Chapter 2
Vitamin E and Cognitive Functions: What Is the Interplay?

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Abstract In our daily activities and social behaviors, cognitive functions play an important and crucial role. Impairment in cognitive function, an early symptom, indicates neurodegeneration and increased risk to more severe dementia such as Alzheimer's disease. Although neurodegenerative disease has complex pathogenesis, oxidative stress has been implicated to play a critical role in it. Even though multiple research and animal model trails have been conducted to find medicine to prevent or treat Alzheimer's disease, vitamin E was proposed as an option many years ago. Use of vitamin E for Alzheimer's disease relies on its antioxidant, neuroprotective as well as anti-inflammatory, and hypocholesterolemia properties. Lower levels of vitamin E have been recorded in patients suffering from Alzheimer's disease compared to non-demented controls. According to these findings, vitamin E, a valuable option might have supportive effects in cognitive impairment and Alzheimer's disease. Though, there is no enough evidence that supports the usefulness of vitamin E in deceleration of dementia and the results are diverse and unconvincing. In this chapter we look back at animal and human studies that examine the neuroprotective effects of vitamin E on cognitive impairment and the explanations for failure of vitamin E in cognition improvement in some cases.

Keywords Alzheimer's disease treatment · Cognitive function impairment · Vitamin E · Tocopherol · Tocotrienol

2.1 Introduction

Cognitive functions have crucial role in our daily activities and social behaviors, involve some mental processes such as thinking, memory, learning, and attention. Cognitive impairment is an identifiable and measureable decrease in cognitive abilities beyond those happening with normal aging, denotes initial symptom of

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neurodegeneration and increased chance for development of very serious dementias, such as Alzheimer's disease (AD) (Alzheimers Association 2015). With the overall aging of population, cognitive disability and subsequent dementias are progressively increasing the worries of general population and medical staffs (van de Rest et al. 2015).

The etiology of cognitive impairment is complex and there are many mysteries needed to be solved by researches. However, oxidative stress has been suggested as an essential figure in pathogenesis of neurodegenerative disease (Chang et al. 2014). Long-chain polyunsaturated fats such as docosahexaenoic acid (DHA; 22:6 n-3) comprise a significant portion of the vertebrate brain (Green et al. 1999); hence, lipid peroxidation is expected to be the contributor to neuropathology (Reed 2011).

Dementia is a heterogeneous syndrome, rather being a specific disease that causes at least diminishing in one cognitive function which is sufficient to reduce the ability to do normal activities (Alzheimers Association 2013). In developed countries, Alzheimer's disease, vascular dementia, mixed dementia, lewy body dementia, Parkinson's disease dementia, and frontotemporal dementia are the most common causes of dementia (Prince et al. 2016). AD is the most prevalent cause of dementia, an advancing neurodegenerative disorder in which individuals suffer from deficits in several cognitive functions, such as memory, language and executive functions, as well as a range of emotional and interactive condition. The impairment is followed by progressive functional deficit (Bejanin et al. 2017). Individuals and health systems are significantly affected emotionally and economically by AD. Recent treatment for AD provides insufficient efficacy and is not able to prevent the disease. The estimations show that by 2025 around 5.2% of the world's population will suffer from dementia, and the prevalence of this disease around the world will increase to 131.5 million cases (Prince et al. 2016).

Mild cognitive impairment (MCI) is a condition in which cognitive functions decline but does not cause major impairment in daily activities and hence does not meet the diagnostic criteria for dementia. The risk of development of dementia is augmented in patients with MCI (Ganguli et al. 2011), although the risk is not considered unavoidable (Bruscoli and Lovestone 2004). It is suggested that oxidative stress plays an important role in the process of cognitive impairment.

Vitamin E consists of a collection of essential lipid-soluble, non-enzymatic, chain-breaking antioxidants which exist in human's body. Laboratory examinations reveal that four tocopherols (α, β, γ, δ) and tocotrienols (α, β, γ, δ) molecules have vitamin E antioxidant effect (Schneider 2005). It is thought that production of free radicals by oxidative stress is suppressed by vitamin E (Mohamed et al. 2018).

