticity, often occur in depressed persons (9). Given that carnitine assists in the activity of several neurotrophic factors, cell membrane lipid metabolism, and neurotransmission in nervous tissues, an increasing body of research has suggested a potential role of carnitine supplementation in treating depression (9).

From a molecular viewpoint, carnitine acts as a carrier of fatty acids across the inner membrane of mitochondria, the site of β -oxidation (10). Of particular interest, acetyl-L-carnitine (ALC) has been shown to be a neuroprotective agent (11).

ALC - acetyl-L-carnitine. **EB** - evidence-based practice. **OR** - odds ratio. **SMD** - standardized mean difference.

DISCLOSURE OF INTEREST: None.

FINANCIAL DISCLOSURE: The authors have indicated no financial conflicts of interest.

STATEMENT OF AUTHORSHIP: All authors were involved in the design and conduct of the study, collection, management, analysis, and interpretation of the data, and in the writing, review, and approval of the manuscript.

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Psychosomatic Medicine, Volume 80, Number 2, February 2018



Mild cognitive impairment

A meta-analysis of 21 placebo-controlled studies of ALC for mild cognitive impairment (MCI) and mild (early) Alzheimer's disease found a **beneficial effect of ALC on both the clinical scales and the psychometric tests with benefits observed in memory, cognitive function and mood**. Doses were mostly 1500 mg to 2000 mg daily and benefits were noticed within 3 months and increased over time.

Int Clin Psychopharmacol. 2003 Mar;18(2):61-71.

Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease

Stuart A. Montgomery, L.J. Thal and R. Arment

OBJECTIVE: The efficacy of acetyl-L-carnitine (ALC) in the treatment of mild cognitive impairment (MCI) and mild (early) Alzheimer's disease (AD) was investigated with a meta-analysis of double-blind, placebo-controlled, prospective, parallel-group comparative studies of at least 3 months duration. The location of the studies was in 10 countries and the study dates varied between studies from 1.6 to 10 years. An effect size was calculated to reflect the results of the variety of measures used in the studies.

DESIGN: A meta-analysis of double-blind, placebo-controlled, prospective, parallel-group comparative studies of at least 3 months duration. The location of the studies was in 10 countries and the study dates varied between studies from 1.6 to 10 years. An effect size was calculated to reflect the results of the variety of measures used in the studies.

RESULTS: The effect sizes from the comparative were integrated into an overall summary effect size. The effect size for the Clinical Global Impression of Change (CGI-C) was calculated separately. Meta-analysis showed a significant advantage for ALC compared to placebo for the integrated summary effect (SMD_{total} = 0.285, 95% confidence interval (CI) = 0.167-0.403) and CGI-C (SMD_{total} = 0.332, 95% CI = 0.18-0.47). The beneficial effects were seen on both the clinical scales and the psychometric tests. The advantage for ALC was seen by the time of the first assessment at 3 months and increased over time. ALC was most effective in all studies, for the Psychogeriatrics (18/61-71) in 2003 (Supportive Evidence 4) studies.

CONCLUSIONS: ALC is a neuroprotective agent (11).

KEY WORDS: acetyl-L-carnitine, dementia, cognitive impairment, Alzheimer's disease, placebo-controlled, meta-analysis.

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RECEIVED FOR PUBLICATION: March 2003; accepted 8 September 2003.

INTRODUCTION

A review of randomized prospective double-blind placebo-controlled clinical trials of the literature on the use of acetyl-L-carnitine (ALC) in the treatment of mild cognitive impairment (MCI) and mild (early) Alzheimer's disease (AD) has suggested that ALC may be effective in improving cognitive deficits or in delaying the progressive decline of AD patients.

ALC is the most common natural short-chain acetyl-carnitine form of carnitine and is actively transported across the blood-brain barrier (Barron et al., 1993). L-carnitine functions physiologically as a shuttle because the carnitine and acetyl-L-carnitine (ALC) fatty acids, thereby participating in cellular energy metabolism and removal of toxic acetylacetates of fatty acids that accumulate when normal pathological conditions do not allow a complete oxidative catabolism (Hagenberger, 1982; Paolo et al., 1996). ALC also acts as a partial direct cholinergic agonist (Hagenberger et al., 1991) and can be converted to acetylcholine (ACh) and AChE (Hagenberger, 1982). In animal models, ALC has been reported to protect against and partially reverse memory impairment in transgenic mouse and aging models (Villal et al., 1996; Paolo et al., 1996; Banti et al., 1998; Makris et al., 1998; Banti et al., 1992). In clinical settings, some groups have

found that ALC (1500 mg daily) significantly improved memory and cognitive function in AD patients (Banti et al., 1998) and in improving cognitive deficits in aged non-AD patients (Banti et al., 1998).

It is possible that an effect in mild cognitive impairment (MCI) and AD may be mediated via the biological effects of acetyl-L-carnitine. In some clinical studies, ALC was effective already after 3-5 months of treatment (Agodi, 1995; Dolaguerre et al., 1993; Banti et al., 1998), which might indicate that its involvement in cellular energy production and its cholinergic function are important for clinical efficacy. However, the mechanism of ALC might be expected to benefit from time alone.

A majority of the early studies indicated that ALC was effective, although a more long-term controlled study (Thal et al., 1996) in mild-to-moderate AD patients lasting for 1 year did not demonstrate any difference from placebo (Hagenberger, 1982). Two other large placebo-controlled 1-year studies in mild-to-moderate AD patients (Spagnoli et al., 1995; Banti et al., 1998) also failed to show a statistically significant superiority of ALC over placebo in clinical as well as in psychometric outcomes. The latter two studies recruited mainly older cases, whereas the majority of the cases in the study of Thal et al. (1996)

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Age related fatigue

In a 6-month randomized controlled trial, centenarians (n=66) with onset of fatigue after even slight physical activity received either 2,000 mg L-carnitine once daily or placebo. Compared to placebo, **L-carnitine-treated centenarians had significant improvements in total fat mass, total muscle mass, plasma concentrations of carnitines (total carnitine, long-chain acylcarnitine, short-chain acylcarnitine), physical fatigue, mental fatigue, fatigue severity, and cognitive function.**

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L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial¹⁻³

Abstract: Malygina, Lina, Casanovi, Silvia, Pini, Giuseppe, Marco, Vincenzo, Valentini, Cristina, and Marinoni, Mirko

Background: Centenarians are chronologically younger, showing increased health, independence, and cognitive functions. L-carnitine is reported to enhance energy metabolism.

Objective: This study evaluated the effects of carnitine on physical and mental fatigue and on cognitive functions of centenarians. Design: This was a placebo-controlled, randomized, double-blind, 2-phase study. Forty-two centenarians with onset of fatigue after even slight physical activity were recruited for the study. The 2 groups received either 2 g L-carnitine once daily (n = 21) or placebo (n = 21). Efficacy measures included changes in total fat mass, total muscle mass, serum carnitine, and acylcarnitine, physical and mental fatigue, and cognitive functions.

