

Effects of vitamin E on neurodegenerative diseases: an update

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Vitamin E deficiency is associated with many neurological problems. Although the mechanisms of vitamin E action in neurodegenerative diseases are not clear, there are many possible mechanisms. Examples of such mechanisms are the protective effects of vitamin E against oxidative stress damage and its suppressive role in the expression of many genes involved in the development of neurodegeneration. Many studies have evaluated the relationship between vitamin E intake or vitamin E levels in body fluids and neurodegenerative diseases. Some studies concluded that vitamin E can play a protective role in neurodegeneration with respect to diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), stroke and amyotrophic lateral sclerosis (ALS). Vitamin E supplementation was also associated with risk factors for some neurodegenerative diseases. In this review, we discuss the possible effects of vitamin E on the development and course of AD, PD, stroke and ALS, and the potential mechanisms involved.

Key words: vitamin E, oxidative stress, neurodegeneration, Alzheimer's disease, Parkinson's disease

INTRODUCTION

Characterized by specific neuronal cell losses, neurodegenerative diseases are among the leading cause of disabilities in elderly people (Knight, 1997; Floyd and Hensley 2002, Ricciarelli et al., 2007). Oxidative stress has important roles in the pathogenesis of neurodegenerative diseases. It is known that oxidative stress levels in the brain increase with age (Floyd and Hensley, 2002). Oxidative stress occurs due to the presence of free radicals in high amounts and/or insufficient levels of antioxidants (Tu and Weissman, 2004).

Reactive oxygen species (ROS) cause cell damage by means of lipid peroxidation and oxidation of proteins and DNA (Halliwell, 1999). Therefore, cells have developed various defense and repair mechanisms in order to cope with oxidative stress. Antioxidants such as vitamin E play important roles in these defense mechanisms (Halliwell, 1999; Ricciarelli et al., 2007). In addition, vitamin E is the main lipophilic antioxidant in

the brain by concentration (Kontush and Schekatolina, 2004). Vitamin E is effective in the neutralization of unstable lipid peroxide radicals produced from polyunsaturated fatty acids (Burton and Traber, 1990; Traber et al., 1990; Ulatowski and Manor, 2015). It is believed that vitamin E, through these mechanisms, may have therapeutic effects in many neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), stroke and amyotrophic lateral sclerosis (ALS) as illustrated in Fig. 1 (Sung et al., 2004; Ascherio et al., 2005; Ricciarelli et al., 2007).

There is a large number of studies in the literature evaluating the correlation between the level of vitamin E in the serum and cerebrospinal fluid, and AD, PD, stroke and ALS (Fernandez-Calle et al., 1992; Graf et al., 2005). However, results of these studies are contradictory (Fernandez-Calle et al., 1992; Paraskevas et al., 2003). Another important research area is the role of vitamin E supplementation. Some studies indicate that vitamin E supplementation has protective roles

in these neurodegenerative diseases, while several others could not find such an effect (Scheider et al., 1997; Miyake et al., 2011; Hughes et al., 2016; Yang et al., 2017).

This review focuses on the potential effects and mechanisms of vitamin E action in AD, PD, stroke and ALS.

Oxidative stress and neurodegenerative diseases

Approximately 50% of the brain’s dry weight is made up of lipids (Behl, 1999). The myelin sheath is characterized by 75–80% lipids and membranes and neurons are rich in poly-unsaturated fatty acids (Poitelon et al., 2020). Therefore, the central nervous system (CNS) is prone to oxidation (Behl, 1999). It is known that oxidative stress has a key role in AD, PD, ALS, stroke and other age-related diseases (Behl, 1999; Abou-Sleiman et al., 2006). The effects of the protective antioxidant system deteriorates with age (Behl, 1999). Additionally, cell membranes become more vulnerable to oxidation with age. Oxidation general-

ly targets lipids (cholesterol, poly-unsaturated fatty acids), proteins and nucleic acids (Grimm et al., 2016; Cheignon et al., 2017). It is believed that increased oxidative stress, abnormal mitochondrial function and excitotoxicity are the most probable mechanisms behind neurodegeneration, even though the causes of AD, PD, ALS and stroke have not been fully explained (Behl, 1999; Abou-Sleiman et al., 2006). In addition, it is believed that oxidative stress may increase the risk of progression of neurodegenerative diseases by causing abnormal protein folding and function (Bossy-Wetzal et al., 2004; Ricciarelli et al., 2007).