It seems that supplementation of vitamin E which is a strong antioxidant could be beneficial for cognitive functions.

The antioxidant properties of vitamin E have inspired researchers around the world to study and assess its effect on a variety of chronic conditions with oxidative stress constitutes such as neurodegenerative disease, cardiovascular disease, and cancers (Alscher and Hess 2017). Vitamin E, a lipid-soluble substance can readily enter the central nervous system and exerts antioxidant effect in the plasma membranes which mainly consist of lipids. Process of peroxidation of lipids harms the

integrity of the plasma membrane by damaging the polyunsaturated fatty acids; it is believed that vitamin E stops this process (Farina et al. 2017). Nano-molar concentration of tocotrienols prevents multiple mechanisms that end up with neuronal dysfunction (Kaneai et al. 2016).

In animal models of CNS ischemia, stroke, and Parkinson's disease, vitamin E proved to be useful and has been named as a neuroprotective substance (Farina et al. 2017; Schirinzi et al. 2019; Socci et al. 1995).

The daily required dose of vitamin E in diet is different according to age and in each country, but the recommended dose is between 3 and 15 mg (Galli et al. 2017). Enough amounts of tocopherols and tocotrienols exist in seed and edible oils such as peanuts, almond, palm oil, olive, soybean, and corn, whereas much lesser levels can be found in plant food with a low amount of lipids, such as vegetables and fruit (Shahidi and De Camargo 2016).

The oxidative stress in brain could be prompted due to vitamin E insufficiency, as proposed the dietary vitamin E avoids protein nitrosylation, in portion. Furthermore, decrease in level of vitamin E was associated with atrophy of cells and decreased branches of Purkinje and vitamin E supplementation could avoid the changes. Cumulatively, this information proposed that sufficient levels of vitamin E are necessary for anatomic integrity and normal functions of the Purkinje neurons (Ulatowski et al. 2014). Abnormal motor movements, ataxia, cognitive impairments, and lipid peroxidation are also linked with insufficient levels of vitamin E (Ulatowski et al. 2014). Specifically, supplementation of tocopherol had prevented lipid peroxidation in Ttpa−/−mouse brains and avoided development of neurological symptoms (Yokota et al. 2001). Fukui et al. (2015) confirmed that cognitive impairment in mice due to long-term vitamin E inadequacy was caused by upsurge of oxidation in brain.

The decline in cognitive abilities was witnessed in the vitamin E deficient three-month-old mice. Additionally, a significant surge in products of lipid peroxidation in the cerebrum, cerebellum, and hippocampus of 6-month-old mice which were fed with vitamin E free diet was observed. In vitamin E deficient mice, serum cholesterol level was significantly high (Fukui et al. 2015).

2.2 Animal Studies and Vitamin E

The importance of oxidative stress process in Alzheimer's disease has already been identified, but it must be remembered that oxidative stress takes place initially in AD, well before the formation of Aβ plaque. Actually, using diverse models of AD, the oxidative stress amplification was established, as shown by increased lipid peroxidation (Praticò et al. 2001; Resende et al. 2008). Additionally, a surge in the functions of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase (SOD) was similarly detected (Resende et al. 2008). These changes markedly happened before the development of Aβ plaques and NFTs, which clearly indicates the early progression of oxidative stress in Alzheimer's disease. (Praticò

et al. 2001; Resende et al. 2008). Interestingly, a decline in levels of vitamin E, along with decreased glutathione (GSH), has been documented in conjunction with surge of levels of oxidative stress markers (Resende et al. 2008). These findings indicate the significance of pathogenic contribution of oxidative stress in AD and proposing that antioxidants use could be beneficial for prevention and treatment of AD specifically vitamin E due to its strong antioxidant effects.