Results: At the end of the study, both the carnitine-treated and placebo-treated centenarians compared with the placebo group showed significant improvements in the following markers: total carnitine (+1.80 compared with 0.00, P < 0.001), total acylcarnitine (+1.00 compared with -0.20, P < 0.001), plasma long-chain acylcarnitine (+0.30 compared with -0.10, P < 0.001), and plasma short-chain acylcarnitine (+0.10 compared with -0.10, P < 0.001). Significant differences were also found in physical fatigue (-4.00 compared with -1.00, P < 0.001), mental fatigue (-3.75 compared with 0.00, P < 0.001), and cognitive functions (+0.00 compared with 0.00, P < 0.001). Conclusions: The study advances the role of carnitine in the maintenance of health, muscle mass, and cognitive functions in centenarians.

KEY WORDS: L-carnitine, acylcarnitine, centenarians, fatigue, cognitive functions

INTRODUCTION: Age is characterized by a slow decline of the physiological functions, with progressive deterioration of organ and system functions. The decline of the organ and system functions is associated with reduced level of the ability to perform energy metabolism. Mitochondria, because of their role in energy production, have attracted the attention of scientists interested in identifying the causes of energy production with aging and age-related diseases. L-carnitine is a naturally occurring



Age related frailty

In a randomized controlled trial, acetyl-L-carnitine (1,500 mg twice daily) was administered to pre-frail older patient over a 3-month intervention. Compared to placebo, **acetyl-L-carnitine treatment significantly reduced C reactive protein, increased serum-free carnitine and acetyl carnitine, improved cognitive function (Mini-Mental State Examination) and improved physical functional (6-minute walk test).**

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Research Article

Acetyl-L-carnitine Shows the Progression from Pre-frailty to Frailty in Older Subjects: A Randomized Interventional Clinical Trial

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Secondary prevention of CVD

An analysis pooling the collective data from 13 clinical trials including 3629 people in total examined the ability of L-carnitine to reduce cardiovascular disease and death in people who had previously had a heart attack (acute myocardial infarction). Compared with placebo or no carnitine the analysis found that L-carnitine supplementation resulted in a:

- 27% reduction in death from all-causes
- 65% reduction in ventricular arrhythmias
- 40% reduction in anginal symptoms

Mayo Clin Proc. 2013 Jun;88(6):544-51.

ORIGINAL ARTICLE

L-Carnitine in the Secondary Prevention of Cardiovascular Disease: Systematic Review and Meta-analysis

James J. DiNicolantonio, PharmD, Carl J. Lavie, MD, Hasan Faruqi, MD, Arthur R. Meneses, MD, and James H. O'Keefe, MD

Abstract

Objective: To evaluate the effects of L-carnitine compared with placebo or control on morbidity and mortality in the setting of acute myocardial infarction.

Methods: A systematic review and meta-analysis of 13 controlled trials (91-1928) was conducted to determine the effects of L-carnitine vs placebo or control on morbidity, ventricular arrhythmias (VAs), angina, heart failure, and mortality. These trials were identified via searches of the Cochrane MEDLINE, EMBASE, and Excerpta Medica Database databases between May 1, 2012, and August 15, 2012.

Results: Compared with placebo or control, L-carnitine was associated with a significant 27% reduction in all-cause mortality (odds ratio, 0.73; 95% CI, 0.54-0.99; P=0.04; meta-OR, 0.76; 95% CI, 0.64-0.90; P<0.01), a highly significant 65% reduction in VAs (OR, 0.35; 95% CI, 0.21-0.58; P<0.001), and a significant 40% reduction in the development of angina (OR, 0.60; 95% CI, 0.40-0.92; P=0.0001), with no reduction in the development of heart failure (OR, 0.93; 95% CI, 0.67-1.29; P=0.22) or myocardial infarction (OR, 0.78; 95% CI, 0.43-1.48; P=0.43).

Conclusion: Compared with placebo or control, L-carnitine is associated with a 27% reduction in all-cause mortality, a 65% reduction in VAs, and a 40% reduction in anginal symptoms in patients experiencing an acute myocardial infarction. Further study with large randomized controlled trials of this intervention and adjuvancy therapy in the secondary setting is warranted.

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Background: Although therapies for acute coronary syndrome (ACS), including primary and secondary prevention, dual antiplatelet therapy (DAPT), statins, angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and calcium channel blockers (CCBs), have significantly improved clinical outcomes, adverse cardiovascular (CV) events still occur frequently after ACS. One promising therapy for improving cardiac health involves using L-carnitine to improve free fatty acid (FFA) and glucose oxidation. Targeting the cardiac metabolic pathway using L-carnitine is an alternative strategy for improving morbidity and mortality in patients who have experienced an acute myocardial infarction (AMI).

L-carnitine, a naturally occurring, plays an important role in energy production in the myocardium and has been shown to transport free fatty acids into the mitochondria, thus increasing the potential substrate for oxidation (metabolism) in the heart.¹ Moreover, L-carnitine has been shown to prevent fatty acid ester accumulation that occurs during ischemic stress, which may lead to fatal ventricular arrhythmias (VAs).^{2,3} An experimental carnitine leak has quickly diminished during an ischemic event, exogenous supplementation with L-carnitine has been shown to rapidly replenish myocardial carnitine levels and improve cardiac metabolic and left ventricular (LV) function.^{4,5} Furthermore, compared with placebo, a meta-analysis of 6 studies demonstrated a significant reduction in LV dilation in the first year after an AMI with the use of L-carnitine.⁶ The prevention of LV dilation and the prevention of early discharge after an AMI is, indeed, clinically important, as LV dilation is a well-documented predictor of progression to heart failure (HF) and death.⁷

Thus, we sought to determine the effects of L-carnitine compared with placebo or control in patients experiencing an AMI by performing a systematic review and meta-analysis of available studies.

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Mayo Clin Proc. • June 2013;88(6):544-51 • doi:10.1016/j.mayocp.2013.04.007
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Clinical use of acetyl-L-carnitine

People who may be more likely to respond:

- Symptoms of pain (e.g., diabetic neuropathy, fibromyalgia, migraine).
- Symptoms of fatigue (e.g., age-related fatigue, chronic fatigue syndrome).
- Older age.
- Low serum acetyl-L-carnitine.
- Elevated inflammatory biomarkers.
- Insulin resistance.

Dose and duration:

- 3 grams daily, in divided doses, for at least 8-weeks (onset of action has been reported in as little as 1-week).



Clinical use of acetyl-L-carnitine

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Creatine

Creatine deficiency

- Muscle creatine levels are typically lower in vegetarians.¹
- Elderly people may not consume as much meat or seafood in their diet due to difficulty digesting these food products.²
- Older individuals >60 years with low dietary creatine intake (<0.95 grams/day) have poorer cognitive function compared to those consuming more dietary creatine (>0.95 grams/day).³
- Around 70% of adults ≥65 years consumed less than the recommended amounts of creatine in their diet (<0.95 grams per day), and low dietary creatine intake was associated with a greater risk of angina pectoris and liver conditions compared to those consuming ≥1.0 grams/day of dietary creatine.⁴
- Higher creatine intake (>1 gram) is inversely associated with all-cause mortality.⁵
- Higher dietary creatine intake is linked to reduced biological age acceleration and mortality risk as estimated by epigenetic biomarkers.⁶

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Brain energy, not just for muscle

Consumption of 20 g creatine-mono-hydrate a day for 4 weeks resulted in a **statistically significant** in brain creatine levels measured by ¹H MRS by, on average, 4.7% in grey matter and 11.5% in cerebral white matter.

