Review Article

ACE Alzheimer's: The Role of Vitamins A, C, and E (ACE) in Oxidative Stress-induced Alzheimer's Disease

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Abstract

Alzheimer's disease (AD), a chronic neurodegenerative disease which is known to progress gradually, has now become a substantial health concern worldwide. Clinically, cognitive declination and progressive dementia are the main characteristics of AD while pathologically, Aß plaques and tau-neurofibrils are the hallmarks. The present literature search has suggested that oxidative stress is one of the most vital risk factors which can potentially lead to the development of AD. Oxidative stress is known to produce the reactive oxygen species which has a potential to increase in the structural and functional abnormalities in the glial cells of the brain and which could further lead to a cognitive decline, and subsequently, dementia. Hence to curb this oxidative stress in the glial cells, antioxidants have been proved to be of great help according to the literature search done in PubMed, Google Scholar, and Scopus. We included meta-analysis, systemic reviews, and original studies. Vitamins A, C, and E are an example of antioxidants that can be used as adjuvants in the treatment of AD. This article focuses on the contemporary literature search and presents forward the evidence-based banes of using Vitamins A, C, and E as an adjuvant therapy for preventing and treating AD.

Keywords: Adjuvant therapy, Alzheimer's disease, Antioxidants, Vitamin A, Vitamin C, Vitamin E

Introduction and Background

Alzheimer disease (AD) was described as "a peculiar severe disease process of the cerebral cortex" by Alois Alzheimer, which was based on the observations of one of his patients. He observed that the patient had a significant loss of memory with deteriorating psychological condition, without any relevant clinical history. Furthermore, he concluded that the patient's postmortem examination revealed a significant decrease in the size of the cortex along with abnormal deposits in the neurons. Today, AD is a major public health concern, especially due to its total economic burden on the healthcare system. AD is also one of the front liner causes of dementia in patients having an age of more than 65 years. The other causes which followed AD in causing dementia are vascular dementia, frontotemporal dementia, Lewy body dementia, and alcohol-associated dementia.[1]

Currently, approximately 25 million people are affected by dementia, of which majority are suffering from AD. AD has been impacting everyone's day-to-day routine which not only includes the patients but also their caregivers and relatives, in both the developing and developed countries.[2]

Due to the advent of medical science, developing countries have seen a rise in the life expectancy.

Hence, 65 years and above age group has become one of the most populous age groups of today. The statistics speaks that this segment of elders having an age 65 and above is stated to increase from 14% of the total population in 2012 to over 20% of the entire population by 2030 in the United States. 81% of Americans who are suffering from AD are aged 75 or above, highlighting the correlation between AD and advancing age. This rise has further contributed to an increase in the incidence and prevalence of AD. In 2016, there were approximately 476,000 new cases of AD in America alone, in the age group of 65 years and above. Moreover, every 66 seconds, one person develops Alzheimer's dementia which emphasizes the importance of this disorder. By 2030, it is projected that this incidence rate will rise to 615,000. The prevalence rate of AD was estimated to be around 5.4 million people in 2016, including 5.2 million having an age of 65 years and above. At present, one in every nine people (aged 65 and older) is seemed to be suffering from AD, while this number rises to one in three people in the age group of 85 and above. This prevalence rate of AD in those aged 65 and older is further projected to rise by 40% to 7.1 million until 2025 and 13.8 million by 2050. Annually, the United States spends over $236 billion on AD patients alone, which could possibly rise further, if the AD is not prevented or cured.[3]

AD is often seemed to be associated with the cognition and memory deficits which arise because of the formation of neurofibrillary tangles (NFTs) and deposition of the amyloid plaques in the nerve cells along with basal forebrain disruption of cholinergic neurons.[4] The cognitive decline related with AD pathogenesis is seemed to be attributed to the decrease in acetylcholine (A.Ch),[5] which also suggests that deficit of A.Ch can be devastating.[6]

Therefore, a major evolution with regard to the treatment plan of AD should include an attempt to prevent the destruction of these cholinergic neurons, and if possible, the increment of the A.Ch levels in the brain should be main aim as well. In addition, several researchers have suggested that reactive oxygen species (ROS) is linked to the etiopathogenesis of AD. It causes a cumulative damage to the cellular macromolecules and also impairs the mitochondrial function. This further leads to a decrement in cellular energy production.[7]