Multiple experimental studies were carried out to determine the efficacy of vitamin E in cognitive impairment in AD and concluded the beneficial properties of vitamin E on health. With the oral supplementation of vitamin E in rates which were infused with Aβ 1–42, the results showed that this vitamin prohibited memory and cognitive impairments (Yamada et al. 1999). Memory impairments and surge in oxidative stress were observed in mice treated with Aβ 1–42 and it caused a rapid increase in activities of the copper, Zn-SOD in cytoplasm and mitochondrial Mn-SOD in the cerebral cortex, as well as hippocampus. The results also indicated that better outcome will be achieved by earlier supplementation of vitamin E (Jhoo et al. 2004).

Nishida et al. examined the implications of alpha-tocopherol deficiency with APPsw AD transgenic mice where the deficiency of alpha-tocopherol in the brain contributes to oxidative stress (Nishida et al. 2006). In the Morris water maze, contextual fear conditioning, and novel object recognition experiments, the double mutant Ttpa−/−APPsw mice getting an alpha-tocopherol-deficient regime developed a severe and developed cognitive impairment, with a surge in Aβ deposits compared to APPsw mice. Though, alpha-tocopherol supplementation to Ttpa−/− APPsw mice moderately inhibited cognitive impairment growth and decreased Aβ deposits in the cerebral cortex and hippocampus. While the condition recovered, the recovery was partial, possibly because only 10% of alpha-tocopherol can be recovered even after alpha-tocopherol supplementation in the brain of Ttpa−/− mice compared to wild form mice (Nishida et al. 2006). Furthermore, the exact same group established that oxidative stress reduced Aβ elimination from the brain and blood due to alpha-tocopherol deficiency and led to the formation of Aβ in the brain and plasma of the Ttpa−/−APPsw mouse, which was reduced by alpha-tocopherol supplementation (Nishida et al. 2009). Alpha-tocopherol deficiency, however, had no effect on the production of Aβ, although its accumulation was attributed to a decrease in the clearance of Aβ. The expression level of the Aβ-degrading peptidase IDE was definitely reduced in the brain of the Ttpa−/− mouse. Moreover, relative to WT, the Aβ aggregates were elevated in the brain of Ttpa−/− mice. The Aβ was also accumulated in the blood due to impairment in clearance. Obviously, in the plasma membrane fraction of the Ttpa−/− mouse liver, the amount of LRP-1, the Aβ receptor that brings Aβ into the liver cells, has decreased, leading to a decrease in the clearance of Aβ and its accumulation in the blood, explaining the cause of increased Aβ levels in the Ttpa−/-APPsw mouse plasma (Nishida et al. 2009). Overall, these findings showed that low levels of vitamin E in Alzheimer's disease models induced cognitive decline and buildup of Aβ, whereas administration of vitamin E reversed the disorders, at least moderately.

Plasma phospholipid transfer protein (PLTP) is responsible for vitamin E transportation and its insufficiency caused reduction in brain's vitamin E levels in mice. A surge in oxidative stress and brain Aβ 1–42 level was demonstrated in PLTP-knockout (PLTP-KO) mice, while the expression of the synaptic function marker, synaptophysin was decreased. Furthermore, memory impairments were observed in PLTP-KO mice 7 days after Aβ 25–35 administration. Supplementation of vitamin E in PLTP-KO mice contributed to the prevention of memory deficits caused by Aβ25–35 and oxidative stress (Desrumaux et al. 2013).

The significance of the timing of vitamin E supplementation was stated by Sung et al. (Sung et al. 2004). Early administration of vitamin E leads to decrease in levels of Aβ1–40 and Aβ1–42 and amyloid deposits in younger Tg2576 mice receiving vitamin E supplements from 5 months of age. This effect was not observed in elder Alzheimer's disease mice receiving the same amount of vitamin E from the age of 14 months after the formation and deposition of amyloid plaques.

Nevertheless, vitamin E administration may hamper oxidative stress induced in both classes (Sung et al. 2004).