Am J Physiol. 1999 Sep;277(3):R698-704.

Increase of total creatine in human brain after oral supplementation of creatine-mono-hydrate

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Abstract. Creatine is a naturally occurring nitrogenous base that is synthesized in the liver and kidney, and its concentration in muscle is high. It is transported to other tissues via the blood. Creatine is converted to creatinine in the blood and excreted in the urine. Creatine is also synthesized in the brain. The aim of this study was to investigate the effect of oral supplementation of creatine-mono-hydrate on brain creatine levels. Ten healthy young men (age 23.5 ± 1.5 years) participated in a randomized, double-blind, placebo-controlled study. They received either 20 g of creatine-mono-hydrate or a placebo daily for 4 weeks. Brain creatine levels were measured by ¹H magnetic resonance spectroscopy (MRS) before and after the 4-week period. The results showed that oral supplementation of creatine-mono-hydrate significantly increased brain creatine levels in both grey matter (4.7%) and cerebral white matter (11.5%). There were no significant changes in muscle creatine levels or in creatinine excretion. These findings suggest that oral supplementation of creatine-mono-hydrate can increase brain creatine levels, which may have implications for brain energy metabolism and cognitive function.

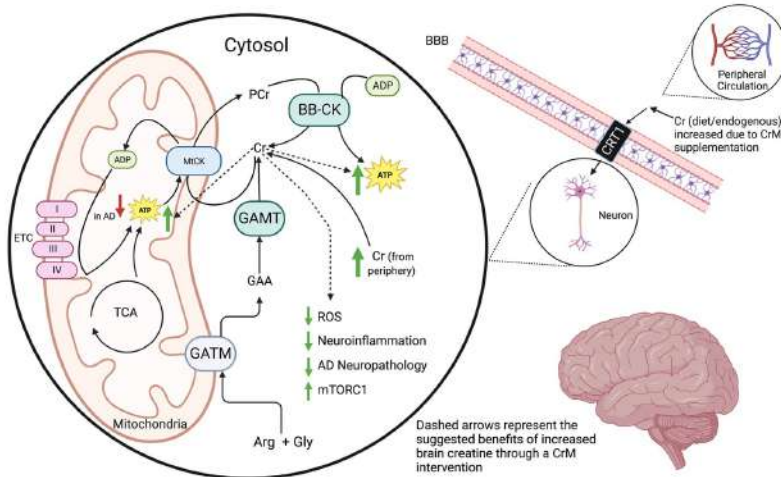
Introduction. Creatine is a naturally occurring nitrogenous base that is synthesized in the liver and kidney, and its concentration in muscle is high. It is transported to other tissues via the blood. Creatine is converted to creatinine in the blood and excreted in the urine. Creatine is also synthesized in the brain. The aim of this study was to investigate the effect of oral supplementation of creatine-mono-hydrate on brain creatine levels. Ten healthy young men (age 23.5 ± 1.5 years) participated in a randomized, double-blind, placebo-controlled study. They received either 20 g of creatine-mono-hydrate or a placebo daily for 4 weeks. Brain creatine levels were measured by ¹H magnetic resonance spectroscopy (MRS) before and after the 4-week period. The results showed that oral supplementation of creatine-mono-hydrate significantly increased brain creatine levels in both grey matter (4.7%) and cerebral white matter (11.5%). There were no significant changes in muscle creatine levels or in creatinine excretion. These findings suggest that oral supplementation of creatine-mono-hydrate can increase brain creatine levels, which may have implications for brain energy metabolism and cognitive function.

Methods. All studies were conducted at 20 °C with the standard imaging protocol. The subjects received either 20 g of creatine-mono-hydrate or a placebo daily for 4 weeks. Brain creatine levels were measured by ¹H magnetic resonance spectroscopy (MRS) before and after the 4-week period. The results showed that oral supplementation of creatine-mono-hydrate significantly increased brain creatine levels in both grey matter (4.7%) and cerebral white matter (11.5%). There were no significant changes in muscle creatine levels or in creatinine excretion. These findings suggest that oral supplementation of creatine-mono-hydrate can increase brain creatine levels, which may have implications for brain energy metabolism and cognitive function.

Conclusion. Oral supplementation of creatine-mono-hydrate significantly increased brain creatine levels in both grey matter (4.7%) and cerebral white matter (11.5%). There were no significant changes in muscle creatine levels or in creatinine excretion. These findings suggest that oral supplementation of creatine-mono-hydrate can increase brain creatine levels, which may have implications for brain energy metabolism and cognitive function.



Creatine physiology in the brain and proposed benefits



Curr Dev Nutr. 2023 Sep 29;7(11):102011.



Creatine for muscle, bone and risk of falls

“Creatine supplementation has shown **potential to enhance bone mineral** in some but not all studies and seems to affect the activation of cells involved in both bone formation and resorption. Creatine has the potential to **decrease the risk of falls** experienced by aging adults which would subsequently reduce the risk of fracture. Finally, preliminary evidence suggests that creatine may have **anti-inflammatory effects** during times of elevated metabolic stress, such as during extended/intense aerobic exercise.”

J Clin Med. 2019 Apr 11;8(4):488..

Effectiveness of Creatine Supplementation on Aging Muscle and Bone: Focus on Falls Prevention and Inflammation

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Abstract: Sarcopenia, defined as the age-related decrease in muscle mass, strength and physical performance, is associated with reduced bone mass and elevated low-grade inflammation. From a healthy aging perspective, interventions which overcome sarcopenia are clinically relevant. Accumulating evidence suggests that exogenous creatine supplementation has the potential to increase aging muscle mass, muscle performance, and decrease the risk of falls and possibly attenuate inflammation and loss of bone mineral. Therefore, the purpose of this review is to: (1) summarize the effects of creatine supplementation, with and without resistance training, in aging adults and discuss possible mechanisms of action; (2) evaluate the effects of creatine on bone biology and risk of falls; (3) evaluate the potential anti-inflammatory effects of creatine and (4) decrease the safety of creatine supplementation in aging adults.