Ischemia triggers processes that increase free radical formation through different pathways. Firstly, glutamate, which activates the N-methyl-D-aspartate (NMDA) receptor and other ionotropic receptors, is released in massive amounts from neurons and glia. Ischemia also causes an increase in intracellular Ca²⁺ concentrations, leading to excessive activation of proteases, lipases, nucleases and protein kinases, as well as increases in nitric oxide synthases (NOS) (Cherubini et al., 2008). This process is called excitotoxicity. As a result, these enzymes damage cellular and extracellular

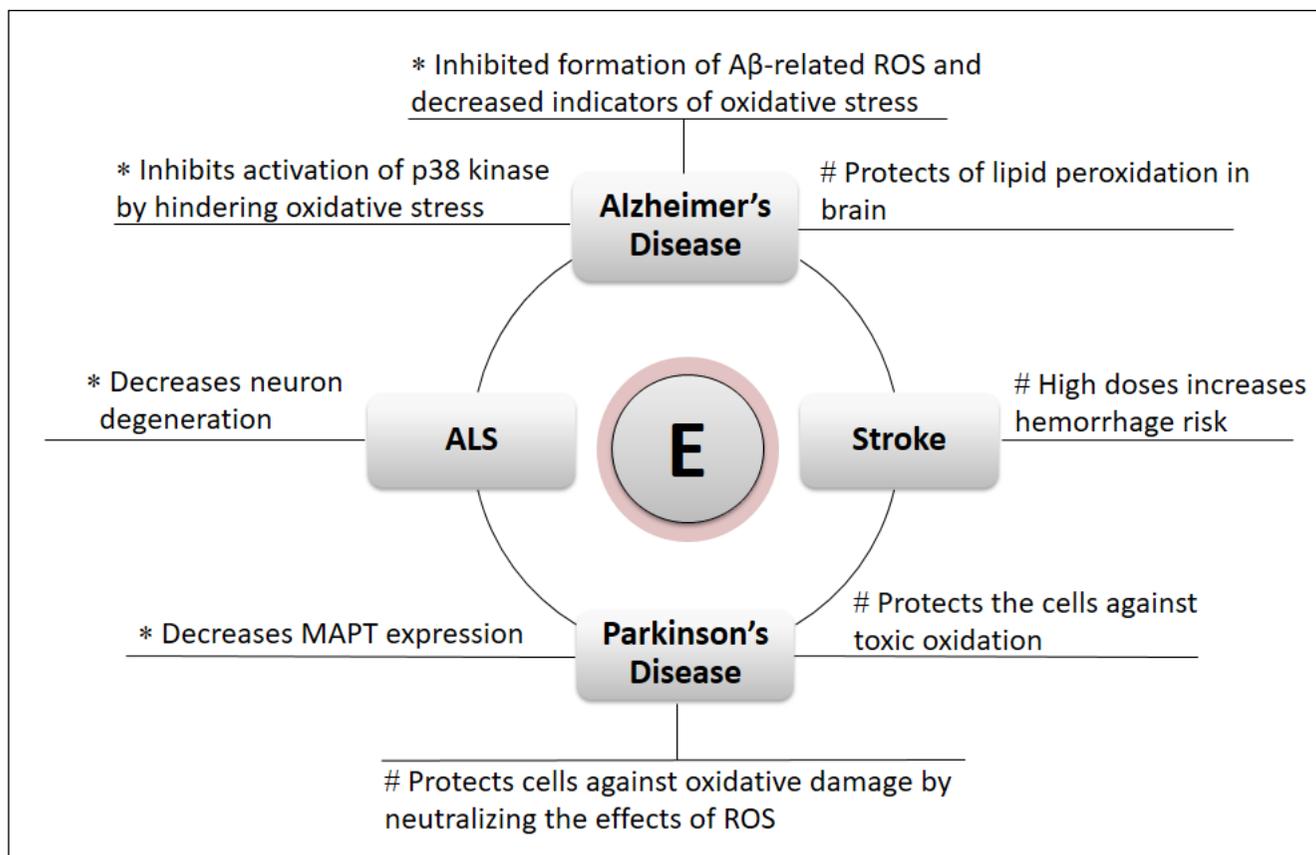


Fig. 1. Mechanisms and effects of vitamin E on neurodegenerative diseases. The protective effects of vitamin E against lipid peroxidation, oxidative damage and toxic oxidation are similar in PD, AD and ALS. * This symbol represents mechanisms. # This symbol represents effects.

structures and kill neurons by increasing ROS formation following nitric oxide release (Rodríguez-Lara et al., 2016). Additionally, excitotoxicity events increase the expression of phospholipase A2 and cyclooxygenase (COX), which directly produce oxygen free radicals. Oxidative stress also increases due to the influx of inflammatory cells such as neutrophils, monocytes and macrophages during reperfusion. These cells secrete immune mediators such as TNF- α and IL-1 β , which increase the expression of pro-inflammatory genes and production of ROS (Cherubini et al., 2008).

Amyloid β formation is related to oxidation and inflammation. Amyloid β is believed to cause potassium efflux from neurons, which can activate inflammasomes and IL-1 β secretion (Salminen et al., 2009). This increases oxidative stress, which causes the generation of ROS. These events further upregulate the generation of amyloid β plaques and increase phosphorylation of the tau protein through various mechanisms (Cassidy et al., 2020).

Vitamin E and neurodegenerative diseases: mechanisms and actions

There are eight forms of vitamin E (α -, β -, γ -, δ -tocopherol, and α -, β -, γ -, δ -tocotrienol), all of which are fat-soluble compounds that are synthesized in plants. α -tocopherol, the most common form of vitamin E in human tissues, has long been considered as a cytoprotective factor with suggested roles in preventing oxidation, as well as inflammatory and degenerative processes (Galli et al., 2017). First described in 1922 by Evans and Bishop as a dietary factor essential to prevent fetal reabsorption in rats (Evans et al., 1922), vitamin E was soon after identified as an antioxidant of polyunsaturated lipids (Galli et al., 2017).