Besides the effects on Aβ deposits, vitamin E caused beneficial effects on Tau hyperphosphorylation, the other component of AD. Supplementation of vitamin E postponed the development of Tau pathology in the central nervous system, reduced oxidative stress, and enhanced motor function in transgenic mice due to effect of different kinase enzymes, such as p38, that caused hyperphosphorylation of tau protein (Feijoo et al. 2005). Primary cortical neurons incubated with Aβ exhibited p38 activation which leads to tau hyperphosphorylation (Giraldo et al. 2014). Presence of phospho-p38 mitogen-activated protein kinase (MAPK) immune reactivity at early stage of the AD was demonstrated in post-mortem brains of the patients (Sun et al. 2003). Giraldo et al. (2014) confirmed that Aβ-induced activation of p38 MAPK caused hyperphosphorylation of tau protein. Additionally, in vivo, higher levels of phosphor-p38 in the hippocampus of APP/PS1 transgenic mice were noted compared to wild type animals, but not in the cerebral cortex, while abolishment of this protein was noted in animals received vitamin E supplementation (Giraldo et al. 2014). Many studies have shown that vitamin E could be capable of counteracting Aβ-induced effects and hyperphosphorylation of tau, affecting both AD hallmarks.

Recently, Azimi et al. (2020) used chronic cerebral hypoperfusion-induced neurodegeneration model in rats to examine the neuroprotective effects of vitamin E (Azimi et al. 2020). Vitamin E increased cell viability in this study and decreased the amount of oxidants in the hippocampus compared to the untreated group. However, compared to untreated control groups using Morris water maze tests, there were no substantial results in enhancing memory and learning with the use of vitamin E alone. Interestingly, the combination of coenzyme Q10 and vitamin E enhanced learning and memory, cell viability and decreased hippocampal oxidant levels compared to the untreated 2VO group (Azimi et al. 2020).

Augmented risk of Alzheimer's disease development is associated with variations of the APOE gene. Better behavioral performance was demonstrated in Apolipoprotein E (Apo E)-deficient mice, receiving vitamin E supplementation for 1 year,

compared to those getting a normal diet. Improved performance was correlated with preserving the dendritic structure in vitamin E treated Apo E deficient mice. In addition, these mice exhibited natural amounts of lipid peroxidation and glutathione. These findings confirmed that dietary vitamin E supplementation has a neuroprotective action in mice with Apo E deficiency against oxidative insults and prevented defects in cognitive and neuropathological changes (Veinbergs et al. 2000). This study correlated the antioxidant effect of vitamin E with the prevention of cognitive deficits. Coherent with these findings, Ishihara et al. (2013) demonstrated that alpha-tocopherol enhanced cognitive performance, minimizing oxidative stress. Transgenic Alzheimer's disease mice exhibited lowered levels of alpha-tocopherol and GSH, whereas oxidized glutathione (GSSG) and lipid peroxidation in the cerebral cortex and hippocampus increased at 4 months of age. Nevertheless, alpha-tocopherol dietary supplementation mitigated the decrease in GSH levels and the rise in GSSG and TBARS. In addition, mice at 6 months of age displayed cognitive decline, but supplementation with alpha-tocopherol could enhance cognitive function. Magnetic resonance imaging using 3-hydroxymethyl-proxyl as a probe measured brain redox status and revealed a 4-month-old rise in reactive radicals' development in the brains of Alzheimer's disease mice, which was decreased by alpha-tocopherol supplementation. These results showed that cognitive dysfunction can be associated with oxidative stress and alpha-tocopherol can boost cognitive performance, minimizing oxidative stress (Ishihara et al. 2013).