Keywords: sarcopenia; dysregulation; mechanisms; exercise; functionality; safety

1. Introduction

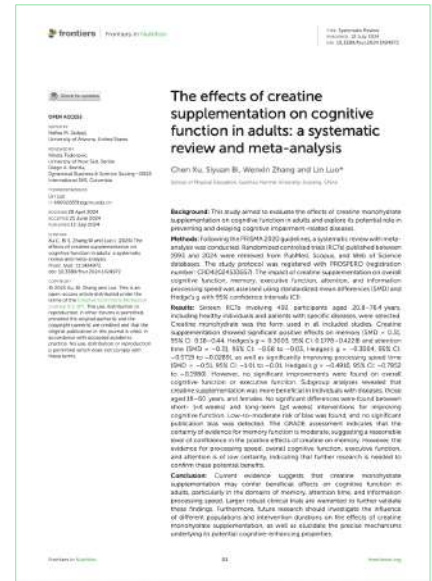
In 2016, the World Health Organization established an International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code for sarcopenia as a means to better diagnose, assess and treat the disease [1]. The European Working Group on Sarcopenia in Older People recently defined sarcopenia as a disease characterized by low muscle strength, muscle quantity/quality and physical performance [1]. Sarcopenia typically occurs in >25% of adults >65 years of age [1] and is associated with reduced bone mass [2] and elevated low-grade inflammation (i.e., “inflammaging”) [3]. The age-related loss in bone mass and bone strength (i.e., osteoporosis) increases bone fragility and, along with an increased risk for falls, this increases risk of subsequent fracture [4]. Inflammaging has a negative effect on muscle protein metabolism and cellular cell function [5], two main contributing factors of sarcopenia (for a comprehensive and detailed review on the mechanisms of sarcopenia, please see [7]). The age-related loss in muscle mass is a result



Creatine for cognitive function

A systematic review and meta-analysis of sixteen randomized controlled trials examining the impact of creatine monohydrate found that **creatine supplementation showed significant positive effects on memory, attention time, processing speed time**, however no significant improvements were found on overall cognitive function or executive function. Subgroup analyses revealed that creatine supplementation was more beneficial in individuals with diseases, those aged 18-60 years, and females.

Front Nutr. 2024 Jul 12;11:1424972.



Creatine for cognition in older age

A systematic review of creatine and cognition in older adults, including two double-blind interventions and four studies cross-sectional studies suggested benefit with **five of the six (83.3%) studies reporting a positive relationship between creatine and cognition** in older adults, particularly in the domains of memory and attention.

Nutr Rev. 2025 Sep 13:nuaf135.



Creatine for Alzheimer's disease

A single-arm pilot trial investigated the feasibility of creatine (20 g daily) for 8-weeks in patients with Alzheimer's disease (n=19). Supplementation significantly **increased serum creatine and brain creatine and improved cognitive function.**

Alzheimers Dement (N Y). 2025 May 19;11(2):e70101.

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RESEARCH ARTICLE

Creatine monohydrate pilot in Alzheimer's: Feasibility, brain creatine, and cognition

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Abstract
BACKGROUND: Preclinical studies suggest that creatine monohydrate (CMH) improves cognition and Alzheimer's disease (AD) biomarkers. However, there is currently no clinical evidence demonstrating the effects of CMH in patients with AD.
METHODS: In this single-arm pilot trial, we investigated the feasibility of 20g/day CMH for 8 weeks in 20 patients with AD. We measured compliance throughout, serum creatinine at baseline, 4 weeks, and 8 weeks, and brain total creatine (TCr) and cognition (National Institute of Health-24-Item Brief, Mini-Mental State Examination [MMSE]) at baseline and 8 weeks.
RESULTS: Nineteen participants achieved the target of >80% compliance with the CMH intervention. Serum Cr was elevated at 4 and 8 weeks ($p < .003$) and brain TCr increased by 11% ($p < .001$). Cognition (improvement global ($p = .02$) and fluid ($p = .004$) composite, the Sorting ($p = .001$), Oral Reading ($p < .001$), and Fluency ($p = .02$) tests).
CONCLUSION: Our data suggest that CMH supplementation is feasible in AD and provides preliminary evidence for future efficacy and mechanism studies.
Trial Registration: ClinicalTrials.gov; NCT05393933, registered on May 20, 2022.

KEYWORDS
Alzheimer's disease, biomarkers, brain creatine, cognition, creatine monohydrate, magnetic resonance spectroscopy, pilot trial

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Address: Smith, Aaron N. 2025, 11(2), e70101.
https://doi.org/10.1002/alz.15001

Clinical use of creatine

People who may be more likely to respond:

- Symptoms of poor cognition, poor memory, mental fatigue.
- Poor muscle strength, physical fatigue.
- Vegetarian or vegan diet.

Dose and duration:

- 3-6 grams, once daily, for at least 4-8 weeks.
- A loading phase of 20 g/day (4 x 5 g) for 5 days and a maintenance dose of 3 to 5 g/day is sometimes recommended. However, similar (intramuscular) phosphocreatine levels can be accomplished by taking 3 g/day over 30 days. After 2 days of loading, maximal accumulation of (intramuscular) creatine occurs and therefore amounts of 20 g/day are unnecessary and will minimise GI side-effects associated with 20 g doses.

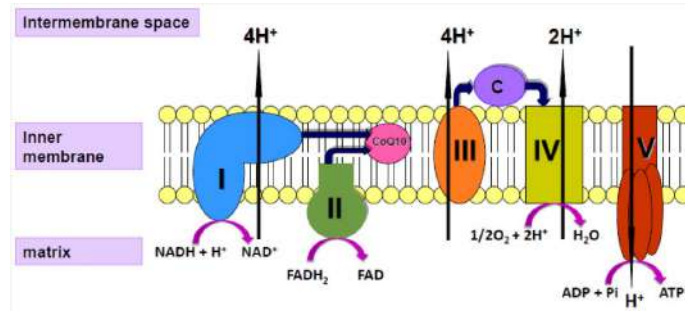
Clinical use of creatine

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CoQ10

CoQ10



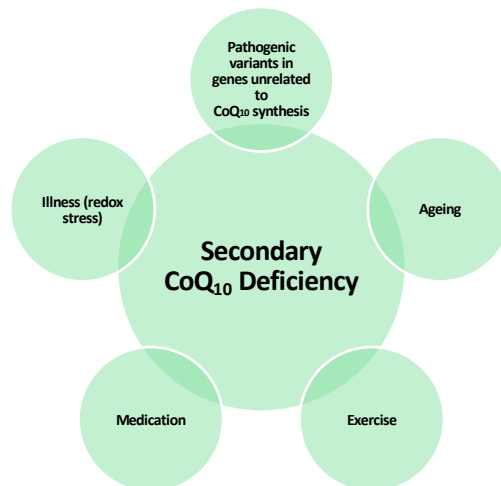
“CoQ10 has a key role in the process of cellular energy supply via oxidative phosphorylation within mitochondria, **shuttling electrons from complexes I and II to complex III** of the mitochondrial respiratory chain; CoQ10 is also a **powerful lipid-soluble antioxidant**, protecting cell membranes from free radical-induced oxidative damage.”

Antioxidants (Basel). 2021 Dec 21;11(1):2.



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Factors causing secondary CoQ₁₀ deficiency



Antioxidants (Basel). 2023 Jul 21;12(7):1469.