A number of studies have pointed to the important effects of vitamin E in promoting health. Firstly, genetic vitamin E deficiency causes many neurological problems (Joshi and Praticò, 2012). This type of deficiency is triggered by mutations in the *TTPA* gene which encodes the tocopherol transfer protein (TTP). This results in a condition called ataxia with vitamin E deficiency (AVED), which is characterized by difficulty coordinating movement (ataxia), aphasia, loss of reflexes and numbness as some of its symptoms (Schuelke, 2016). The biological half-life of vitamin E in the brain is very short, which makes the brain particularly sensitive to its deficiency. In addition, expression levels of mutations in *TTPA* are markedly elevated in brain samples from human patients afflicted with oxidative stress-related neurodegenerative diseases such as AVED and AD. Taken together,

these findings demonstrate that vitamin E and TTPA may have critical roles in neurodegenerative diseases (Joshi and Praticò, 2012; Ulatowski and Manor, 2015).

As a lipid-soluble, chain-breaking antioxidant, vitamin E plays a key role in maintaining the integrity of cellular membranes by protecting them against oxidative stress caused by the peroxidation of polyunsaturated fatty acids (Ricciarelli et al., 2007; Lee and Ulatowski, 2019). With its chain-breaking antioxidant function, vitamin E also has both a protective and curative effect on cellular membranes in the CNS (Joshi and Praticò, 2012). Given these functions, there is good indication that vitamin E may have a unique, original and special role in neurological diseases (Ulatowski and Manor, 2015).

Antioxidant vitamins protect cells against oxidative damage by neutralizing the effects of ROS (Ricciarelli et al., 2007). Vitamin E is one of the strongest dietary antioxidants which protects proteins, lipids and nucleic acids from oxidation as it is an oxygen radical scavenger (Niki et al., 1989; Fariss and Zhang, 2003). It has been shown that application of vitamin E to cell membranes protects the cells from toxic oxidation (Fariss, 1997; Fariss and Zhang 2003).

The antioxidant properties of tocopherols regulate oxidative damage; however, vitamin E also shows non-antioxidant features that regulate cell signaling and inflammation (Cook-Mills and McCary, 2010). The anti-inflammatory activity of vitamin E, as well as its antioxidant features, may together confer it a neuroprotective role (Ricciarelli et al., 2007). Since chronic inflammation is associated with neurodegenerative diseases (McGeer and McGeer, 2001), it is important to understand how vitamin E inhibits inflammation. The anti-inflammatory role of vitamin E does not seem to be related to its antioxidant activity. Several molecular mechanisms are involved in the anti-inflammatory effects of vitamin E (Reiter et al., 2007). Among others, it has been shown that vitamin E supplementation reduces the production of prostaglandin E2, which is a mediator of inflammation. This is caused by inhibiting the enzymatic activity of cyclooxygenase 2 (COX-2), which is a rate limiting enzyme involved in the conversion of arachidonic acid to prostaglandins (Lewis et al., 2019). Tocotrienols downregulate Src, mitogen activated protein kinases (MAPKs) and extracellular signal-regulated kinases (ERKs) in neurons. In addition, α -tocotrienol and α -tocopherol bind to 5-lipoxygenase (5-Lox) to inhibit it independent of its antioxidant activity. Since 5-Lox and signaling through the Src/MAPK/ERK pathways play an important role in inflammatory responses, tocotrienols may influence inflammation by inhibiting their activities (Cook-Mills and McCary, 2010).

β - and γ -secretase enzymes and this transformation produces insoluble 39–43 kDa peptide fragments. It is known that among the amyloid β fragments, isophorone has cytotoxic effects that accelerate oxyradical formation and causes neurodegeneration (dos Santos Picanco et al., 2016).

Neurofibrillary tangles are the second most important indicator of AD. Hyperphosphorylated tau proteins are the most significant components of neurofibrillary tangles. Phosphorylated tau accumulates in neurons during AD. Phosphorylated tau loses its normal function stepwise and compounds microtubules, before coming to a stable state that is prone to aggregation (Xia and Mo, 2016).

Biosynthesis of cholesterol and an increase in cholesterol levels are correlated with an increase of proteolysis mediated by β - and γ -secretase enzymes (Chin and Tay, 2018). This relationship was confirmed in animal studies, as it has been shown that amyloid plaque formation increases in rats fed a high cholesterol diet (Refolo et al., 2000).

Glutamate dysfunction is an important potential mechanism in the etiology of AD. Glutamate is a key excitatory neurotransmitter in the CNS, playing an important role in memory formation and learning (Esposito et al., 2013). The accumulation of excess amounts of glutamate in the brain leads to the hyperactivation of the glutamate-N-methyl-D-aspartate (NMDA) receptor, which leads to excitotoxicity due to intracellular calcium overload, resulting in cell death. This is a potential mechanism underlying neurodegeneration in AD). Amyloid β formation affects glutamate accumulation, which increases NMDA receptor activity. Activation of the NMDA receptors in turn increases amyloid β production, creating a positive feedback loop (Wang and Reddy, 2017; Chin and Tay, 2018). In addition, constitutive activation of this pathway also increases phosphorylation of the tau protein, which causes the destabilization of microtubules, leading to synapse loss and neuronal death (Esposito et al., 2013).

