

Review Article

New Strategy of Micronutrients Combined with Dietary and Lifestyle Adjustment for Alzheimer's Disease Therapy and Partial Restoration

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ABSTRACT

Alzheimer's disease (AD), known as one of the most common cause of dementia, could lead to memory loss, difficulty with thinking and behavioral changes. To date, AD has been continuously regarded as an incurative disease of the aged and therefore as a big challenge for clinical neurology both in the therapy and prevention, which brings about heavy burden to not only the patients and their family, but also the society. In this review, it has been proposed a new strategy that would be synthetically implemented for the prevention and even partial restoration of AD clinically, in which multiple micronutrients, combined with diet and lifestyle adjustment, were used for AD patients and people who already had the pro-phase symptoms. Based on these notions, evidence and beneficial methods are put forward. It is promising to install a better and more efficacious AD administrative system, with aim to reduce the incidence rate and elevate the life quality of AD patients in a sooner future.

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1. Introduction

Alzheimer's disease (AD), as one of the most common cause of dementia, is characterized by the senile plaque and neurofibrillary tangles (NFTs) mainly formed and deposited in the hippocampal area of AD patients. Individuals, who are 65 years or older, have higher and higher risk of developing this neurodegenerative disease due to the coming of aging society worldwide. Distinctive manifestations including progressive cognitive, learning and memory disorders occur in typical AD patients, accompanied with other neurological and/or mental symptoms, such as weakness, depression, etc. Until now, it is still a challenge that seems to unable to overcome to effectively reduce the incidence or the progression rate of AD, with few curative therapeutic strategies. Even so, several pathological reactions that contribute to degeneration and death of neurons in AD have been identified in last few decades, including such factors as increased oxidative stress, chronic inflammation, A β 1-42 peptides generated from the cleavage of amyloid precursor protein (APP), high cholesterol levels, etc., which currently attract more and more attention and become key target factors that are attached importance to AD in both experimental researches and clinical trials.

Despite these advances in our understanding of AD, there were few evidence-based strategies found to reduce the risk or to improve the therapeutic efficacy of AD. Current drug therapies are mainly based on the symptom-attenuation rather than on the amelioration of the causes of the disease. They can exert modest beneficial effects on attenuating such main symptoms as anxiety, dementia and fear, but with unpleasant side effects. Of note, they did not effect on increased oxidative stress or chronic inflammation which plays a key role in the development and progression of AD.

It has been demonstrated recently that antioxidant strategy, when combining with standard therapy, could improve the management of this disease more than that produced by standard therapy alone. This novel therapeutic strategy that has been preliminarily used clinically is mainly on the basis of antioxidants that are long proved to have the ability to neutralize free radicals and reduce chronic inflammation. Therefore, it is indispensable to develop antioxidant-based therapeutic strategies and simultaneously reduce the risk of AD in high-risk populations, such as older individuals and individuals with a family history of AD levels, so as to significantly elevate the level of AD administration in a manner of more intensive and precise.

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In recent years, some reports indicated that a micronutrient preparation containing dietary and endogenous antioxidants, vitamin D, B-vitamins, and certain minerals played certain roles in reducing the risk of AD and resisting the unfavorably factors that raising along with age, such as chronic oxidative stress [1]. However, there are few researches and outcomes regarding the effects of micronutrient when combined with antioxidants, and other beneficial methods on the improvement of AD prevention, treatment and prognosis. It is needed systematic researches in a larger population with multi-center studies, and for much longer term follow-up and elaborate survey. Apart from these, the pathogenesis of AD still awaits further elucidation.

Therefore, it is an indispensable strategy to get AD relieved not only in its incidence rate, but also increase the therapeutic effects and the life quality by the help of effective methods with which to reduce the level of oxidative stress all along during all the course of AD. It seems that micronutrient, when combines with antioxidants, and other beneficial methods, is becoming a promising strategy for the amelioration of AD treatment and prognosis as well, which are deserved to be intensively studied before extensive application.

2. Current Treatments of AD

Currently, there are a lack of effective treatments of AD due to they have failed to resist the progression of the AD. Commonly prescribed drugs are cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and NMDA antagonist (memantine). Cholinesterase inhibitors has been approved to take action on cognitive functional improvement by increasing the acetylcholine levels in cholinergic neurons. The efficacy of these drugs are dependent on the vitality of surviving cholinergic neuron. Whereas NMDA receptor antagonist takes its action by means of holding back the action of glutamate on inducing fear and anxiety in AD patients. In randomized, double-blind, parallel-group clinical trials, all acetylcholinesterase inhibitors (AChEIs) have shown varying degrees of efficacy than placebo in improving cognitive function in patients with mild to moderate AD. Among donepezil, galantamine, and rivastigmine, donepezil was found slightly more effective than the others [2], but there was not any difference found between any two drugs other than donepezil. It has been demonstrated that in the hispanic population, the safety and beneficial effects of donepezil on cognitive function were similar to those found in the general population [3].

