

The Beneficial Role of Vitamin D in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common form of dementia in the elderly individuals and is associated with progressive neurodegeneration of the human neocortex. Patients with AD have a high prevalence of vitamin D deficiency, which is also associated with low mood and impaired cognitive performance in older people. Genetic studies have provided the opportunity to determine which proteins link vitamin D to AD pathology (ie, the major histocompatibility complex class II molecules, vitamin D receptor, renin-angiotensin system, apolipoprotein E, liver X receptor, Sp1 promoter gene, and the poly(ADP-ribose) polymerase-I gene). Vitamin D also exerts its effect on AD through nongenomic factors, that is, L-type voltage-sensitive calcium channels, nerve growth factor, the prostaglandins, cyclooxygenase 2, reactive oxygen species, and nitric oxide synthase. In conclusion, vitamin D clearly has a beneficial role in AD and improves cognitive function in some patients with AD. Calcitriol, 1 α ,25-dihydroxyvitamin D₃, is best used for AD because of its active form of vitamin D₃ metabolite and its receptor in the central nervous system.

Keywords

calcitriol, Alzheimer's disease, dementia, vitamin D

Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly individuals and is associated with the progressive loss of memory and cognitive function. A high incidence of fractures, especially of the hip, is reported in patients with AD.¹ There is evidence of aberrations in the vitamin D-endocrine system in patients with AD. Sato et al² studied bone mineral density (BMD) and its relation to the biochemical indices of patients with AD. They reported that the BMD of patients with AD was significantly less than that of age-matched controls; in 26% of patients with AD, serum 25-hydroxyvitamin D₃ (25OHD) was at a deficient level (5-10 ng/mL); and in 54%, it was at an osteomalacic level (<5 ng/mL). Concentrations of ionized calcium were significantly lower than in patients, and their concentrations of serum bone Gla-protein and urinary hydroxyproline were significantly higher than those of controls. In another study, there was no significant difference in bone density between participants with mild dementia and normal cognitive women; however, there were significant differences in parathyroid hormone (PTH) and vitamin D levels between groups.³ Moreover, elevated PTH concentrations are associated with a 5-year cognitive decline in a general aged population, independent of ionized calcium concentrations and renal function,⁴ suggesting that there is a high prevalence of subclinical hypovitaminosis D in demented patients. Furthermore, patients with AD with lower BMD, low concentrations of serum ionized

calcium, and 25OHD with compensatory hyperparathyroidism were found to have an increased risk of hip fracture.⁵ Whether vitamin D deficiency is a cause or consequence of AD is unknown. In addition, abnormal cellular calcium homeostasis has been noted in AD. Nuclear microscope analysis revealed evidence for increased overall levels (free and protein bound) of calcium in patients with AD,⁶ in which calcium levels are greater in neurofibrillary tangle-bearing neurons than in neurons lacking tangles.⁷ These findings might suggest a relationship between vitamin D and AD. In the present article, therefore, we review the role of vitamin D in patients with AD.

Genetic Factors Related to Vitamin D in AD

Studies have suggested that several genes in the major histocompatibility complex (MHC) region promote susceptibility to AD. Located in the MHC region, human leukocyte antigen (*HLA*) genes have been implicated in AD susceptibility. Increased MHC class II glycoprotein expression on microglial

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cells has been reported in AD brains.⁸⁻¹⁰ A significantly increased level of MHC class II expression was also detected in AD retinae.¹¹ Moreover, the number of HLA-DR and interleukin 2 (IL-2) receptor-positive cells was increased in the post-mortem brain of patients with AD and correlates with the number of senile plaques.¹² Shalit et al¹³ observed a slight increase in HLA-DR levels in the mild stage of AD without changes in CD4, CD8, and IL-2 levels. In the moderately severe stage, however, there was a significant increase in HLA-DR and CD4 and a slight decrease in CD8, suggesting that peripheral immune reaction in AD may be correlated with the clinical stage of the disease. Furthermore, following long-term therapeutic immunization of an AD mouse model bearing the DRB1*1501 allele, amyloid- β (A β) peptide was effectively cleared from the brain parenchyma, and brain microglial activation was reduced.¹⁴ This suggests that HLA-DR alleles directly associate with specific A β T-cell epitopes with the highly immunogenic properties of the abundant DRB1*1501 allele in this mouse model of AD. Conversely, calcitriol is known to stimulate phagocytosis but suppresses MHC class II antigen expression in human mononuclear phagocytes.^{15,16} Calcitriol also decreases interferon- γ -induced HLA-DR antigen expression on normal and transformed human keratinocytes.^{17,18}

Genetic studies provide an opportunity to link molecular variations with epidemiological data. DNA sequence variations, such as polymorphisms, exert both modest and subtle biological effects. Vitamin D receptor (VDR) and 1 α -hydroxylase, the enzyme responsible for the formation of active vitamin D in the human brain, were found in both neurons and glial cells in a regional and layer-specific pattern¹⁹; VDR was restricted to the nucleus while 1 α -hydroxylase was distributed throughout the cytoplasm. In patients with AD, VDR expression has been reported to be reduced in different layers of the hippocampus,²⁰ which is more vulnerable in AD. The VDR Aa, but not the FokI, genotype has been reported to associate with AD.^{21,22}