2.3 Human Studies and Vitamin E

2.3.1 Epidemiological Studies

A correlation between vitamin E supplementation and a decreased risk of development of Alzheimer's disease has been shown in epidemiological studies. A prospective study in 1998 with 633 persons 65 years or older had shown that none of the 27 consumers of vitamin E supplements had Alzheimer's disease after an interval of 4.3 years of follow-up (Martha Clara Morris et al. 1998). Another cohort research, in 2002, from the Netherlands, supported this result with a 6-year follow-up (Engelhart et al. 2002). In the same year, another cohort study, performed between 1993 and 2000, reported the findings of 815 persons aged 65 years or older without Alzheimer's disease at the start of the study and followed for an average of 3.9 years. The results of the study demonstrated that diet with vitamin E without other antioxidant substances could be accompanied with a decreased risk of rising of Alzheimer's disease. Though, this relationship was not demonstrated among the individuals having the APOE4 allele (Morris et al. 2002). Another cross-sectional and prospective study (Cache County, Utah) stated that administration of vitamin E and vitamin C together is linked with lower incidence and decreased prevalence of Alzheimer's disease. However, they did not find significant evidence of protecting properties of these antioxidant substances used alone (Zandi et al. 2004). Results

from another prospective cohort research (The Rotterdam Study) that followed overall 5395 individuals, 55 years or older for 9.6 years, showed decrease in the long-term risk of Alzheimer's disease development. Prominently, the significant findings were only existed in those people with higher vitamin E contained food intake. Nonetheless, the risk of dementia was not decreased in participant with average vitamin E intake (Devore et al. 2010). Analyzed data from another dementia cohort study (The Canadian Study of Health and Ageing) from 1991 to 2002, included 560 patients, revealed that intake of vitamin E supplements was related with fewer risk of cognitive impairment (Basambombo et al. 2017).

In comparison, three other studies found no correlation between the use of vitamin E and decrease in risk of cognitive impairment. The first study included 2969 follow-up participants for 5.5 years every 2 years, concluding that the supplementary intake of vitamin E and vitamin C separately or concurrently did not decrease the chance of Alzheimer's disease or dementia during 5.5 years of follow-up (Gray et al. 2008). The other study, included 3385 men from The Honolulu-Asia Aging Study, demonstrated that vitamin E and vitamin C supplementations could be protective against vascular dementia and may recover cognitive function in later stages of life. However, there was no significant protective effect for Alzheimer's dementia (Masaki et al. 2000). The third study that included 980 participants, 65 years and older in the Washington Heights-Inwood Columbia Aging Project, did not detect any association between dietary supplementation or total administration of vitamin E and reduced chance of Alzheimer's disease (Luchsinger et al. 2003). However, from these observational studies we cannot prove absolute value of vitamin E in MCI and Alzheimer's disease, it needs more complex clinical trials.

2.3.2 Clinical Trials

Clinical trials have mixed and inconsistent results on usefulness of vitamin E for prevention and treatment of cognitive impairment and AD. For the first time, a research by Sano et al. in 1997 revealed some information about vitamin E effectiveness as treatment in cognitive impairment and AD. Administration of vitamin E was focused mainly in patients with Alzheimer's disease who have moderately severe deterioration in cognitive functions (Sano et al. 1997). In this study 341 AD were included and 2000 IU per day of vitamin E or placebo were administered for 2 years (Sano et al. 1997). As outcomes, the study measured interval to incident of death, damage to capacity of accomplishing simple tasks of regular life, hospitalization, or severe dementia (Sano et al. 1997). The result concluded that this dose of vitamin E decelerates Alzheimer's disease progression. Another double-blind trial in 2005 enrolled 769 mild cognitive impairment's patients and vitamin E 2000 international unit per day or placebo was given for 3 years (Petersen et al. 2005). The results show no advantage in vitamin E compared to placebo group (Petersen et al. 2005). Remarkably, in a study in 2009 participants who received

vitamin E 800 IU/day for 6 months found two distinct subclasses in the supplemented vitamin E class. First subclass titled "respondents" to vitamin E, after the treatment the parameters of oxidative stress were lower and also marks on cognitive examinations were preserved. Though, in second subgroup called "non-respondents," they did not find beneficial effect of vitamin E and not prevented the oxidative stress. Likewise, the level of cognition declined even more than placebo group. They concluded that cognitive functions are preserved in those patients once vitamin E reduces oxidative stress. Conversely, it could be detrimental, if vitamin E fails to prevent oxidative stress (Lloret et al. 2009).

