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Review Article

Internal Medicine Section

Vitamin Supplementation as an Adjuvant Treatment for Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD) is a slowly progressing neurodegenerative disorder representing a major health concern worldwide. This disorder is characterised by progressive dementia and cognitive decline. The pathological hallmarks of AD include the presence of Aβ plaques and tau neurofibrils. Research has shown that oxidative stress represents a major risk factor associated with AD pathology. Accumulation of Aβ plaques and relative lack of antioxidant defence mechanisms, including cellular antioxidant enzymes and dietary antioxidants like vitamins, assist in the exacerbation of oxidative stress. Reactive Oxygen Species (ROS) produced as the result of oxidative stress, that increase structural and functional abnormalities in brain neurons, which then manifests as dementia and decline in cognition. Data from numerous epidemiological studies suggests that nutrition is one of the most important yet modifiable risk factors for AD. Since oxidative stress contributes a great deal in the development and progression of AD, anything that could attenuate oxidative stress would help in decreasing the prevalence and incidence of AD. There is increasing evidence that supports the use of different antioxidant as an adjuvant treatment for AD. Vitamins are one such antioxidant that can be used as an adjuvant in AD treatment. This paper will focus on the evidence, based on current literature, linking the use of vitamin supplementations as an adjuvant treatment for AD.

Keywords: Antioxidant vitamins, Oxidative stress, Reactive oxygen species

INTRODUCTION

Alzheimer's Disease (AD) was first described by Alois Alzheimer in 1907. He described this condition in a 51-year-old female who presented with symptoms of psychiatric disturbance along with swift deterioration of memory [1]. Decades later, it is now recognized that AD is one of the major causes of dementia in population under 65 years, other causes being dementia with Lewy Body Dementia (LBD), Frontotemporal Dementia (FTD), Vascular Dementia (VaD) and alcohol associated dementia [2]. AD represents a major public health problem and in United States alone, a person develops AD every 68 seconds and Americans spend more than $200 billion annually on Alzheimer's related expenses [3]. Results of population based studies have shown that risk factors associated with the development of AD include increasing age, certain genetic factors (e.g., presence of apolipoprotein E epsilon 4 allele), fewer years of education and head trauma [4].

AD dementia must be differentiated from other causes of dementia like LBD, FTD and VaD [5]. Moreover, due to the variability of the brain regions affected, AD can present with dysfunction of different domains like vision, sensory-motor functions, judgment and personality [6]. In order to distinguish AD from other causes of dementia, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) has put forth the clinical criteria for establishing a diagnosis of AD. According to this criterion, AD is characterized by: (I) Progressive decline in cognitive functions, which may include impairment of memory, or (Ia) Loss of ability to comprehend words and verbal commands (aphasia); (Ib) Inability to complete tasks involving coordination of muscles (apraxia); (Ic) Inability to recognize and make use of familiar objects (agnosia); (Id) Inability to plan, organize and execute routine activities; (II) All indications mentioned above under 'I' getting worse with the passage of time; (III) All other causes of dementia and cognitive decline are excluded [6,7].

The first ever reported histopathological features of AD include the presence of extracellular amyloid plaques and intracellular Neurofibrillary Tangles (NFT). But recently, newer histopathological features have been identified. These features include degeneration of neuronal synapses, loss of neurons in the hippocampus and aneuploidy. However, current histopathological criteria for establishment of AD still take into account of only the presence of extracellular amyloid plaques and intracellular NFT [8]. Among the most accepted hypotheses that try to explain the pathogenesis of AD is the Aβ cascade hypothesis. Previously, mutation in beta-Amyloid Precursor Protein (APP), which is implicated in the normal function of neurons and cerebral development, has been speculated as the basic cause of accumulation of Aβ proteins and the pathogenesis of AD [9]. Later, mutations in other genes like *presenilin* 1 and *presenilin* 2 were also discovered to be involved in the generation of Aβ pools [10]. But how Aβ aggregation contributes in the pathophysiology of AD largely remains unclear. Previously the intercellular Aβ plaques were thought to be toxic for cells. But recent data has suggested the role of intracellular Aβ proteins, which actually don't get sequestered into the extracellular plaques, as the toxic triggers dictating the progression of AD [11]. Also, it has been recently shown that intracellular accumulation of Aβ proteins precedes the formation of extracellular Aβ proteins plaques and NFT formation [12]. The role of intracellular Aβ protein in the progression of AD is backed by recent experiments on transgenic mice that have shown that increased deposits of Aβ proteins within the cells are associated with accelerated cell death [13].