Potential mechanism of vitamin E in Alzheimer's disease

Amyloid β accumulation in AD increases free radical formation, and also indirectly causes the formation of pro-oxidants by stimulating inflammatory cells. It is thought that vitamin E may contribute to protection against lipid peroxidation in the brain thanks to its antioxidant activity. For example, in neuronal cultures, vitamin E has been shown to inhibit the formation of amyloid β -related ROS and lead to decreased indicators of oxidative stress (Yatin et al., 2000).

It is also known that inflammatory pathways are important in the pathogenesis of AD. It has been observed

that there are increased levels of the pro-inflammatory cytokines IL-1 β , IL-6 and TNF α in both the brain and cerebrospinal fluid in AD. It has also been found that both TNF α and IL-1 β increase levels of APP and amyloid β peptides (Heppner et al., 2015). Prostaglandins and free radicals are secreted by microglia astrocytes and resident macrophages in the CNS are present in increased numbers around senile plaques (Stuchbury and Münch, 2005). Prolonged microglia activation leads to the release of pro-inflammatory cytokines, which initiates a pro-inflammatory cascade and subsequently contributes to neuronal damage and loss (Wang et al., 2015). For example, overexpression of TNF- α can lead to increased amyloid β levels and reduce its clearance, which increases neuronal loss, leading to cognitive decline that includes learning and memory deficits in AD (Tobinick, 2009). An inhibitor of TNF- α synthesis suppresses amyloid β -induced activation of microglia, neuronal degeneration, memory dysfunction, and attenuates inflammation markers in the setting of neuroinflammation and AD (Zhang and Jiang, 2015). The inflammatory process itself leads to amyloid β aggregation, tau formation, synaptic damage, neuronal loss and the activation of other inflammatory participants (Wang et al., 2015). In addition, several studies suggest that pro-inflammatory cytokines in the CNS cross the blood-brain barrier and can contribute to cognitive decline in AD patients (Perry et al., 2007; Holmes et al., 2009). Increasing evidence therefore shows that inflammation plays a key role in AD pathogenesis.

Mitochondria are uniquely poised to play a pivotal role in both survival and death pathways in neurons because they are regulators of energy metabolism and apoptosis (Moreira et al., 2006). The dysfunction of proteins involved in electron transport in the mitochondria has been associated with the pathophysiology of AD (Blass and Gibson, 1991), as well as in PD and ALS (Hirai et al., 2001). Mitochondrial dysfunction plays an important role in the pathogenesis of AD as it decreases the formation of adenosine triphosphate (ATP) and increases the production of ROS. Impaired mitochondria lose the capacity to buffer Ca²⁺ and also release several pro-apoptotic factors, leading to apoptosis. Altogether, mitochondrial alterations contribute to AD pathogenesis (Moreira et al., 2010).

Oligomerization of amyloid β , which has an important role in AD, induces phosphorylation of p38 MAPK through increased oxidative stress. p38 also induces the hyperphosphorylation of tau proteins, which are involved in AD pathogenesis. Vitamin E inhibits activation of p38 by hindering oxidative stress, and thus prevents phosphorylation of tau proteins (Giraldo et al., 2014). It has been found that vitamin E supplementation prevents p38 activation. At the same time, vitamin E inhib-

its RCAN1, a calcineurin negative regulator, which causes dephosphorylation of tau protein (Giraldo et al., 2014).

The relationship between AD and vitamin E has been studied in a number of ways, some of which include evaluation of levels of plasma and serum vitamin E equivalents in AD and healthy subjects, vitamin E supplementation and dietary intake, as well as effects of the vitamin at the cellular level. Table I shows studies that examined serum and/or plasma levels of vitamin

E, Table II shows the studies that looked at vitamin E supplementations, Table III includes studies on dietary vitamin E intake and Table IV shows *in vitro* cell culture studies. These studies show that vitamin E levels in the sera of individuals with AD are very low, and that higher levels of vitamin E decrease AD risk. It has also been observed that dietary intake of vitamin E generally decreases AD progression, and that vitamin E acts as a protector, especially in individuals with a low risk of AD.

Table I. Studies evaluating serum and/or plasma vitamin E levels in Alzheimer's disease (AD).

References	Purpose and study population	Analysis method	Conclusion
Guan et al.	To evaluate the effects of vitamin E supplementation on oxidative stress biomarkers in individuals with and without AD.	Vitamin E levels were measured with HPLC.	Use of 400 mg/day of vitamin E for six months significantly decreased urinary 8-iso-PGF2 levels ($p < 0.05$). It was suggested that oxidative stress (8-iso-PGF2) in AD was eliminated by the antioxidant effect of vitamin E.
Mangialasche et al.	Evaluation of the correlation between all forms of plasma vitamin E and mild cognitive impairment and AD; 168 individuals with AD, 166 with mild cognitive impairment and 187 healthy individuals.	<ul style="list-style-type: none"> • α-tocopherol quinone (TQ) • 5-NO2-γ-tocopherol • All tocopherols All tocotrienols Measured with HPLC.	Tocopherol, tocotrienol and total vitamin E levels in individuals with AD and mild cognitive impairment were found to be lower than those in healthy individuals. Both diseases were found to be correlated with vitamin E damage levels.
Mangialasche et al.	Evaluation of the effects of all plasma vitamin E forms on AD; 232 individuals over the age of 80.	α -, β -, γ - and δ -tocopherol and tocotrienol levels were measured with HPLC.	It was found that individuals whose plasma levels of total tocotrienol, tocopherol and vitamin E were in the 3rd tertile had a higher risk of AD progression. It was also observed that while α -tocopherol is effective in inhibiting disease progression, the β form is generally the most effective.