However, in 2014, Dysken et al. (2014) enrolled 613 patients who were suffering slight to modest AD and an equal dose of 2000 IU per day of vitamin E or placebo in a double-blind, placebo-controlled, parallel group, randomized clinical trial and the results indicated that vitamin E administration decreased cognitive deterioration in patients who suffered from slight to modest cognitive impairment (Dysken et al. 2014).

PREADVISE study in 2017 found that low dose of vitamin E (400 IU per day) is not able to prevent dementia by administration of low doses of the vitamin to 7540 asymptomatic elderly men (Kryscio et al. 2017). They also examined the consequences of supplementation of vitamin E and selenium on AD prevention and found that vitamin E and selenium and as well as their combination could not prevent dementia (Kryscio et al. 2017).

Nevertheless, efforts to obtain an appropriate cure for AD with vitamin E based formulations have continued.

There are also several studies testing the efficacy of various types of vitamin E or co-administration of vitamin E with other substances that may have beneficial effects on dementia progression (Ibrahim et al. 2017).

2.4 Critical Analysis and Reflection on Vitamin E Neuroprotective Effects

Since oxidative stress is considered to be a preliminary hallmark of cognitive impairments such as Alzheimer's disease, the scientific community has made several attempts to use antioxidant treatment as a potential therapy. As it was discussed earlier, however, evidence is indicating the inadequate efficacy of vitamin E in decelerating progression of dementia; the data is diverse and uncertain. Nevertheless, why do vitamin E and other antioxidants are not able to alter the progression of cognitive decline in AD? This issue indicates the inconsistency of oxidative stress: attempts to enhance mechanisms against oxidative stress have not proven efficacious (Halliwell 2012). Halliwell figured out three possibilities: the extrapolation of animal-to-human outcomes, the lack of basic dietary status measures in cohort studies in human, and certain antioxidant substances may have pro-oxidant effects (Halliwell 2013). It was mentioned above that vitamin E plasma levels in patients

with AD are low; therefore, we have proof of "baseline nutritional status." It is a fact that measurement of the baseline vitamin E often does not take place before the start of the key studies. The extrapolation of findings from animal models to humans, however, is not trivial. The correct oxidative stress calculation methods are still under discussion and are often not precise or relevant (Kalyanaraman et al. 2012; Ribou 2016). Many studies about the role of oxidative stress in cognitive impairment and AD are not novel and techniques may not be up to date. It is highly advisable to track the antioxidant effects by using assays of an oxidative stress biomarker. However, it may not be easy to pick a good biomarker for oxidative stress. To be specific about the results, the study of oxidative stress on particular proteins involved in the disease has been suggested. A particular pathological mechanism and a method for clinical monitoring and evaluation of outcomes may better reflect these markers (Frijhoff et al. 2015).

The hopelessness of supplementation of vitamin E in altering the oxidative stress, as it was observed by Lloret et al., is a model of the significance of controlling oxidative stress in patients (Lloret et al. 2009). In this study, it was demonstrated that cognitive progress was only seen in patients with reduced oxidative stress, but non-respondents deteriorated their cognitive test performance. Another important point is vitamin E bioavailability, which is multifaceted and affected by many causes, such as the variations in absorption, the intake of competing food, sex, age, smoking, weight, and genetic polymorphisms. Plant sterols, eicosapentaenoic acid and retinoic acid, and dietary fibers are classified as substances that compete with vitamin E absorption (Bieri et al. 1981; Bjørneboe et al. 1990; Richelle et al. 2004). Additionally, in man, the rate of absorption of vitamin E into the blood ranges from 20 percent to 80%, primarily owing to variations in nutrient's quality and type of vitamin E. Lipoproteins are used to transport vitamin E into the bloodstream (Kolleck et al. 1999). In particular, high-density lipoprotein (HDL) particles provide entry into the brain and spinal cord of alpha-tocopherol in vivo, and high-density lipoprotein levels differ greatly among individuals (Goti et al. 2000). Inside the cell, vitamin E attaches to alpha-TTP, a greatly expressed carriage protein in the brain of patients with Alzheimer's disease, particularly in oxidation (Ulatowski et al. 2012).