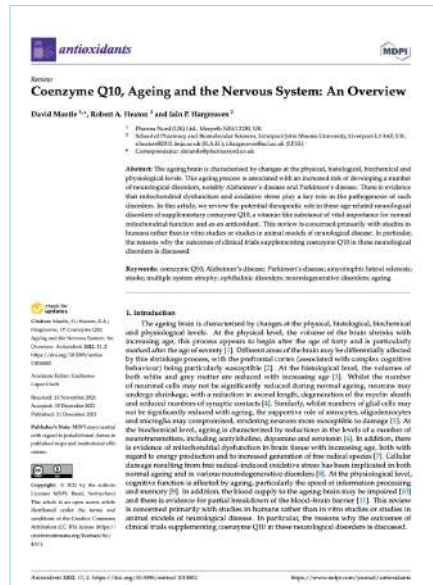


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CoQ10 decline with age

“Relatively little data are available in the published literature regarding changes in CoQ10 levels in various human tissues as a function of age. However, in general terms, optimum CoQ10 production occurs around 25 years of age, with a subsequent age-related decline that may vary in different tissues. For example, in heart tissue, the production of CoQ10 at age 65 is approximately half of that at age 25 years.”

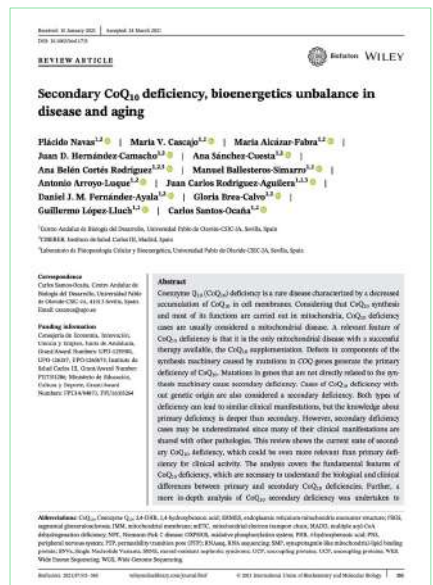
Antioxidants (Basel). 2021 Dec 21;11(1):2



CoQ10 decline and healthspan

“Through its relationship with mitochondrial dysfunction, CoQ10 deficiency has been associated with many age-related diseases, such as type 2 diabetes or insulin resistance, cardiovascular disease, neurodegeneration, chronic kidney disease, liver disease, inflammaging and immunosenescence, or sarcopenia.”

Biofactors. 2021 Jul;47(4):551-569



CoQ10 for inflammaging

A meta-analysis of thirty-one double-blind randomized controlled trials (n=1517) of CoQ10 supplementation in the general population, including older age participants, on inflammatory biomarkers demonstrated that **supplementation can significantly reduce the levels of circulating CRP, IL-6 and TNF-α** and increase the concentration of circulating CoQ10. Dose response analysis proposes that daily supplementation of **300-400 mg had a superior anti-inflammatory effect.**

Mol Nutr Food Res. 2023 Jul;67(13):e2200800.

Efficacy and Optimal Dose of Coenzyme Q10 Supplementation on Inflammation-Related Biomarkers: A GRADE-Assessed Systematic Review and Updated Meta-Analysis of Randomized Controlled Trials

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Background: Coenzyme Q10 (CoQ10) has become a popular nutritional supplement due to its wide range of beneficial biological effects. Previous meta-analyses show that the administration of CoQ10 on inflammatory biomarkers remains controversial. This meta-analysis aims to assess the efficacy and optimal dose of CoQ10 supplementation on inflammatory indicators in the general population.

Methods and results: Databases were searched up to December 2022 resulting in 6713 articles, of which 33 are retained for full-text assessment and included 1517 subjects. Double-blind randomized controlled trials (RCTs) of CoQ10 supplementation are eligible if they contain Co reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). CoQ10 supplementation can significantly reduce the level of circulating CRP (SMD: -1.43, 95% CI: [-1.87 to -0.99], p < 0.001), IL-6 (SMD: -0.47, 95% CI: [-1.01 to -0.03], p < 0.001), and TNF-α (SMD: -1.06, 95% CI: [-1.58 to -0.55], p < 0.001) and increase the concentration of circulating CoQ10.

Conclusion: This meta-analysis provides evidence for CoQ10 supplementation to reduce the level of inflammatory markers in the general population and proposes that daily supplementation of 300-400 mg CoQ10 shows superior inhibition of inflammatory factors.

1. Introduction

Coenzyme Q10 (CoQ10) is a fat-soluble vitamin that plays a crucial role in cellular energy production and acts as a powerful antioxidant. It is essential for the mitochondrial electron transport chain, where it facilitates the transfer of electrons from NADH and FADH2 to oxygen, ultimately leading to the production of ATP. Additionally, CoQ10 acts as a potent antioxidant, protecting cells from oxidative damage caused by free radicals. In the context of inflammation, CoQ10 has been shown to modulate the expression of various inflammatory markers, including CRP, IL-6, and TNF-α, which are key indicators of systemic inflammation. This meta-analysis aims to evaluate the efficacy and optimal dose of CoQ10 supplementation in reducing these inflammatory markers in the general population.



CoQ10 for cognitive impairment

In a randomized controlled trial, participants diagnosed with mild cognitive impairment (n=69) received either ubiquinol (200 mg once daily) or placebo for 1 year. Supplementation increased plasma CoQ10 and a **subgroup with higher plasma levels (5 µg/mL) exhibited improved cerebral vasoreactivity and reduced inflammation**, although the effect supplementation on neurological improvement was negligible.

Antioxidants (Basel). 2021 Jan 20;10(2):143.

Ubiquinol Supplementation Improves Gender-Dependent Cerebral Vasoreactivity and Ameliorates Chronic Inflammation and Endothelial Dysfunction in Patients with Mild Cognitive Impairment

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Abstract: Ubiquinol may protect endothelial cells from multiple mechanisms that cause endothelial damage and vascular dysfunction, from contributing to dementia. A trial of 69 participants diagnosed with mild cognitive impairment (MCI) received either 200 mg/day ubiquinol (Ub) or placebo for 1 year. Cognitive assessment of patients was performed at baseline and after 1 year of follow-up. Patients' cerebral vasoreactivity was measured using transcranial Doppler ultrasonography, and levels of C-reactive protein (CRP) and interleukin-6 (IL-6) in plasma samples were quantified. Cell viability and necrosis cell death were determined using the microvascular endothelial cell line HMEC1. Coenzyme Q10 (CoQ10) levels increased in patients supplemented for 1 year with ubiquinol versus placebo and the placebo group. Although higher levels were observed in male patients, the higher CoQ10 concentrations in male patients improved cerebral vasoreactivity (CBV) and reduced inflammation, although only in Ub-supplemented men. Neurological improvement was negligible in this study. Furthermore, plasma time Ub-supplemented patients improved the viability of endothelial cells, although only in Ub-supplemented patients. This suggests that ubiquinol supplementation could be recommended in such a concentration of 200 mg/day in plasma in MCI patients as a complement to conventional treatment.