The annual cost of donepezil, galantamine, and rivastigmine was not significantly different [5]. These drugs do not affect the level of oxidative stress or chronic inflammation primarily responsible for neurodegeneration in AD brain; therefore, their efficacy does not last for a long period of time. The progression of the disease continues to occur

because of oxidative stress- and chronic inflammation-induced progressive neuronal death. The addition of agents that can reduce oxidative stress and chronic inflammation to the current therapeutic modalities may prolong the effectiveness of AChEI in improving cognitive function in AD patients. Therefore, we propose that antioxidants that neutralize free radicals and reduce inflammation and a nonsteroidal anti-inflammatory drug (NSAID) that reduces inflammation should be utilized in combination with standard therapy in order to improve the current management of AD.

As for other reagents of AD treatment, Statins are commonly used to reduce senile plaques and inflammation marker TNF-alpha by using atorvastatin and pitavastatin were only obtained from the AD transgenic mice [4], without verification in human AD. Another agents useful to AD therapy, known as neurotrophic molecule J147, which plays a critical role in the restoration of the learning and memory. But this outcome was just limited in AD mice model, either [5].

3. Limitations of Current Medications in AD

It has been proposed that the gradual loss of cognitive functions in AD is due to the loss of cholinergic neurons; therefore, cholinergic drugs (acetylcholinesterase inhibitors) are used to improve the function of surviving neurons in AD patients. However, these agents do not protect cholinergic neurons against the damaging effects of oxidative and nitrosylative stresses and chronic inflammation. Consequently, neurons continue to die, and the beneficial effects of cholinergic drugs do not last long.

4. Recommended Micronutrients and Low Dose of NSAID in Combination with Standard Therapy in Patients with Dementia with or without AD

Based on the current situation and limitation of AD therapies above mentioned, antioxidants are recommended to reduce oxidative stress, chronic inflammation, and release and toxicity of glutamate, and aspirin can enhance anti-inflammation effects of antioxidants. Therefore, addition of a multiple micronutrient preparation and a low-dose aspirin in combination with standard therapy may prolong the beneficial effects of current drugs in patients with dementia with or without AD by protecting surviving neurons from damage produced by increased oxidative stress, chronic inflammation, and glutamate. The proposed combination of micronutrients recommended for primary prevention is applicable to those who are at the various stages of AD and taking medications. The daily doses are divided into two doses (half in the morning and half in the evening preferably with meal) and are administered orally (Table 1).

TABLE 1: The useful supplementary multiple micronutrient and dietary strategy for AD prevention.

Nutraceuticals Food supplements	
Bioactive substances	Vitamins, salts, amino acids, plant extracts
Supplied as pharmaceutical preparations	Supplied by diet
Prevention or treatment of diseases	Compensation for food shortage

In most studies, the serum levels of vitamin B12 in AD patients were significantly lower than that of controls, and this may in part contribute to degeneration of neurons [6]. Indeed, vitamin B12 supplementation increased choline acetyltransferase activity in cholinergic neurons of cats [7] and improved cognitive functions in AD patients [11]. An analysis of published data revealed that there was no adequate benefit from folic acid supplementation with or without vitamin B12 on cognitive function or mood of healthy elderly people [12]. So, appropriate vitamin B12 supplementation can increase the activity of choline acetyltransferase, thus would do good to the improvement of cognitive functions of AD patients.

5. Diet and Lifestyle Recommendations for AD

Even though there is no direct link between the diet- and lifestyle-related factors and the initiation or progression of AD, it would be beneficial to avoid exposure to aluminum and excessive consumption of iron, copper, manganese, or zinc. It is always useful to include a balanced diet that contains low fat and high fiber with plenty of fruits and vegetables. Among fruits, blueberries and raspberries are particularly important because of their protective role against oxidative injuries in brain. Lifestyle recommendations include daily moderate exercise, reduced stress, no tobacco smoking, and reduced exposure to noise and electromagnetic fields. Diet- and lifestyle-related recommendations (Figure 1) can be adopted together with the proposed micronutrients for primary prevention, secondary prevention, and treatment strategies.