Pathogenesis of Oxidative Stress-Induced AD

AD susceptibility to an oxidative damage can be linked to several factors which include relatively lesser concentration of the antioxidants, significantly increased levels of polyunsaturated fatty acids which is generally rapidly targeted by ROS, higher concentrations of metallic ions, and high usage of oxygen.[8]

Oxidation can be fatal for the various cell components such as the proteins, carbohydrates, lipids, and the genetic constitution which includes the DNA and RNA.[9] It can not only accelerate the production of the inducible nitric oxide synthase (NOS) but also augment the activity of neuronal NOS (nNOS) which can further increase the production of NO. NO on interaction with the superoxide anions forms a highly reactive peroxynitrite anion which, subsequently, impairs the sulfhydryl groups of the cells.[10] **Figure 1** depicts this process.

Furthermore, oxidative stress has the potential to alter the protein structure. Impaired protein structure can further augment the oxidative damage. ROS causes these proteins to be oxidized and creates a modified structure which may get dimerized and aggregated.[11] These oxidized proteins, which are both structurally and functionally abnormal, gather as accumulates within the cytoplasm of the neurons and is seen in the form of NFT (tau aggregates) and Aß plaques.[12] Alternatively, Aß plaques can also cause increased formation of ROS which forms a vicious cycle. This pathway is shown in **Figure 2**.

Aß (1–42) is a common species of Aß proteins seen in AD.[13] Aß (1–42) peptides are known for its toxicity which can be attributed to a residue of methionine at position 35.[14] Oxidation (by ROS) of methionine leads to the production of methionine sulfoxide, which may lead to the formation of methionine sulfone.[15]

As a preventive mechanism, methionine sulfoxide is generally reduced into methionine by the action of methionine sulfoxide reductase (MSR).[16] However, the activity of MSR is

Figure 1: Role of nitric oxide in Alzheimer's disease pathogenesis

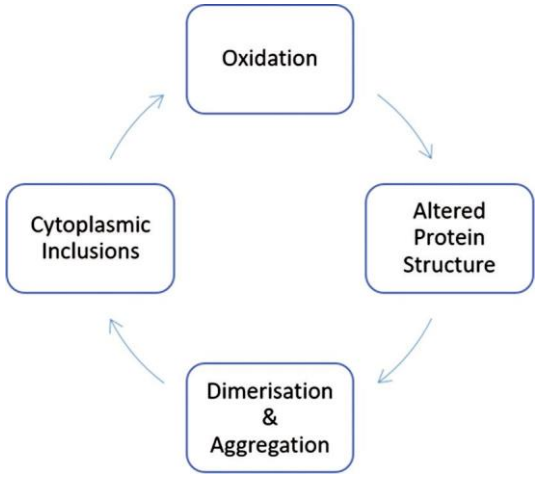

Figure 2: Displaying correlation between oxidation and protein dimerization, thus forming a vicious cycle

also observed to be impaired in AD.[17] Hence, methionine's oxidation can augment methionine sulfone production which is generally associated with aging and abnormal folding, further increasing the chance of developing AD.

Methionine peroxide plays a crucial role in oxidative stress and toxicity caused by Aß (1–42) peptides. The oxidation of an atom present in the single pair of electrons in the methionine leads to the production of sulfuranyl radicals (MetS.+).[14,18] Sulfuranyl radical stimulates the production of ROS such as sulfoxides and superoxides by their interaction with the molecular oxygen.[19]

This significant oxidative damage may be due to absence or reduced function of various antioxidant mechanisms in the body.

Glutathione (GSH) is an important antioxidant, which can protect the brain tissues through detoxification of damaging ROS.[20] The most important element that leads to an increased oxidative stress in patients with AD is increased levels of GSH.[21] The other participants of the antioxidant mechanism, which also displays an important role, are catalase (CAT) and superoxide dismutase (SOD).

SOD, also an antioxidant, is responsible for converting the toxic superoxide ions into hydrogen peroxide which is quite less toxic.[22] This reaction is augmented by CAT one step further, and H2O molecules are formed from hydrogen peroxide.[23] According to the recent researches, the levels of SOD and CAT are seemed to be diminished in the AD patients.[24]

Glutathione reductase (GR) and glutathione peroxidase (GPx) also feature in cellular defense mechanism which counteracts the oxidative stress. Interestingly, GPx augments the metabolism of hydrogen peroxide and lipid hydroperoxides[25] while GR accelerates the reaction which helps in the regeneration of GSH.[26] To summarize, it is the oxidative stress coupled with the impaired cellular defense mechanism against the free radicals that are responsible for the development of AD. **Figure 3** depicts AD pathogenesis.