Table II. Studies on vitamin E supplementation in Alzheimer's disease (AD).

References	Population	Source of vitamin E	Conclusion
Wang et al.	The study was conducted in APPswe/PS1dE9 transgenic rats.	100 mg/kg α -TQ (four weeks)	It was found that oxidative stress and amyloid β oligomers decreased. IL-6 and IL-1 production was inhibited.
Sinha et al.	The study was conducted in 4–6 month and 22–24 month-old rats.	1.5 mg/100 g (body weight) α -tocopherol	α -tocopherol had positive effects on age-related cognitive parameters.
Petersen et al.	769 individuals with mild cognitive impairment.	2,000 IU vitamin E supplementation	Vitamin E had no effect on individuals with medium range cognitive impairment.
Dysken et al.	613 individuals with mild and medium range cognitive impairment.	2,000 IU α -tocopherol/day supplementation was given for five years.	AD-related scores decreased more slowly than placebo.
Krysio et al.	3,786 individuals over the age of 60.	400 IU/day vitamin E (six years)	It was found that vitamin E has no effect on dementia, a primary cause of AD.

Table III. Studies on dietary vitamin E intake in Alzheimer's disease (AD).

References	Population	Vitamin E evaluation method	Conclusion
Morris et al.	3,718 individuals over the age of 65.	Vitamin E intake levels were evaluated with Harvard BTS.	It was observed that all tocopherol levels (not only α -tocopherol) have a protective effect against AD progression risk.
Devore et al.	5,395 individuals over the age of 55.	Vitamin E intake levels were evaluated with BTS (9.6 years of follow-up, on average)	Dementia progression risk was found to be lower in individuals with higher dietary vitamin E intake in the beginning. Individuals whose vitamin E intake levels are in the 3rd tertile have 25% less risk than the ones in the 1st tertile (AD).
Moris et al.	815 individuals over the age of 65.	Vitamin E intake levels were evaluated with BTS (for 3.9 years on average).	Vitamin E had a protective effect against AD in individuals whose <i>apo e4</i> allele (AD risk factor) was negative.
Laurin et al.	2,459 male individuals 45–68 years of age.	Vitamin E intake levels were evaluated by means of a 24-hour food consumption record.	Midlife vitamin E intake was not found to be correlated with late-life dementia and/or Alzheimer's risk.

Table IV. Cell culture studies of Alzheimer's disease (AD).

References	Purpose	Conclusion
Grimm et al.	Evaluation of the effects of different α -tocopherol forms on amyloid β formation in neuron culture	Amyloid β levels increased after exposure to all tocopherol forms. Tocopherols also increased formation of β and γ secretases.
Ayasolla et al.	Evaluation of the effect of vitamin E on Alzheimer-related indicators in rat astrocytes.	TNF- α , IL-1H levels, which increase inducible NOS (iNOS) expression, were suppressed with vitamin E.

Multi-effects and mechanisms of vitamin E on Parkinson's disease

Parkinson's disease

PD is the second most common neurodegenerative disease which affects 6 million people worldwide (Lesage and Brice, 2009; Bhimani, 2014). PD is characterized by rigidity and shaking which affect mobility, real-like dreams and hallucinations affecting sleep quality, confusion and depression (Carter et al., 2008; Pretzer-Aboff et al., 2009). In PD, patients suffer from pathological loss of dopaminergic neurons in the substantia nigra pars compacta in the midbrain. The loss is responsible for motor symptoms of the disease (Jiang and Dickson, 2018).

Data in the literature shows that brains of PD patients have low levels of endogenous antioxidants (glutathione and co-enzyme Q10), increased dopamine oxidation and high iron levels (Lan and Jiang, 1997; Götz et al., 2000; Sutachan et al., 2012). Oxidative metabolism of dopamine causes the formation of highly cytotoxic hydroxyl radicals, by producing peroxides which react with ferrous iron (Olanow, 2003). It was also reported that lipoprotein oxidation increases in the substantia nigra of PD patients (Dexter et al., 1994). In PD patients, increased oxidative stress is correlated with the degeneration of dopaminergic neurons (Lv et al., 2015). In addition to these mechanisms, one of the possible risk factors underlying PD are genetic variants (Wüst et al., 2016). To date, molecular genetic analyses have identified over 500 distinct DNA variants in five disease genes associated with familial PD; α -synuclein (*SNCA*), parkin (*PARK2*), PTEN-induced putative kinase 1 (*PINK1*), DJ-1 (*PARK7*) and Leucine-rich repeat kinase 2 (*LRRK2*) (Nuytemans et al., 2010). By phosphorylating PARKIN, PINK1 regulates the turnover of damaged mitochondria (Lopez-Fabuel et al., 2017). In addition, the presenilin-associated rhomboid-like (PARL) protein, a serine protease located in the inner mitochondrial membrane, interacts with and processes PINK1 (Wüst et al., 2016).