Keywords: coenzyme Q10; brain health; oxidative stress; endothelial function; mild cognitive impairment

1. Introduction

Although the causes of sporadic Alzheimer's disease (AD) are unknown, both genetic and environmental factors play important roles. Lifestyle factors that increase the risk of cardiovascular disease, increase brain aging, and oxidative stress have been linked to AD [1-3]. Patients with mild cognitive impairment (MCI) have an impairment affecting one or more higher cognitive functions—memory loss—the ability to maintain functional independence and skills in their daily living. It often represents a prodromal



CoQ10 and Alzheimer's disease

- Low levels of CoQ10 in blood are associated with an increased risk of developing Alzheimer's disease.¹
- A 16-week randomized controlled trial in subjects with mild to moderate Alzheimer disease found no benefit of 1200 mg CoQ10 daily. Changes in blood CoQ10 levels following supplementation were not measured.²
- Potential reasons for treatment failure include³
 - Low bioavailability supplement formulation (supplement absorption should always be quantified via plasma CoQ10).
 - It is unknown if supplementary CoQ10 can penetrate the blood–brain barrier.
 - Co-administration of a high dose of vitamin E may inhibit access to the brain for CoQ10, via competition for shared lipoprotein or other carrier types.
 - Alzheimer's disease is etiologically heterogeneous, and it is unknown what patient characteristics might influence response to CoQ10.

1. Atherosclerosis. 2014 Dec;237(2):400-3.
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CoQ10 for cardiovascular ageing

“CoQ10 deficiency has been observed in patients with congestive heart failure, angina pectoris, coronary artery disease, cardiomyopathy, and hypertension. The clinical benefits of CoQ10 supplementation in prevention and treatment of cardiovascular diseases have been observed in many trials. CoQ10 may be recommended to patients at risk for or diagnosed with cardiovascular disease as an adjunct to conventional treatment.”

Clin Chim Acta. 2015 Oct 23;450:83-9.



Clinical use of CoQ10

People who may be more likely to respond:

- Plasma CoQ10 <1μmol/l (does not reflect tissue levels).
- Elevated inflammatory biomarkers (CRP, IL-6, TNF-α).
- Elevated oxidative stress (malondialdehyde, total antioxidant capacity, SOD activity).
- Nutrient-drug interactions (statins, beta blockers, propranolol and metoprolol, phenothiazines and tricyclic antidepressants).

Dose and duration:

- 100-300 mg daily, in divided doses, for at least 8-12 weeks.

Clinical use of CoQ10

References:

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Dietary patterns



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Less sugar

Ten healthy normal weight adults were submitted to a high fructose diet (+3.5 g fructose/kg fat-free mass per day) for 7 days. There was a marked impact on a large cluster of genes related to energy metabolism, mitochondrial function, and lipid oxidation, thus supporting the concept that overconsumption of fructose-containing foods could contribute to metabolic deterioration in humans.

Mol Nutr Food Res. 2016 Dec;60(12):2691-2699.

Mol. Nutr. Food Res. 2016; 60(12): 2691-2699 | DOI: 10.1002/mnfr.201600490 | 2691

RESEARCH ARTICLE

Fructose overfeeding in first-degree relatives of type 2 diabetic patients impacts energy metabolism and mitochondrial functions in skeletal muscle

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Scope: The aim of the study was to assess the effects of a high-fructose diet (HF) on skeletal muscle transcriptome response to healthy offspring of patients with type 2 diabetes, a subgroup of cardiovascular genes in metabolic disorders.

Methods and results: Ten healthy normal weight first-degree relatives of type 2 diabetic patients were submitted to a HF (0.5 to 2.5 g fructose/kg fat-free mass per day) during 7 days. A global transcriptomic analysis was performed on skeletal muscle biopsies overlaid with in vivo experiments using primary myotubes. Transcriptome analysis highlighted profound differences in gene expression and mitochondrial pathways representing the whole-body metabolic state. The preferential use of carbohydrates instead of fats. Bioinformatics tools pointed out possible transcription factors and signaling pathways, such as PDK1 and SIRT6. In vivo experiments in human myotubes suggested an indirect action of fructose on skeletal muscle, which seemed to be independent from fructose use and/or excretion.

Conclusion: This study shows, therefore, that a large cluster of genes related to energy metabolism, mitochondrial function, and lipid oxidation was downregulated after 7 days of HF, thus supporting the concept that overconsumption of fructose-containing foods could contribute to metabolic deterioration in humans.

Keywords: Energy metabolism / Gene expression / High-fructose diet / Lipid oxidation / Skeletal muscle

Additional supporting information may be found in the online version of this article at: <http://www.blackwell-synergy.com/doi/full/10.1002/mnfr.201600490>

1 Introduction

In parallel to the dramatic rise in metabolic diseases and obesity observed over the past 30 years, the globalization of obesity is reported in processed food intake in a marked increase in chronic overeating in almost all countries [1–3], and epidemiological studies demonstrated that the consumption of sugar-sweetened beverages (SSBs) is associated with an increased risk of obesity [4, 5].

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Lower unhealthy fat

Insulin-sensitive subjects were fed an isoenergetic high-fat diet (HFD) (50%) for 3-days with muscle biopsies before and after intervention. Oligonucleotide microarray analysis revealed 297 genes were differentially regulated by the HFD. Six genes involved in oxidative phosphorylation (OXPHOS) decreased.

Diabetes. 2005 Jul;54(7):1926-33.

A High-Fat Diet Coordinately Downregulates Genes Required for Mitochondrial Oxidative Phosphorylation in Skeletal Muscle

Lucara M. Sparks, Hui Xi, Robert A. Essi, Randall Myant, Matthew W. Halverson, George A. Bray, and Steven H. Sulz

Obesity and type 2 diabetes have been associated with a high-fat diet (HFD) and reduced mitochondrial mass and function. We hypothesized a HFD and altered expression of genes involved in mitochondrial function and biogenesis. To test this hypothesis, we fed 10 insulin-sensitive males an isoenergetic HFD for 3 days with muscle biopsies before and after intervention. Oligonucleotide microarray analysis revealed 297 genes were differentially regulated by the HFD. (Folded over control, P < 0.001). Six genes involved in oxidative phosphorylation (OXPHOS) decreased. Four were members of mitochondrial complex I, NDUFB, NDUFB2, NDUFB3, and NDUFB4. One was NDUFA10, a complex II and a mitochondrial carrier protein. SLC16A1, Pparg, and peroxisome acyl-CoA oxidase 1 (ACOX1) were upregulated by -30%, P < 0.01 and -25%, P < 0.01, respectively. In a separate experiment, we fed C57BL/6 mice a HFD for 12 weeks and found that this same OXPHOS gene set (11 NDUFBs) were downregulated by -30%, cytochrome C and PGC1α were upregulated by 40%. Combined, these results suggest increased energy HFD downregulates genes necessary for OXPHOS and mitochondrial biogenesis. These changes mirror those observed in diabetic and insulin-resistant and, if untreated, type 2 diabetic subjects. Dysfunction in the premitochondrial constant state (diabetes, HFD, HDM).

A high molecular and structural level analysis of skeletal muscle and mitochondrial function is altered in diabetes as well as in insulin-resistant and obese subjects. In all the aforementioned conditions, the mitochondrial level of expression of the nuclear DNA and synthesis of mitochondria is strongly associated with insulin resistance [1]. We recent studies...