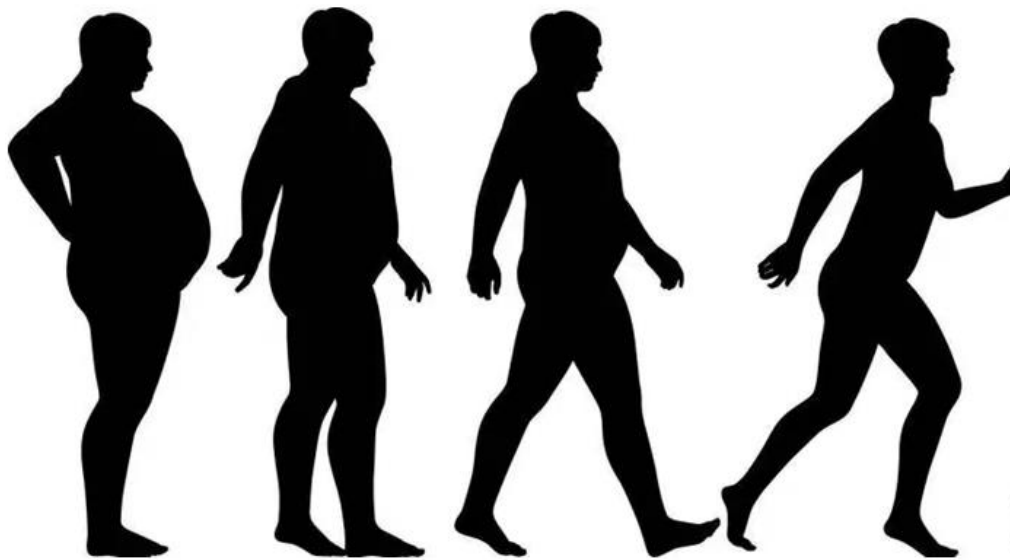


FIGURE 1: Appropriate exercise reduces the incidence rate or postpones the occurrence of AD.

6. Discussion

There are many reports indicated that increased oxidative stress has been widely considered as one of the earliest biochemical events which initiate neurodegeneration in AD. Other biochemical defects, such as mitochondrial dysfunction, increased levels of chronic inflammation, generation of A β 1-42 peptides from APP, aggregation of A β peptides, hyperphosphorylation and acetylation of tau, inhibition of proteasome, formation of extracellular senile plaques and intracellular NFT occur subsequent to increased oxidative stress. Additionally, mutation in APP, *presenilin-1*, and *presenilin-2* genes increased the generation of A β peptides which damage neurons by producing more free radicals. Increased oxidative stress together with other biochemical and genetic defects participate in the progression and final stage of neuronal death in AD. At present, there are no effective strategies to reduce the incidence of AD.

It is proposed that a combination of agents which can increase antioxidant enzymes by activating Nrf2/ARE pathway without ROS stimulation and which can directly scavenge free radicals may be

necessary to reduce oxidative stress and chronic inflammation optimally in AD. Dietary and endogenous antioxidants, curcumin, resveratrol, and omega-3 fatty acids can fulfill the above requirements for reducing oxidative stress and chronic inflammation optimally. Thus, a preparation of the above antioxidants in combination with low dose NSAIDs, such as aspirin, may be useful in reducing chronic inflammation optimally. As we summarized and concluded in this review, clinical studies using the proposed micronutrient recommendations for AD primary and secondary prevention should be initiated and would be a promising strategy.

The current drug treatments are based on the symptoms rather than the causes of AD and has produced transient benefits on some symptoms such as improving cognitive function; however, these drugs do not have any effect on increased oxidative stress and chronic inflammation that are responsible for neuronal degeneration. The effectiveness of cholinesterase inhibitors in improving cognitive function lasts as long as cholinergic neurons are viable. Excessive release of glutamate may induce fear and anxiety in AD patients. Glutamate is also toxic to nerve cells. Therefore, memantine, an antagonist of glutamate receptor

NMDA, is used to improve these symptoms of AD. The currently used drugs have severe side effects. The micronutrient strategies recommended for primary prevention can also be used in combination with standard medications to improve the management of AD by reducing the progression of the disease and prolonging the efficacy of drugs on the symptoms.

Dietary recommendations include low-fat and high-fiber diet and reduced consumption of iron, copper, and zinc. Lifestyle recommendations include quitting tobacco smoking and reducing exposure to noise and electromagnetic fields.

Taken together, it has been proposed that micronutrient with a NSAID recommendations in combination with standard therapy for improved management of AD should be initiated, and combined with dietary and lifestyle adjustment are effective in prevention or improved management of AD likewise a novel, simple and more effectively auxiliary strategy both for prevention and treatment of AD, which is worth studying on a large scale.

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Conflicts of Interest

None.

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