Vitamin E in Parkinson's disease

Polymorphisms in the microtubule-associated protein tau (*MAPT*) gene are associated with an increased

risk of PD, and *MAPT* methylation is negatively associated with *MAPT* expression (Coupland et al., 2014). Vitamin E decreases *MAPT* expression by increasing *MAPT* gene methylation and it may decrease PD risk (Coupland et al., 2014). Vitamin E is thus regarded as a neuroprotective agent against PD due to these effects (Sies et al., 1992).

There is a large number of *in vitro* animal and human studies that have evaluated the correlation between vitamin E and PD (Table V). These studies examined the effect of dietary vitamin E intake, supplementation at high doses and serum levels of vitamin E on PD. These studies showed that vitamin E supplementation may generally decrease PD risk, but there was no correlation between vitamin E levels in serum or cerebrospinal fluid and PD. Studies evaluating the effects of dietary vitamin E intake on PD have conflicting results (Scheider et al., 1997; Miyake et al., 2011; Hughes et al., 2016; Yang et al., 2017). In light of this data, vitamin E supplementation can be considered to prevent PD and/or ameliorate its prognosis. However, more studies are required to determine a therapeutic dose for routine application.

Multiple effects and mechanisms of vitamin E on stroke

Stroke is among the top reasons of death in the world and is also the most common reason of permanent disability. Ischemic strokes make up 87% of all stroke cases, occurring when there is a disruption in the blood flow from the artery that supplies the brain with blood rich in oxygen. Hemorrhagic stroke is another type of condition which occurs when blood begins to leak from an artery in the brain. Brain cells are suppressed and damaged due to the leaking blood. Temporary ischemic attack is characterized with neurological dysfunction resulting from decreasing blood flow in the brain without a permanent brain damage (Centers for Disease Control and Prevention, 2018).

High blood pressure, diabetes mellitus, arrhythmia, hyperlipidemia, smoking, sedentary lifestyle and bad nutritional habits are among the risk factors of stroke. It is known that decreasing blood pressure protects people from the adverse outcomes of

Table V. Effects of dietary or vitamin E supplementation on serum vitamin E levels in Parkinson's disease (PD).

References	n	Study focus	Study design	Conclusion
Pasbakhsh et al.	40 rats	Vitamin E and PD	24 IU/kg vitamin E supplementation.	Protective effect on the locus coeruleus neurons in Parkinson's patients.
Coupland et al.	SK-N-F1 cells	Incubation of cells with vitamin E	0.50 and 100 mM vitamin E.	Protective effect against PD by increasing <i>MAPT</i> methylation.
Molina et al.	34 PD patients and 47 healthy individuals	Vitamin E levels in serum and cerebrospinal fluid	Vitamin E levels in the serum and cerebrospinal fluid were compared between the groups.	There was no correlation between PD prognosis and vitamin E levels in the serum and cerebrospinal fluid ($p>0.05$).
Parkinson study group	Treatment-naive 800 PD patients	2,000 IU/day vitamin E supplementation	Vitamin E supplementation was given before levodopa use.	Vitamin E supplementation did not affect the frequency of side effects that may arise due to levodopa use.
Fukushima et al.	82 PD patients and 82 healthy individuals	Serum vitamin E and copper level	Serum vitamin E and copper levels were compared between the groups.	Serum vitamin E/copper ratio and serum E vitamin levels were not different between the groups ($p>0.05$).
Paraskevas et al.	72 PD patients and 39 healthy individuals	Serum vitamin E level	Serum vitamin E levels were compared between the groups.	Serum vitamin E levels in patients with vascular parkinsonism were found to be lower than some groups ($p<0.05$).
Kim et al.	104 PD patients and 52 healthy individuals	Serum vitamin E level	Serum vitamin E levels were compared between the groups.	Serum vitamin E levels were not different between the groups ($p>0.05$).
Tohgi et al.	14 treatment-naive PD patients, 8 PD patients under L-dopa treatment, 15 healthy individuals	α -tocopherol concentration in cerebrospinal fluid	α -tocopherol levels in the cerebrospinal fluid were compared between the groups.	α -tocopherol concentrations in treatment-naive PD patients were lower than the control group ($p<0.001$).
Dexter et al.	12 PD patients and 12 healthy individuals	α -tocopherol concentrations in brain tissues	α -tocopherol concentrations in brain tissues were compared between groups.	No difference was observed among the groups ($p>0.05$).
Yang et al.	38,937 female and 45,837 male participants	Dietary vitamin E, vitamin C and β -carotene intakes and total antioxidant capacity of participants	The correlation between PD and consumption of these vitamins was examined.	PD risk and dietary vitamin E and β -carotene intake were found to have a negative correlation ($p<0.05$).
Hughes et al.	1,036 PD patients	Dietary antioxidant vitamin intakes were evaluated in the patients	The correlation between PD and dietary antioxidant vitamin intake was examined.	There was no correlation between PD and dietary vitamin E intake ($p>0.05$).
Miyake et al.	249 PD patients and 368 healthy participants	Nutritional status and food consumption were evaluated in the patients	The correlation between PD and dietary nutrition intake was examined.	Dietary vitamin intake in high amounts decreased PD risk ($p<0.05$).
Scheider et al.	57 PD patients and 50 healthy participants	Consumption of 102 foods considered to be rich in vitamins E and C was evaluated	Correlation of dietary vitamin E and C intake with PD was examined.	There was no statistically significant correlation between PD and dietary vitamin E intake ($p>0.05$).
Taghizadeh et al.	60 PD patients	Placebo was given to 30 patients and 400 IU vitamin E supplementation + 1,000 mg n-3 fatty acids supplementation was given to the other 30 patients for 12 weeks	Unified PD rating stage (UPDRS) scores of patients were calculated before and after the supplementations.	Better increases in UPDRS scores were observed in the intervention group than the placebo group ($p<0.05$).
Nicoletti et al.	54 PD patients and 93 healthy individuals	Serum vitamin E levels	Serum vitamin E levels in the groups were compared and evaluated.	There was no significant correlation between PD and serum vitamin E levels ($p>0.05$).