More phytochemicals

“Curcumin, resveratrol, and flavonoids (quercetin EGCG, genistein) most markedly activate the mTOR-regulated gene expression and the posttranscriptional modification of mitophagy-related factors, in addition to promoting the mitogenesis, mitochondrial dynamics, and mitophagy, suggesting that they might be the most promising neuroprotective phytochemicals at least in vitro.”

Int J Mol Sci. 2019 May 17;20(10).



Mitochondria in Neuroprotection by Phytochemicals: Bioactive Polyphenols Modulate Mitochondrial Apoptosis System, Function and Structure

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Abstract: In aging and neurodegenerative illnesses, loss of distinct type of neurons characterizes disease-specific pathological and clinical features, and mitochondria play a pivotal role in neuronal survival and death. Mitochondria are now considered as the organelle to modulate cellular signal pathway and functions, not only to produce energy and reactive oxygen species, oxidative stress, deficit of neurotrophic factors, and multiple other factors impact mitochondrial function and induce cell death. Many functional plant polyphenols, major groups of phytochemicals, are proposed as one of most promising mitochondria-targeting molecules to promote the activity and structure of mitochondria and neurons. Polyphenols can scavenge reactive oxygen and nitrogen species and activate nuclear respiratory transcription factors to regulate expression of genes, coding antioxidant, anti-apoptotic and 2-protein family, and prevention of neurodegeneration. In mitochondria, polyphenols can directly regulate the mitochondrial apoptosis system either by preventing or promoting it. Polyphenols also modulate mitochondrial biogenesis, dynamics (fusion and fission), and autophagy-degradation to keep the quality and number. This review presents the role of polyphenols in regulation of mitochondrial redox state, death signal system, and biogenesis. The bioactive roles properties of polyphenols are associated with conventional regulator of mitochondrial apoptosis system involved in the neuroprotective and anti-oxidative functions. Mitochondria-targeted phytochemicals have been used in the preclinical studies to develop a novel series of neuroprotective and antioxidant compounds, which promote the brain stability and effectiveness. Phytochemicals have shown the multiple beneficial effects in mitochondria, but further investigations is required for the clinical application.

Keywords: phytochemicals; mitochondria; oxidative stress; apoptosis; neuroprotection; inflammation; mitogenesis; biogenesis; mitophagy

1. Introduction
More than 1.5 billion years ago, mitochondria originate from bacterial endosymbionts within some ancestral type of eukaryotes, with containing the nucleus, cytoskeleton, and endomembrane system, but lacking mitochondria [1]. Analysis of mitochondrial genes and genomes organization indicates that mitochondrial genes are derived from a prokaryotic-like ancestor. The rapid evolution enabled mitochondria to acquire specialized factors of bioenergy and bioinformation in the eukaryotes: (a) cellular energy production, (b) calcium (Ca²⁺) and iron homeostasis, (c) cell division, apoptosis, autophagy, (d) stress reduction, and (e) synthesis of proteins, lipids, heme, and non-coding RNAs. Mitochondria produce and use reactive oxygen species (ROS) through oxidative phosphorylation in the...



Lower energy density

Six months of 25% caloric restriction in healthy humans increased the expression of genes involved in mitochondrial biogenesis and mitochondrial DNA copy number. The activity of key mitochondrial enzymes of the tricarboxylic acid cycle, β -oxidation, and the electron transport system, conversely, were unchanged.

PLoS Med. 2007;4(3):e76.

Calorie Restriction Increases Muscle Mitochondrial Biogenesis in Healthy Humans

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ABSTRACT

Background: Calorie restriction without malnutrition extends life span in a range of organisms including insects and mammals and lowers free radical production by the mitochondria. However, the mechanism responsible for this adaptation is poorly understood.

Methods and Findings: The current study was undertaken to examine muscle mitochondrial biogenesis in response to calorie restriction alone or in combination with exercise in 36 young (30.0 ± 1.0 y), overweight (body mass index, 29.8 ± 0.7 kg/m²) individuals randomized into one of three groups for an 8-mo intervention: Control, 10% of energy requirement, CR, 25% calorie restriction and CR. CR alone resulted in weight loss (12.5%), increased energy expenditure (8%), and in the CR group, 24.4% was unchanged, but in CR and CR+EX it was significantly reduced from baseline over the 8 mo period for the loss of metabolic mass (CR: -3.5 ± 0.4 kg; CR+EX: -4.0 ± 0.4 kg; p = 0.0001 and 0.0001, respectively). Mitochondrial DNA content increased by 33% ± 3% in the CR group (p = 0.0001) and 27% ± 4% in the CR+EX group (p = 0.0001) with no change in the control group (p = 0.94). However, the activity of key mitochondrial enzymes of the TCA (isocitrate dehydrogenase, isocitrate lyase, alpha-ketoglutarate dehydrogenase, alpha-ketoglutarate lyase, succinate dehydrogenase, succinate thiokinase) was unchanged. DNA damage was reduced from baseline in the CR (CR: 0.20 ± 0.11 arbitrary units; p = 0.0001) and CR+EX (CR+EX: 0.14 ± 0.11 arbitrary units; p = 0.0011) but not in the control. In primary cultures of human myotubes, a 40% caloric deficit (providing 40% of the energy required for mitochondrial biogenesis) failed to reduce SIRT1 protein levels suggesting that additional factors may regulate SIRT1 activity during CR.

Conclusions: The observed increase in muscle mitochondrial DNA in association with a decrease in white body fat suggest caloric restriction and DNA damage suggest that calorie restriction improves mitochondrial function in young, non-obese adults.

Trial Registry: ClinicalTrials.gov NCT00120625



Dietary ketosis

“...the dramatic shift in energy metabolism and subsequent increase in circulating ketones induced by a ketogenic diet can enhance mitochondrial function and endogenous antioxidant defence. The primary mechanism behind these adaptations appears to be the increased demand for fat oxidation resulting from carbohydrate restriction. However, ketones themselves have important metabolic and signalling effects that enhance mitochondrial function and endogenous antioxidant defence...”

J Nutr Metab. 2018 Feb 11;2018:5157645.

Review Article

Nutritional Ketosis and Mitohormesis: Potential Implications for Mitochondrial Function and Human Health

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Abstract: Mitochondrial function and metabolism are central to human health and disease. Mitochondrial dysfunction is a hallmark of many chronic diseases, including cardiovascular disease, obesity, neurodegenerative diseases, and cancer. Mitochondrial dysfunction is also a key feature of aging. The primary mechanism behind these adaptations appears to be the increased demand for fat oxidation resulting from carbohydrate restriction. However, ketones themselves have important metabolic and signalling effects that enhance mitochondrial function and endogenous antioxidant defence in response to nutritional stress, as well as the potential mechanisms leading to these adaptations.

1. Introduction

All cells of the human body require ATP for fundamental energy needs to support life. Mitochondria produce the majority of ATP. Impaired mitochondrial function is implicated in the majority of adult onset neurodegenerative and degenerative health conditions including obesity, cardiovascular disease, cancer, diabetes, sarcopenia, and neurodegenerative diseases [1]. Much of this association between mitochondrial function and disease can be attributed to excessive mitochondrial production of reactive oxygen species (ROS) [2].