Another important culprit in the development of AD is oxidative stress and ROS [14]. Several factors make brain particularly vulnerable to the damage caused by oxidative stress. These factors include relatively lower levels of antioxidants in the brain, higher levels of polyunsaturated fatty acids in the brain (these fatty acids rapidly fall prey to ROS), presence of metallic ions in the brain and higher oxygen utilization by this organ [15]. Increased oxidative stress causes damage to the constituents of cells like carbohydrates, lipids, proteins, RNA, DNA [16]. Indirect mechanisms can exacerbate the damage caused by direct effects

of oxidative stress. Oxidative stress accentuates the expression of Inducible Nitric Oxide Synthase (iNOS) and potentiates the action of neuronal NOS (nNOS). This increases the production of nitric oxide (NO), which can then interact with superoxide anions to form peroxynitrite anions. Peroxynitrite anions are short lived, highly reactive molecules that can interact and damage a variety of structures in the cellular environment, especially with the compounds containing sulfhydryl groups [17].

Oxidative stress alters the protein structure and altered protein structure in turn further accelerates oxidative stress. It seems both these processes are interrelated. ROS induce protein oxidation, thereby modifying protein structure and causing their dimerization and aggregation [18]. These structurally and functionally abnormal proteins get accumulated in the form of cytoplasmic inclusions and are seen in the form of NFT (tau aggregates) and Aβ plaques [19]. On the other hand, Aβ plaques can also lead to the increased production of ROS. Aβ (1-42) is the more abundant and more toxic species of Aβ proteins seen in AD [20]. Aβ (1-42) peptides possess a residue of methionine at the position 35, which is thought to be responsible for the toxicity of Aβ (1-42) peptides [21]. Oxidation of methionine leads to the formation of methionine sulfoxide, which can undergo irreversible oxidation to form methionine sulfone [22]. Methionine sulfoxide reductase can guide the enzymatic reduction of methionine sulfoxide back into methionine [23]. Furthermore, activity of methionine sulfoxide reductase is also found to be impaired in AD [24]. Methionine peroxide plays a pivotal role in the toxicity and oxidative stress caused by Aβ (1-42) peptides. The lone-pair of electrons on the S atom of methionine undergoes one atom oxidation and as a result sulfuranyl radicals ($MetS.^{+}$) are generated [21,25]. Sulfuranyl radicals can trigger the generation of other ROS like superoxides and sulfoxides by interacting with molecular oxygen [26].

Another important factor that greatly aggravates the severity of oxidative stress in AD is the relative absence or decreased function of different antioxidant mechanisms of the body. Glutathione is a major antioxidant that confers protection to the brain tissues by causing detoxification of damaging ROS [27]. One of the basic reasons of oxidative stress build-up in AD is the decreased levels of glutathione in the brain [28]. Other important members of cellular antioxidant mechanism include Superoxide Dismutase (SOD) and Catalase (CAT). SOD is the antioxidant responsible for converting toxic superoxide ions into less toxic hydrogen peroxide [29]. CAT takes this reaction one step further and turns hydrogen peroxide into water [30]. Investigations showed that the levels of SOD and CAT were declined in patients with AD [31]. Gluthathione peroxidase (GPx) and glutathione reductase (GR) represent other important constituents of the cellular defence mechanism against oxidative stress. GPx is responsible for the metabolism of lipid hydroperoxides and hydrogen peroxide [32] and GR governs the reaction that helps in the regeneration of Gluthathione (GSH) [33]. In nutshell, both increase in the oxidative stress and decrease in the cellular defence mechanism against ROS contribute in the pathogenesis of AD.

As mentioned earlier, AD has got a large global burden and the treatment process is very expensive. Therefore, it is the need of the hour to come-up with novel therapeutic strategies for the treatment of AD that are proficient and cost-effective at the same time. One such method is the supplementation of diet with antioxidant vitamins. So, the basic purpose of this review article is to take into account the current literature regarding the use of vitamin supplementation as an adjuvant treatment of AD and determine the efficacy of this treatment strategy.

DISCUSSION

Recently, there has been build-up of interest in exploring novel approaches for the treatment of AD. Dietary modification is one such approach that has shown to influence the development, progression and treatment of AD. Use of antioxidants has shown significant promise in decreasing oxidative stress, inflammation and neuronal loss in neurodegenerative disorders. Vitamins are potent antioxidants and therefore can be used as an adjuvant therapy for the treatment of AD.