Hence, antioxidants could play a crucial role in AD prevention. Antioxidants, especially like Vitamins A, C, and E, are easily available in nature and could be considered as fighting force against this slow and deadly disorder.

ACE Alzheimer's: Vitamins A, C, and E (ACE) Therapy

Evidence suggests that diet is a very important "modifiable" risk factor that plays a significant role in the development of AD or cognitive decline, depending on the food one consumes! There are certain foods that are rich in substances known to delay a decline in cognitive function.

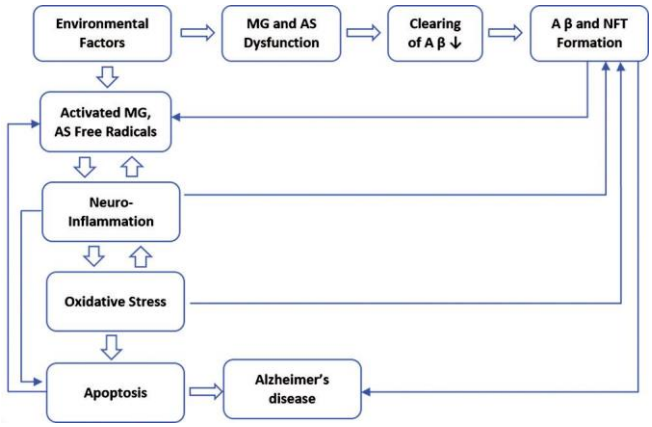

Figure 3: Pathogenesis of Alzheimer's disease (MG: Microglia; AS: Astrocyte; AP: Amyloid protein beta; NFT: Neurofibrillary tangles)

Studies have shown that one can prevent the development of irreversible neurocognitive decline by consuming foods that are rich in fruits, green leafy vegetables while reducing the intake of processed foods, refined carbs, and diet that is high in saturated fats.[27] AD patients are always at risk of developing the nutritional deficiencies due to the physiological and psychological factors.

Studies have shown significantly lower serum levels of certain essential fat and water -oluble vitamins in patients with AD as compared to individuals with intact neurocognitive function. [28] Conversely, serum levels and activity of antioxidants are found to be lower in subjects with AD, thus establishing a relationship between Vitamins A, C, and E, antioxidants, and incidence of AD.[29]

Moreover, there is evidence to show that dietary intake of Vitamins A, C, and E increases antioxidants and influences activity against free radicals implicated in AD.[30] It has been observed that Vitamin A prevents the formation of beta-amyloid plaques!.[31] Similarly, Vitamins C and E have also been proven to be beneficial in preventing/delaying the progression to irreversible neurocognitive decline.[1]

Thus, it is essential to further explore these vitamins and their importance in the prevention and treatment of AD.

Role of Vitamin A

Vitamin A is essential for the development of the central nervous system, in childhood, adolescence as well as adulthood. It not only protects but also assists in the rejuvenation of the neuronal cells at the time of recovery from neurodegeneration.[32]

In a study by Bourdel-Marchasson *et al*.,[33] it was observed that the AD patients had substantial reduced levels of Vitamin A and beta-carotene in their CSF and blood. After stratification of

age, sex, and cardiovascular comorbidities, they found that the average alpha-tocopherol and retinol serum concentration was lower in AD patients as compared to that of the control subjects.

The development of neurodegenerative disorders has shown to be influenced by Vitamin A and beta-carotene. A recent meta-analysis has shown that the serum levels of folic acid, vitamin A, vitamin B12, vitamin C and vitamin E were reduced in patients with AD.[34] A similar study by Foy *et al*. showed a significantly reduced level of plasma chain-breaking antioxidants, including Vitamins A, C, and E, in patient with dementia versus the control group ($P < 0.01$).[35] Inhibition of formation and destabilization of Aß fibrils are an additional effect of Vitamin A and beta-carotene.[32]

Aß fibrils oligomerization is an important mechanism which often leads to neuronal toxicity in AD. However, Vitamin A supplementation has shown to be effective in decreasing the aggregation and oligomerization of Aß40 and Aß42 fibrils. It has also been observed that Vitamin A and beta-carotene prevent the decline of cognitive function in AD. Moreover, higher levels of these vitamins have been associated with better memory performance and spatial learning in these patients.[32,36,37]

Role of Vitamin C

The previous studies both *in vivo* and *in vitro* have condoned that Vitamin C plays a significant role in brain normal function. Decreased plasma levels despite adequate intake in patients further confirmed the belief of protective effects of Vitamin C in the spectrum of neurodegenerative diseases.[38]

A study by Polidori *et al*. concluded that particular serum concentration of Vitamin C might be significantly important for the protection against AD and other clinical manifestations of vascular and cognitive aging.[39] Therefore, it can be inferred that antioxidant vitamins provide protection against oxidative stress-induced damage in AD.