Although mitochondrial ROS (mtROS) are generally considered harmful, which is contrary to the role of high concentrations involve levels of ROS that promote biological processes such as proliferation, differentiation, and immunity [3]. Adaptations that enhance resistance to oxidative stress are also induced by mtROS [4], possibly decreasing mt

ROS production during basal conditions. This adaptive response is called mitohormesis [4-6] and is a pressing mechanism through which lifestyle interventions that enhance mitochondrial function may, in turn, enhance resistance to chronic and degenerative diseases.

By chronically shifting energy metabolism towards fat oxidation and fatty acid oxidation, ketones do not only have a profound effect on mitochondrial function. However, despite the rapidly growing amount of research on ketogenesis and their effects on various disease states, very little attention of this research has focused on mitochondrial function or oxidative stress. The well-established mechanism of oxidative stress induced by a ketogenic diet [7, 8] clearly indicates a potential connection with mitochondrial function. In fact, oxidative stress and mitochondrial [9, 10, 11]. Therefore, the purpose of this review is to describe the current, but limited, understanding of how ketogenesis may affect mitochondrial function and resistance to oxidative



Ketosis, fasting and calorie restriction

A study evaluating the effects of 1-month of calorie restriction (CR), intermittent fasting (IF), a ketogenic diet (KD), and an ad libitum habitual diet (AL) on mitochondrial function in monocytes and its modulation by the gut microbiota (n=44) found that **CR, IF and KD interventions had an increase in the maximal respiration oxygen consumption rate in monocytes compared to that in the AL group.** The improvement in mitochondrial function was associated with a decrease in monocyte dependence on glycolysis after the IF and KD interventions. **Serum lipopolysaccharide and intracellular signalling in monocytes decreased with the three interventions to those in the AL group.**

Clin Nutr. 2024 Aug;43(8):1914-1928.

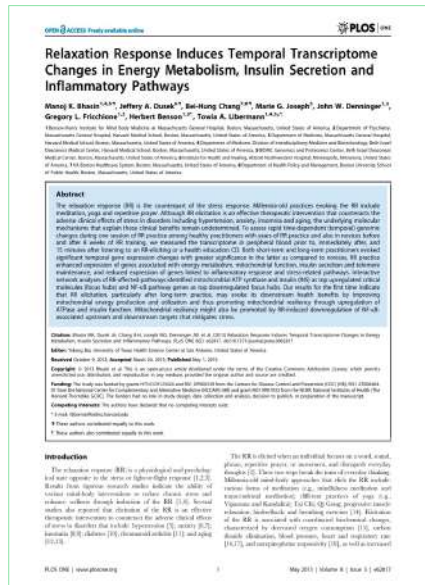


Lifestyle medicine

Relaxation

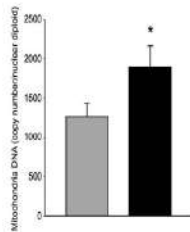
Relaxation practice for 8-weeks (yoga, meditation, repetitive prayer) enhanced expression of genes associated with energy metabolism, mitochondrial function, insulin secretion and telomere maintenance, and reduced expression of genes linked to inflammatory response and stress-related pathways.

PLoS One. 2013 May 1;8(5):e62817.



Exercise

In healthy, older (average age 67 years) men and women 30 minutes of moderate exercise 4-6 days a week for 12-weeks increased cell mitochondria number by 53%.



J Gerontol A Biol Sci Med Sci. 2006 Jun;61(6):534-40



Assessment of mitochondrial function



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Assessing function

“At this time, there are no clinically available tests to directly measure mitochondrial ATP production. [...] there are several indirect measures of mitochondrial dysfunction. Most readily available are blood levels of lactate and pyruvate.”

Integr Med (Encinitas). 2014 Apr; 13(2): 8–15.



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THE PATH AHEAD

Mitochondria—Fundamental to Life and Health
Joseph Pizzorno, ND, Editor in Chief



In the past few years, I have become progressively more aware of the fundamental importance of optimal mitochondrial function for health and the growing body of research showing that dysfunction is surprisingly common and associated with most chronic disease. In my IACJ 12.5 editorial, Lara and I presented helpful clinical points on mitochondrial health from the Institute of Nutritional Medicine conference in Dallas last spring. In my IACJ 13.1 editorial, I stated that glutathione is “... vital to mitochondrial function and maintenance of mitochondrial DNA (mtDNA).” I have found the mitochondrial connection to health so interesting and important that I have now developed a 90-minute lecture on the topic and think the time has come for an editorial.

As illustrated in Table 1, with such a long list of common diseases now caused by or aggravated by mitochondrial dysfunction, it is difficult to overstate its importance.

How Much ATP Does the Body Produce Every Day?
I wish there were some way to cover up the answer—before you, dear reader, answer this question.

Table 1. Partial list of Diseases Caused or Aggravated by Mitochondrial Dysfunction

- Early aging
- Amyotrophic lateral sclerosis
- Alzheimer’s disease
- Autism
- Cardiovascular disease
- Chronic fatigue syndrome
- Dementia
- Diabetes

Blood Molecules to Assess Mitochondrial Function

Molecule	Specificity	Sensitivity	Notes
mtDNA copy #/cell	74% in MDDs	100% in MDDs	
Lactate	34–62%	83–100%	Post prandial best
Pyruvate	50–75%	87%	
Lactate:Pyruvate	69-100%	11-82%	
GDF-15	High	78%	

All are measures of patients with primary mitochondrial disorders.

Hubens WHG, et al. Blood biomarkers for assessment of mitochondrial dysfunction: An expert review. *Mitochondrion*. 2022 Jan;62:187-204.
 Shayota BJ. Biomarkers of mitochondrial disorders. *Neurotherapeutics*. 2024 Jan;21(1):e00325.

Credit: Pizzorno, J. [Presentation]. NMI Summit 2024.



Clinical assessment of CoQ10

CoQ10 is an actionable biomarker of mitochondrial function. Assessments include:

- Plasma reference levels are typically in the range of 0.5–1.7 mM, however plasma CoQ10 status, which is the result of dietary intake and hepatic synthesis, does not reflect that of other tissues.
- Skeletal muscle and skin fibroblasts reference ranges are 140–580 pmol/mg and 39–75 pmol/mg, respectively, and reflect tissue CoQ10 levels.
- Cerebral spinal fluid is considered the appropriate surrogate to evaluate cerebral CoQ10 status, and a tentative reference range of 5.7–9.0 nM has been established.

Hargreaves I, Heaton RA, Mantle D. Disorders of Human Coenzyme Q10 Metabolism: An Overview. *Int J Mol Sci*. 2020 Sep 13;21(18):6695.



“The science behind chronic illness calls for a focus **not on the average** but on **the individual**. Precisely because everyone of us in, in fact, unique, an operating model that treats us as average can’t possibly be effective.”
- Jeffery Bland PhD.