The primary function of the renin-angiotensin system (RAS) is to maintain fluid homeostasis and regulate blood pressure. Several components of the RAS and their receptors are found in the central nervous system (CNS),²³⁻²⁶ suggesting their involvement in brain activity. Angiotensin-converting enzyme (ACE) activity was reported in homogenates of postmortem brain tissue from patients with AD and was correlated with A β plaque load.²⁷ Increased binding of radioactively labeled ACE inhibitor to ACE was noted in AD temporal cortex.²⁸ Another report also demonstrated elevated neuronal and perivascular ACE immunoreactivity in AD parietal cortex.²⁹ Recently, ACE activity was found to be increased in peripheral blood of later-onset AD, but there was no correlation with the level of A β in peripheral blood.³⁰ The role of ACE in AD remains controversial; ACE has been shown to inhibit A β aggregation and to lower the levels of secreted A β in living cells, an effect that was blocked with ACE inhibitor,^{31,32} whereas ACE inhibitor was reported not to have an effect on cerebral A β levels and plaque deposition in vivo in another study.³³ Although short-term treatment with ACE inhibitors failed to increase A β formation in the brain, long-term treatment enhanced A β deposition in aged amyloid

precursor protein (APP) transgenic mice.³⁴ The ACE I/I genotype and I allele showed an increased risk of AD,^{35,36} but the D/D genotype was associated with a reduced risk.³⁷ The I/I genotype has been linked to smaller volumes of the hippocampus and the amygdala³⁸ and to trends toward increased brain A β 42 load compared to the D/D genotype.³⁹ There is also an interaction between vitamin D and the RAS. The combination of ACE inhibitors with the ACE DD genotype has been shown to decrease the level of calcitriol.⁴⁰ In addition, genetic disruption of the VDR resulted in overstimulation of the RAS with increasing renin and angiotensin II productions, leading to high blood pressure and cardiac hypertrophy. Treatment with captopril reduced cardiac hypertrophy in VDR knockout mice,⁴¹ suggesting that calcitriol may function as an endocrine suppressor of renin biosynthesis. Vitamin D has also been reported to decrease ACE activity in bovine endothelial cells.⁴²

Apolipoprotein E (ApoE) has important functions in systemic and local lipid transport and is a major genetic factor identified in AD. Carriers of at least one ApoE ϵ 4 allele have an increased risk of developing AD.^{43,44} Apolipoprotein E has been shown to be significantly altered in the cerebrospinal fluid (CSF) of patients with AD.⁴⁵ In addition, capillary cerebral amyloid angiopathy has been identified as a distinct ApoE ϵ 4-associated subtype of sporadic AD,⁴⁶ which may determine the clinical phenotype of AD.⁴⁷ Patients expressing this ApoE genotype are known to have significant impairment in memory retention. ApoE, however, was not found to be a risk or a protective factor for AD in an Ecuadorian population.⁴⁸ On the other hand, calcitriol has been known to induce macrophages to exhibit specific saturable receptors for low-density lipoprotein (LDL) and acetyl-LDL; the LDL receptor of 1,25OHD-induced macrophages was found to exhibit specificity for ApoB and E-containing lipoproteins.⁴⁹ In ApoE knockout mice, an animal model with dyslipidemia, high oxidative stress, and pronounced atherosclerosis after uninephrectomy, animals developed less plaque growth and calcification with vitamin D analog treatment (paricalcitol) compared to control groups.^{50,51}

Cholesterol has been reported to link to the pathology of AD. Ullrich et al⁵² demonstrated that cholesterol-treated rats showed impaired learning and long-term memory associated with a reduced number of cholinergic neurons in the nucleus of Meynert and decreased acetylcholine levels in the cortex. Amyloid precursor protein levels were also enhanced in the cortex of treated rats. Statins, inhibitors of cholesterol synthesis, lowered serum A β levels in humans with elevated cholesterol levels.⁵³ In transgenic AD mouse models, hypercholesterolemia accelerated cognitive dysfunction and increased APP processing and β -amyloid accumulation, as well as increasing the inflammatory response.⁵⁴ The liver X receptors (LXRs) play a key role in regulating genes that control cellular cholesterol efflux, membrane cholesterol efflux, and membrane composition, and are widely expressed in cells of the CNS. Liver X receptor is expressed in 2 isoforms, LXR α and LXR β , but only LXR β is expressed in the brain. Liver X receptor β is known to play a key role in A β and cholesterol modulation.⁵⁵ In mice, expression of the *LXR* gene causes a decrease in cellular A β secretion.⁵⁶