stroke, while diabetes increases stroke risk at every age. Atrial fibrillation, or arrhythmia, increases the risk of stroke by five times (Wolf et al., 1987). It has been found that the risk of stroke is approximately two times higher among smokers than non-smokers. As the daily number of cigarettes rises, the risk of stroke increases (Soares-Miranda et al., 2015;

Markidan et al., 2018). Inadequate physical activity is also correlated with high risk of stroke (Soares-Miranda et al., 2015). Nutrition also plays a major role in stroke as it does in all cardiovascular diseases (Benjamin et al., 2018). For example, the Mediterranean diet is correlated with a low risk of hemorrhagic stroke (Tektonidis et al., 2015).

Studies related to stroke and vitamin E

In a large study by Voko et al. (2003) 5,197 individuals with no cognitive impairment were tracked by means of food consumption frequency for approximately 6.4 years. It was found that dietary vitamin E intake protects against ischemic stroke in smokers. The failure to reach the same result in other individuals could be associated with the fact that the study was conducted in the general population, not on individuals with high cerebrovascular risk. In another study that included 41,620 male and female participants, there was a positive correlation between dietary vitamin E intake and hemorrhagic stroke. The reason of this unexpected result could be explained by the antiplatelet and anticoagulant effects of vitamin E (Del Rio et al., 2010). A study conducted among 80,244 individuals between 45 and 74 years of age in Japan demonstrated that dietary α -tocopherol intake decreased the risk of all stroke types, including ischemic stroke (Ue-sugi et al., 2017). According to results of a meta-analysis study, dietary vitamin E intake in high amounts was found to be correlated with low stroke risk. Since vitamin E is a lipid soluble antioxidant that has the ability to sequester ROS, it might improve atherosclerotic plaque stability. In addition, vitamin E can inhibit platelet aggregation and thrombus formation (Cheng et al., 2018).

In another study, individuals 50–69 years old taking 50 mg α -tocopherol supplementation were tracked for approximately six years. Results of the study revealed that vitamin E increases stroke risk in hypertensive individuals. This may be because vitamin E may have increased bleeding risk because it acts synergistically with the blood diluent effect of aspirin (Leppälä et al., 2000). In a study conducted in rats, supplementation at a dose of 44 mg/kg body weight (2,600 mg/human/day-equivalent) increased blood pressure and showed side effects in the CNS of hypertensive rats with stroke risk. The study stated that α -tocopherol supplementation leads to impairments in the CNS in rats (Miyamoto et al., 2009). Another study supports these findings. Supplementation of α -tocopherol in high amounts (its equivalent in humans is 1,860 IU) increased neuro-inflammatory indicators in rats after stroke. This finding can be attributed to increased microglial activation and oxidative stress in the rats (Khanna et al., 2014). In another study, serum α -tocopherol levels in male smokers were found to be correlated with low ischemic risk (Leppälä et al., 1999). In line with these data, it can be concluded that in general, dietary vitamin E intake may decrease the risk of stroke. However, vitamin E supplementation in stroke patients is controversial as it has side effects. For this

reason, supplementation should not be recommended for stroke patients and dietary intake should not exceed recommended levels.

Multi-effects and mechanisms of vitamin E on amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis

ALS was defined by the French neurologist Charcot as a neurodegenerative disease which affects upper and lower motor neurons (Oskarsson et al., 2018). The average onset of ALS is between 58 and 60 years of age and the incidence is around two per 100,000 persons (Gunnarsson and Bodin, 2018). However, during the seventh decade of life in the US, the incidence increases to five cases per 100,000. Although the pathogenesis of ALS is not completely known, ALS-related neuropathologic features and gene mutations have been shown to significantly add to the etiology of the disease (Oskarsson et al., 2018).