Vitamin A and Beta-Carotenes

Results of some studies have found that serum plasma and Cerebrospinal Fluid (CSF) levels of vitamin A and beta carotenes were significantly low in AD patients when compared to controls [34]. Vitamin A and beta carotene have shown to influence multiple aspects of neurodegenerative disorders. Vitamin A plays an important role in neuron development in early life and remains active in adult nervous system. Moreover, this vitamin has shown to protect and assist in regeneration of neurons during neurodegeneration [35]. Another effect of vitamin A and beta carotenes is that they inhibit the formation and promote the destabilization of Aβ fibrils [35]. Furthermore, oligomerization of Aβ fibrils is an important mechanism contributing to neuronal toxicity in AD. Vitamin A has shown to decrease the aggregation and oligomerization of Aβ40 and Aβ42 fibrils [36]. Vitamin A and beta carotene have also been found to decrease the decline of cognition in AD. In addition, higher level of these vitamins has also been associated with better memory performance and spatial learning in such patients [34-36].

B Vitamins

Among B vitamins, pyridoxine (B6), folic acid (B9), and cobalamin (B12) have shown to have potential in managing symptoms of AD. Hyperhomocysteinaemia is an independent and important risk-factor for a number of diseases including AD [37]. Homocysteine is responsible for increasing toxicity for neurons in a number of ways. One such way, is by its ability to trigger the generation of ROS and increase the oxidative stress [38]. Vitamin B6, B9 and B12 have shown to decrease the level of homocysteine, thereby helping in the control of this modifiable risk-factor for AD [39].

Low levels of vitamin B6 have been implicated in the pathogenesis of AD. Study of patients with AD showed that white matter lesions were common in the patients having low serum pyridoxine levels [40]. Cu (II) complexes of Aβ peptides represent an important trigger of metal centered oxidative stress in AD. Pyridoxine has shown to inhibit this mechanism of oxidative stress [41]. The results of a randomized, double blinded trial on 89 patients with AD showed that the use of multivitamin supplements (including vitamin B6, B9 and B12) is an excellent adjuvant when used in combination with usual therapy for AD ($p = 0.008$) [39]. Another study proved the same point where multivitamin supplementations was found to decrease the levels of homocysteine in treatment group as compared to placebo group ($p < 0.001$) [42].

Low level of serum folate is another predictor for AD. A study inducting 816 individuals showed that there is a statistically significant ($p=0.014$) relationship between decreased serum level of folate and AD [43]. The role, folate plays in AD is perhaps due to its ability to mitigate the serum level of homocysteine and resultant oxidative stress caused by it [44]. Moreover, inadequate supply of folate has also been linked with significant shrinkage of cerebral cortex [45]. In addition, reduced plasma levels of folate has also been linked with the induction of other mechanisms of AD pathogenesis including increased calcium influx into the cells leading to subsequent apoptosis, accumulation of NFT and aggregations of Aβ peptides [46]. A 10-year-study was performed to find the relation between dietary habits and relative risk of developing AD. The study included 579 individuals and a follow-up was performed after 9.3 years. During that time 57 participants developed AD. Result of the study showed that increased intake

of folate was associated with significantly decreased risks for developing AD [47]. Another study included 965 patients without dementia and follow-up was performed after a period of almost 6 years. The result of the study confirmed a statistically significant relation (p= 0.02) between higher folate intake and lower incidence of AD [48].

The plasma levels of vitamin B12 were also found to be deficient in cases of AD [49]. It is also an established fact that deficiency of vitamin B12 exacerbates several aspects of AD including cognitive decline and dementia in patients with AD. Dementia and cognitive decline were quite prominent in AD patients with subnormal vitamin B12 levels as compared to patients with normal plasma levels of B12 vitamin [50]. Elevated plasma level of homocysteine is an important risk factor for gray matter atrophy. Using high dose of B vitamins, including 0.8mg B9, 20mg B6 and 0.5mg B12, over a period of 2 years has been demonstrated to decrease homocysteine induced gray matter atrophy [51]. Therefore, vitamin B12 supplementation can be used as an excellent adjuvant for the treatment of cognitive decline associated with age or neurodegenerative diseases including AD [52].

Vitamin C

Like other antioxidant vitamins, the plasma levels of vitamin C were found to be significantly lower in patients with AD despite adequate intake of this vitamin in the diet [53]. This again proves the fact that oxidative stress induces damage in AD and antioxidant vitamins offer certain degree of protection against this stress. Vitamin C alters the progression of AD by interfering with different aspects of AD pathology. Results of numerous invitro and invivo studies have shown that vitamin C can decrease oxidative stress. Vitamin C can hinder the structural progression of AD by preventing the oligomerization of Aβ peptides [54]. Brain injury induces oxidative stress and decreases the level of antioxidants like vitamin C and SOD. Supplementation with vitamin C improves the level of SOD, which in turn helps in lowering the oxidative stress and resultant brain injury [55].

Some studies have suggested that normal intake of vitamin C; even without additional supplementation can have neuroprotective effects in patients with AD. Adequate vitamin C intake can decrease cognitive decline in AD patients [56]. Results from a prospective observational study (n=4740) suggested that additional supplementation with antioxidant vitamins like vitamin C and E over a time period of 3 years was associated with both decreased incidence and prevalence of AD [57].

