

A Call to Reduce the Incidence of Alzheimer's Disease

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ABSTRACT

Objective: Data is to be reported briefly that appear to indicate that if specific neuro-protective means are applied clinically, the incidence of progressive amnesic cognitive impairment and Alzheimer's disease with severe dementia will be reduced as major health problems for the elderly population in the developed world.

Methods: Much evidence is mini-reviewed suggesting that clinical trials with the dithiol compound alpha lipoic acid and particularly with the stabilized sodium salt of the natural stereoisomer of alpha lipoic acid combined with vitamin C supplementation will reverse mitochondrial bioenergetic decline and will delay the serial progression of late cognitive decline and Alzheimer's disease before severe dementia.

Results: The cited evidence in animals and humans indicates that randomized clinical trial of stabilized sodium R-lipoate supplementation as a micronutrient and as an antioxidant with iron chelating ability, combined with vitamin C, likely will retard significantly the progression of amnesic cognitive impairment and Alzheimer's disease.

Conclusion: A call for urgency with randomized clinical trial appears warranted to reduce the prevalence of worsening of mild cognitive impairment and Alzheimer's disease by such micronutrient and antioxidant means.

INTRODUCTION

Alzheimer's disease (AD) is one of the major health problems in the United States and the developed world. Because the presence of clinical AD doubles with every 5 years after 60, preventing the onset of clinical AD by 5 years would reduce the AD population by half.^{1,2}

About 5.5 million persons in the United States have AD, and the odds of receiving a diagnosis of AD after the age of 85 exceeds one in three.³ Death is said to occur within 3 to 9 years after the diagnosis of AD is made.³ The disease trigger may be some aging-related process other than and before the beta-amyloid hypothesis.³

Oxidative stress-mediated damage in cerebral tissue in AD involving oxidations of nucleic acids, proteins, and lipids are all prominent in the early stages of AD. This oxidative stress damage has been shown to precede the cardinal pathologic manifestations in AD of cerebral plaques laden with beta-amyloid peptide and dystrophic neurites and neurofibrillary tangles of tau proteins.⁴ Similar oxidative damage occurs

in mild cognitive impairment (MCI) preceding AD.⁵

MCI is conceptualized as cognitive decline preceding diagnosable AD.⁶ Prevention of MCI and decline in AD dementia will probably be most effective when the intervention strategy targets a process closely relevant to the disease pathogenesis.^{6,7} Disruption of iron homeostasis is a likely primary seminal event in AD.⁷⁻¹⁰ The critical aging-related process as the disease trigger in AD relates to the oxidative stress-mitochondrial dysfunction hypothesis³ and the oxidative mitochondrial cascade hypothesis of Swerdlow and Khan, in which oxidative damage to DNA, RNA, protein, and lipid is amplified.¹¹ Inflammatory glial reactions result secondarily.³

Mitochondrial-based oxidative stress increases with age.¹¹ The oxidative damage to mitochondrial DNA in human brain is markedly age-dependent, much more so in mitochondrial DNA than in nuclear DNA.¹² However, in a recent review concerning mechanisms in AD³, it was reported that randomized clinical trials of antioxidants in AD have generally failed.¹³ Therefore, the oxidative stress hypothesis for AD may not seem promising for more antioxidant randomized trials. An example is the anti-inflammatory treatment with hydroxychloroquine for 18 months, which did not slow the rate of decline in minimal or mild AD.¹⁴

Nevertheless, randomized clinical trials of alpha lipoic acid or of the sodium salt of R-alpha lipoic acid given orally and synergistically combined with vitamin C have not been done.³ Such trials are now warranted and called for in elderly persons with MCI and AD for the **following reasons**:

1. The continuing prevalence of AD in developed countries with devastating effects personally, socially, and economically. The total costs of care of persons diagnosed with Alzheimer's disease age 65 and older in the U.S. will increase five-fold in 2050 from its 172 billion dollars in 2010, according to an Alzheimer's Association's recent trajec-

tory.

2. A reported pilot study in nine patients with AD with mild to moderate degrees of cognitive impairment and mild to moderate degrees of dementia of 1.3 to 4.0 years duration.¹⁵ The individuals were given 600 mg of racemic alpha lipoic acid once daily for an average period of 337 ± 80 days. The result was stabilization of neuropsychological tests and no dementia deterioration during the study, which was done without adverse effects.¹⁵
3. Alpha lipoic acid and its reduced metabolic product dihydrolipoic acid (DHLA) both inhibited formation of beta-amyloid fibrils from beta-amyloid protein in vitro.¹⁶
4. Alpha lipoic acid is synthesized in vitro as a racemic d,l mixture. The d stereoisomer is the natural form, also named R-alpha lipoic acid.¹⁷ R-lipoic acid or its reduced form, DHLA, is located in mitochondrial membranes where it serves as an important coenzyme in alpha-keto acid dehydrogenases.^{17,18} R-lipoic acid delivered in the plasma can cross the blood brain barrier and be reduced to DHLA.^{19,20} DHLA is easily oxidized, and it has a powerful reducing potential of - 0.32 V, making DHLA a very powerful and perhaps "master" intracellular antioxidant. It also increases glucose uptake and glucose metabolism, improving the energetic state of cells.¹⁸⁻²¹ DHLA is also an effective chelator of iron.^{19,20} It also is able to regenerate vitamin C, vitamin E, and glutathione from their oxidized products.^{19,20} Vitamin C can regenerate uric acid from its harmful urate free radical.^{22,23} Vitamin C (L-ascorbic acid) at a readily attainable extracellular concentration of 1.6 mg/dl (89 μ M) completely inhibited oxidation caused by ferrous iron of 9.8 μ M (or free hemoglobin of 12 mg/dl) and 20 μ M hydrogen peroxide in the Fenton reaction, which forms hydroxyl free radicals.²³ Hydroxyl radicals react very quickly