Potential mechanisms of amyotrophic lateral sclerosis

An increase in the levels of oxidative damage biomarkers in ALS patients indicates that oxidative stress plays important roles in the pathogenesis of the disease (Bonfont-Rousselot et al., 2000; Barber and Shaw, 2010). Additionally, mutations in the copper/zinc superoxide dismutase gene (*SOD1*), which is vital in antioxidant defense mechanisms, were reported in some ALS patients (Rosen et al., 1993). Mutations in this gene may cause oxidative damage by increasing levels of hydroxyl radicals (Wiedau-Pazos et al., 1996; Bogdanov et al., 1998). Other pathogenic mechanisms of ALS, other than oxidative stress, include the accumulation of misfolded proteins, mitochondrial dysfunction, neuroinflammation, apoptosis and increased cellular glutamate concentrations (Spreux-Varoquaux et al., 2002; Bendotti and Carrì, 2004; Brooks et al., 2004; Vijayvergiya et al., 2005; Kiaei et al., 2006; Patel and Hamadeh, 2009).

Vitamin E in amyotrophic lateral sclerosis

Different treatment methods are being examined in the prevention ALS and/or improving its prognosis. Medical nutrition therapy is a potential treatment being investigated for ALS (Patel and Hamadeh, 2009). In studies, ALS has been positively correlated with glutamate (Nelson et al., 2000), fat (Sienko et al., 1990), fish and milk consumption (Felmus et al., 1976; Pierce-Ruhland and Patten, 1981), while negatively

correlated with lycopene (Longnecker et al., 2000) and dietary fiber intake (Nelson et al., 2000). Besides these nutrients, antioxidant vitamin supplements were also shown to be important in nutrition therapy (Patel and Hamadeh, 2009). Studies that examined the correlation between ALS risk and dietary antioxidant vitamin intake mostly focused on vitamin E (Ascherio et al., 2005; Veldink et al., 2007). These studies suggest that dietary vitamin E supplementation and increased cerebrospinal α -tocopherol levels decrease oxidative stress by reducing the risk of *de novo* mutation that may occur in the *SOD1* gene, and this mechanism can decrease neuron degeneration and ALS risk (Hideo et al., 1996). Additionally, vitamin E may reduce progression of ALS and neuronal damage by decreasing the peroxidation of lipids and nutritional polyunsaturated fatty acids (Veldink et al., 2007; Asl et al., 2018). 4-Hydroxynonenal, a product of lipid peroxidation, is reported to increase ALS risk by contributing to glutamate excitotoxicity (Pedersen et al., 1998).

Studies on vitamin E in amyotrophic lateral sclerosis

It has been reported that vitamin E decelerates the clinical course of ALS in rats with mutations in the *Sod1* gene (Gurney et al., 1996). A study evaluating the correlation between dietary nutrient intake and ALS indicated that dietary vitamin E intake decreased the progression risk of ALS (Veldink et al., 2007). Another study showed that vitamin E supplementation decreases the risk of death risk in ALS patients. In addition, other vitamin supplementations did not have the same inverse correlation (Ascherio et al., 2005). Another study found that supplementation of vitamin E at a dose of 500 mg/day for three months decreased levels of oxidative stress biomarkers in plasma (Desnuelle et al., 2001). However, studies evaluating the effect of supplementation of vitamin E at doses of 600 mg/day (Galbusera et al., 2006) and 5,000 mg/day (Graf et al., 2005) in ALS patients determined that supplementation does not have a statistically significant effect on the progression of the disease and life quality of patients. In light of these data, it can be concluded that vitamin E supplementation may have important protective roles in ALS and its prognosis. However, before adopting vitamin E as a viable treatment option, determining the effective dose and further human studies are required.

Increased serum levels of α -tocopherol have been correlated with low ALS risk (Freedman et al., 2013), and another study showed that α -tocopherol levels in the cerebrospinal fluid of ALS patients were lower than in healthy individuals (Hideo et al., 1996). However, other studies could not find such a correlation

between serum levels of vitamin E and ALS risk (Iwasaki et al., 1995), or changes in α -tocopherol levels in cerebrospinal fluid and serum in ALS patients (De Bustos et al., 1998). Due to such contradictory results, it is required to conduct further studies examining vitamin E levels in serum and cerebrospinal fluids of ALS patients.

CONCLUSION

The effect of vitamin E, a strong antioxidant, on neurodegenerative diseases has been long under investigation. Generally, it can be concluded that dietary vitamin E and its intake as a supplement may decrease the risk of PD and ALS; however, in some studies, correlations have not been observed between these diseases and vitamin E levels in the serum and cerebrospinal fluid. It has been found that serum and/or plasma vitamin E levels in AD patients were quite low, and high serum and dietary levels are protective against the disease. Therefore, it is important to track serum and/or plasma vitamin E levels constantly in disease progression.

Vitamin E supplementation in stroke patients is controversial as it has side effects. It was found that supplementation at very high doses increases stroke risk by scaling up hemorrhage risk. The effects of dietary vitamin E on stroke risk are very inconsistent. For this reason, supplementation is not recommended for stroke patients and dietary intake should not exceed recommended levels.

In light of these data, vitamin E supplementation may be taken into consideration depending on the type of disease in order to prevent risk and/or the progression of neurodegenerative diseases. However, further studies are required to determine therapeutic doses in humans.

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