The development of AD can be halted by Vitamin C due to its actions on various aspects of AD's pathology. Various studies, both *in vivo* and in vitro, concluded that Vitamin C helps in decreases the oxidative stress by hindering the Aß peptide oligomerization.

Brain damage causes a reduction in the levels of antioxidants such as SOD and Vitamin C and causes oxidative stress in the tissue. Vitamin C supplementation seems to help in increasing the SOD levels, which consecutively not only decreases the oxidative stress but also prevents the brain injury further.[40] It has been hypothesized that even a normal dietary intake of Vitamin C can have a neuroprotective effect in AD patients.

Furthermore, the cognitive decline has been observed to decrease significantly in the AD patients having an adequate Vitamin C intake.[41] Moreover, a recent observational study (n = 4740) which took place over 3 years concluded that extra supplementation with vitamins possessing antioxidant properties such as Vitamin C and E may be associated with a decrease in incidence and prevalence rates of AD.[42]

Role of Vitamin E

Vitamin E represents a cluster of 8 antioxidants composed of 4 tocotrienols and 4 tocopherols. Studies have shown that reduced serum level of Vitamin E may be responsible for an increased risk of neurodegenerative disorders such as AD and mild cognitive impairment (MCI). Moreover, vitamin E metabolic products such as 5-nitro-γ-tocopherol are often seemed to increase substantially in AD and MCI.[43]

If there is a deficiency of Vitamin E which is a potent antioxidant, it can result in extensive destruction of the neurons which has also been implicated before in cerebellar atrophy patients.[44] Aß plaques induced oxidative stress is considered to be a major risk factor for causing neuronal cell death and followed by neurodegeneration in AD.

Vitamin E is also known as a scavenger of free radicals, and thus, is renders protection to neurons.[45] Vitamin E also provides protection against AD through various other methods. For example, glutamate formed by the 12-lipoxygenase pathway induces excitatory cytotoxicity and subsequent neuronal cell death. This inflammation-induced neuronal death can be reduced by Vitamin E.[46]

Furthermore, Vitamin E consumption has been associated with the regeneration of SOD, increased levels of which are shown to decline AD.[47] Among the different types or forms of Vitamin E, the best protection against AD is provided by a-tocopherols and γ-tocopherols.[48] A study by Berti *et al*. showed that an increased consumption of fresh fruit and vegetables, low-fat dairies, fish, whole grains, and reduction in intake of sweets, fried potatoes, high-fat dairies, butter, and processed meat was an AD-protective nutrient combination, essentially highlighting the importance of Vitamins E, A, and C in AD patients.[49]

A recent study on 5395 individuals proved the protective role and effect of the dietary antioxidant supplementation against AD. Among all the antioxidants used, results indicated that the most substantial degree of protection versus AD and dementia (P = 0.02) was provided by Vitamin E. Moreover, only 30 international units of alpha-tocopherols if supplemented with normal diet could help in the prevention and treatment of AD.[50]

Future Trails in the Treatment of AD

Other antioxidants also play an important role in preventing AD. Probiotics, especially lactic acid bacteria, could help in

decreasing the oxidant level in the body.[51] Vitamins B, D, and K could also be an adjuvant therapy.[52] More research including meta-analysis and randomized control trials should be conducted so as to prove the importance of Vitamins E, A, and C in AD. We, therefore propose a term ACE Alzheimer's as an adjuvant strategy to curb this ever-extending chronic disorder.

Conclusion

AD is a vital age-related neurodegenerative disorder. Antioxidants can help in fighting against the oxidative stress, which is an important mechanism responsible for the development and progression of this disease. The use of Vitamins E, A, and C as an antioxidant for adjuvant therapy for AD has been given consideration. Thus, further clinical research is necessary to study the potential of these vitamins for integration into clinical treatment and to accelerate the recovery of patients affected by this disorder.

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