with many different organic molecules in their immediate vicinity, with oxidation, notably with sugars, DNA bases, organic acids, and amino acids.^{23,24}

A detailed review of lipoic acid as a micro-nutrient with diverse antioxidant and pharmacologic properties was published in 2004.²⁰ It was emphasized in another review that lipoic acid, particularly R-lipoic acid, has a cholinergic neuro-protective effect and lipoic acid is a multimodal agent in AD.²⁵ It acts as an anti-inflammatory drug and is a modulator of redox-sensitive signaling.^{20,25} Further, it induces an antioxidant stress response, including regulation of heme oxygenase-1.^{26,27} Holmquist et al²⁵ concluded that a double blind, placebo-controlled Phase 2 trial is urgently needed before lipoic acid can be safely recommended as a therapy for AD.

5. R-lipoic acid and vitamin C decline in cells with aging and oral supplementation with R-lipoic acid in old rats improved mitochondrial function, decreased oxidative damage, and reversed the age-associated effects on vitamin C concentration.^{17,28} Oral supplementation with R-lipoic acid also improved memory loss in old rats associated with brain mitochondrial decay and RNA/DNA oxidation.²⁹ Similar feeding of R-lipoic acid to old rats did not significantly change the increased total iron in old rat brains.³⁰ In contrast, Suh et al³¹ found that dietary supplementation with R-lipoic acid reversed the age-related iron accumulation, monitored by inductively coupled plasma atomic emission spectrometry, and depletion of antioxidants in the cerebral cortex of old rats. DHLA chelates and inactivates redox-active transition metal ions in small-molecular complexes in vitro without affecting iron- or copper-dependent enzyme activities.³² In humans with AD, plasma vitamin C was found lower in proportion to the degree of cognitive impairment.³³

6. The plasma pharmacokinetics of oral doses of racemic alpha lipoic acid in healthy humans are known.³⁴ Oral 600 mg doses are cleared from the plasma within 2 hours, and only a mean of 12.4 % of lipoic acid and its metabolites are excreted in the urine in 24 hours after oral doses.³⁵ R-lipoic acid is relatively unstable and tends to polymerize, whereas the sodium salt, sodium R-lipoate, is much less prone to polymerize and it displays higher plasma concentrations in humans.³⁶ The stabilized sodium salt is available as a nutraceutical.
7. A suggested antioxidant therapy to try to retard progression of MCI and AD would be 300 mg of R-lipoic acid contained in the form of sodium R-lipoate inside size 00 capsules (stabilized by sodium carbonate) and combined with vitamin C, to total net weight of 600 mg. A convenient recommended dosage in a randomized clinical trial might be two capsules daily. Such antioxidant therapy may reduce free radical damage as well as reducing inflammatory activities.^{3,13} Oxidative DNA damage in peripheral blood lymphocytes could be measured serially as an objective test for trial efficacy.³⁷ Intramuscular administration of deferoxamine, an iron chelator, significantly improved daily living skills and slowed the clinical progression of dementia in a two-year single blind study in patients living at home under 74 years of age with probable AD.³⁸
8. Recently, it was demonstrated that there was increased redox-active iron and free radical generation in human brains of elderly individuals who had preclinical Alzheimer disease and mild cognitive impairment.³⁹ Hager et al⁴⁰ reported that in a follow-up open-label study in 43 patients from the same institution¹⁵ were given 600 mg racemic alpha lipoic acid daily for up to 48 months. The AD progressed extremely slowly in patients with mild dementia, but not so slowly in patients with moderately advanced

dementia.⁴⁰ R-alpha lipoic acid is a naturally occurring cofactor for the mitochondrial enzymes pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase.⁴⁰ These authors concluded that state-of-the-art Phase 2 trial is urgently needed. Stabilized sodium R-lipoate given orally is more potent than racemic alpha lipoic acid.

CONCLUSION

Randomized neuroprotective trial in the elderly is warranted especially with combined use of stabilized sodium R-alpha lipoate and vitamin C. Such treatment is expected to delay the serial progression of amnesic cognitive impairment and to reduce significantly the incidence of Alzheimer's disease in the developed world.

Potential Conflicts of Interests: None disclosed.

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