Bioavailability of vitamin E is also affected by age and gender. Vitamin E levels rise in plasma after 60 years, but fall after the age of 80 (Campbell et al. 1989). Females tend to have much higher extreme alpha-tocopherol plasma levels than males, possibly owing to variations in high-density lipoprotein levels between sexes (Leonard et al. 2005).

Smokers, however, have lower serum alpha-tocopherol levels than who do not smoke, while the variations can be due to variances in nutritional habits (Galan et al. 2005; Shah et al. 2015). Obesity has a negative correlation to serum levels of alpha-tocopherol (Gunanti et al. 2014). In particular, regardless of gender, there were correlations between waist-to-hip ratio and also waist circumference with the concentration of alpha-tocopherol in serum (Öhrvall et al. 1993; Wallström et al. 2001).

Finally, genetic polymorphisms in genes that encode those proteins which are included in the biotransformation of vitamin E may similarly describe inter-individual bioavailability variations (Borel et al. 2007, 2015,).

Studies have made it clear that vitamin E homeostasis has been linked with more than 50 distinct single-nucleotide polymorphisms (SNPs).

The efficiency of vitamin E in passing through the blood–brain barrier and increasing levels in the brain is another point. Therefore, it is vital to demonstrate the effectiveness of vitamin E in reducing brain oxidative damage (Galasko et al. 2012). Much other research might be confusing because of the supplementation of vitamin E or because of the supplementation of a group of vitamins, nutrients, and formulations used (Cervantes and Ulatowski 2017).

It is now believed that the moderate physical exercise along with the Mediterranean diet is the first line protection method against the development and progress of Alzheimer's disease. In the majority of cases, however, the research underlining this principle were observational. Therefore, broad, multicenter randomized clinical trials are expected to explain the actual relation between modest exercise and balanced Mediterranean cognition regime in the elderly. Obviously, a diet containing enough antioxidants can be more acceptable than the ingestion of antioxidants in a drug form, since their bioavailability may vary (Solfrizzi et al. 2011).

The brain which has a complex structure is an additional important factor. Oxidative stress results in neuronal damage and neurodegeneration, apoptosis, and cells death, so that neuronal networks modify and compensatory response is activated. Interestingly, in young well and healthy individuals who carry ApoE4/4 reductive stress was found instead of oxidative stress (Badia et al. 2013). This situation makes the active effectiveness of antioxidant therapy enormously complicated. It is incredibly difficult to correctly reshape or regenerate the lost neural network and even more difficult if we consider this issue to be an aging brain or a brain that compensates.

2.5 Conclusion

The current clinical evidence remains inconclusive, despite a clear justification for the importance of vitamin E for prevention and treatment of Alzheimer's disease. Epidemiological studies have shown different outcomes about vitamin E supplementation but it was consistent that intake of large amount of vitamin E from diet can be beneficial. Many clinical studies have failed to reproduce the promising results documented in animal studies, despite significant results in experimental studies using antioxidants in Alzheimer's disease models. However, only the alpha-tocopherol isoform has been used in clinical researches yet and has many drawbacks. Lack of assessment of participants' antioxidant and dietary levels at baseline is one of the drawbacks. Therefore, sufficient evidences do not exist to support or discard the presumption that vitamin E could be an effective option to delay and prevent the Alzheimer's disease and still this subject is an area of researches.

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