Vitamin D

The analysis of current literature on the relationship between vitamin D deficiency and AD revealed a direct relation between decreased serum level of vitamin D and AD. Vitamin D levels are found to be significantly lower in patients with AD as compared to normal controls [58]. Until recently, the role of vitamin D deficiency in the progression of AD was unknown. But genetic studies have been able to explain this relation in more detail. Results of genetic studies found a very strong relationship (p<0.001) between over-expression of vitamin D receptors (VDR) or vitamin D supplementation with the suppression of APP transcription [59]. Another mechanism through which vitamin D deficiency cause brain injury is via enhanced inflammation due to different types of VDR polymorphisms [60]. Vitamin D depletion has also been linked to brain atrophy [61]. The role of vitamin D in the pathogenesis of AD does not end here. Vitamin D somehow also helps in the clearance of Aβ plaques, a distinct feature of AD and low levels of vitamin D have also been linked with increased incidence of cognitive decline [62].

There have been encouraging results regarding the adjuvant supplementation of vitamin D as a treatment protocol for AD. The results from a large population based study, which was conducted on 5,596 women (age around 80 years), showed that women who were deficient in vitamin D intake scored less on Short Portable Mental State Questionnaire (SPMSQ) as compared to females with adequate vitamin D intake (p<0.001) [63]. Memantine is considered as one of the first line drugs for the treatment of mild to moderate AD [64]. Result of a study conducted on 43 AD patients showed that use of vitamin D as an adjuvant supplement in addition to memantine treatment is far superior to the use of memantine monotherapy (p< 0.001) [65].

Vitamin E

Vitamin E represents a group of 8 antioxidants (containing 4 tocotrienols and 4 tocopherols). It has been reported that decreased levels of plasma vitamin E is associated with increased risk of neurodegenerative disorders like AD and Mild Cognitive Impairment (MCI). Moreover, the level of vitamin E damage products (5-nitro-γ-tocopherol etc.) increases significantly in AD and MCI [66]. Vitamin E deficiency can lead to destruction of neurons and has been implied in the cases of cerebellar atrophy [67]. Vitamin E acts as potent antioxidant which can slow down the progression of AD at multiple levels. Increased oxidative stress induced by Aβ plaques is a known risk-factor for the neuronal death and resultant brain injury in AD. Vitamin E acts as a scavenger for these free radicals and provides certain degree of neuroprotection [68]. Vitamin E also offers protection against AD via some alternate methods. For instance, glutamate-induced neuronal cell death is the result of inflammation caused by 12-lipoxygenase pathway. Vitamin E can inhibit this inflammation induced neuronal death [69]. Moreover, consumption of vitamin E has also been linked with the regeneration of SOD, which undergoes decline in AD [55]. Among the different forms of vitamin E, α-tocopherols and γ-tocopherols provide greatest degree of protection against AD and cognitive decline [70].

A population based cohort study included 5395 individuals to evaluate the efficacy of dietary supplementation with antioxidants to provide protection against AD. Results showed that among all the antioxidant used, vitamin E provided significant degree of protection (p = .02) against dementia and AD [71]. Moreover, use of multivitamin supplements containing 30 International Units (IU) of alpha tocopherols can act as beneficial adjuvant for the treatment of several neurodegenerative disorders like AD and Parkinson's disease [72].

Vitamin K

There have been some studies that link the deficiency of vitamin K to AD [73]. The exact role of vitamin K still needs to be described. But it is believed that the protection offered by vitamin K in AD is due to its ability to reduce oxidative stress. This fact is backed by findings that vitamin K can prevent oxidative stress induced cell death following the activation of 2-lipoxygenase pathway [74]. Moreover, higher serum phylloquinone concentration is also linked with improved cognitive functions [75].

There is a lack of clinical trials on humans that could explain the relationship between vitamin K supplementation and improvement in AD. However, results of animal experimentation has shown that supplementation of diet with vitamin K can decrease the degradation of neurons and decline of cognitive functions [76].

CONCLUSION

Alzheimer's disease represents one of the most important age related neurodegenerative disorders. Oxidative stress represents one of the most important mechanism involved in the development and progression of this condition. Use of antioxidants is a novel approach that can help treat this condition. The use of several antioxidant vitamins as an adjuvant treatment for AD has always

been underestimated. There is a need for more clinical research to study their potential, such that it can be incorporated into clinical practice to speed-up the recovery of patients suffering from this disorder.

Authors' Contributions

ABB conducted the literature search, complied data and wrote the manuscript. MU assisted ABB and performed the revision. Both authors approved the final version.

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