A synthetic LXR agonist is reported to decrease A β production in vitro and in AD mouse models.⁵⁷ Interestingly, high serum 25OHD concentrations are associated with a favorable serum lipid profile, for example, total cholesterol and high-density cholesterol (HDL-C).⁵⁸ Low levels of active vitamin D, calcitriol, are also associated with low HDL-C levels.⁵⁹ Moreover, calcitriol has been shown to suppress foam cell formation by reducing acetylated LDL (AcLDL) and oxidized LDL (oxLDL) cholesterol uptake by macrophage.⁶⁰ In addition, calcitriol inhibits the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA reductase), required for cholesterol biosynthesis.⁶¹ In male VDR knockout mice, serum total cholesterol and LXR β levels were significantly higher than those in wild-type mice.⁶² There is crosstalk between LXR α and VDR signaling in the regulation of bile acid metabolism, suggesting a possible contribution of the VDR to the modulation of bile acid and cholesterol homeostasis.⁶³

Binding sites for the transcription factor Sp1 have been implicated in the transcription of several genes by hormones. In cultured human fibroblasts, the level of CYP24 (25-OHD 24-hydroxylase) messenger RNA (mRNA) plays a key role in the metabolism of 1,25-dihydroxyvitamin D₃ (1,25OHD) and increases up to 20 000-fold in response to calcitriol. Two vitamin D-responsive elements (VDREs) located upstream of the CYP24 gene are primarily responsible for the increased mRNA levels and Sp1 acted synergistically with these VDREs for the induction.⁶⁴ The mVDR promoter is controlled by Sp1 sites⁶⁵ and functions as the transactivation component of the VDR/Sp1 complex to trigger gene expression.⁶⁶ Furthermore, abnormal Sp1 transcription factor has been reported in AD.^{67,68} The Sp1 transcription factor may be involved in regulating the expression of several AD-related proteins. The regulatory region of the APP gene contains sites recognized by the Sp1 transcription factor, which has been shown to be required for the regulation of APP and A β .⁶⁹ BACE₁, the major β -secretase involved in cleaving APP, promoter contains a functional Sp1 response element, and overexpression of the Sp1 transcription factor potentiates BACE gene expression and APP processing to generate A β .⁷⁰ Sp1 and signaling molecule against decapentaplegic peptide (Smad) transcription factors cooperate to potentiate transforming growth factor β -dependent activation of APP.⁷¹

Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear protein that contributes to both neuronal death and survival under stress condition. Poly(ADP-ribose) polymerase cleavage is enhanced in peripheral blood mononuclear cells from mild cognitive impairment patients.⁷² Enhanced PARP activity is reported in AD and has been suggested as a marker for AD.⁷³ The PARP polymers increased with age in the brains of an Alzheimer's mouse model, and A β -activated PARP polymers induced astrocytic metabolic failure and neuronal death in response to oxidative stress.⁷⁴ Poly(ADP-ribose) polymerase 1 polymorphism is shown to modify the risk of AD in both an independent manner and through interaction with proinflammatory IL-1A.⁷⁵ The PARP-1 gene is highly associated with AD susceptibility. The PARP haplotypes, Ht3-TT and Ht4-CC, were significantly associated with an increased risk of AD, whereas

the Ht1-TC haplotype showed a protective effect against AD when compared with control participants.⁷⁶ Furthermore, PARP-1 levels decreased in NB4 acute promyelocytic leukemia cells in response to calcitriol treatment.⁷⁷ Vitamin D exerts a concentration-dependent inhibitory effect on PARP-1 in human keratinocyte cells.⁷⁸ Vitamin D-induced downregulation of PARP was also enhanced by nicotinamide in human myeloblastic leukemia cells.⁷⁹ Furthermore, PARP was attenuated in hippocampal tissue from rats that received dexamethasone and vitamin D,⁸⁰ suggesting that the anti-inflammatory effect of dexamethasone and vitamin D derives from their ability to downregulate microglial activation.

The Nongenetic Role of Vitamin D in AD

Disturbance of glucose metabolism is a prominent characteristic in the brains of patients with AD, and type 2 diabetes mellitus (DM) has been identified as a risk factor for AD.⁸¹⁻⁸³ Moderate hyperinsulinemia can elevate inflammatory markers and β -amyloid in the periphery and the brain,⁸⁴ suggesting that hyperinsulinemia is a risk factor for AD. Human and experimental animal studies have demonstrated that neurodegeneration is associated with peripheral insulin resistance.⁸⁵ Moreover, metabolic syndrome, a clustering of cardiovascular risk factors including obesity, hypertension, dyslipidemia, and hyperglycemia has been reported to be associated with AD, especially in women.⁸⁶ Metabolic syndrome is more frequent among patients with AD than controls.⁸⁷ Pasinetti et al⁸⁸ demonstrated that high-caloric intake based on saturated fat promoted AD type β -amyloidosis, and conversely, that dietary restriction based on reduced carbohydrate intake was able to prevent it. In a C57BL/6 mouse model of obesity and type 2 DM, high-fat diet feeding for 16 weeks doubled mean body weight, caused type 2 DM, marginally reduced mean brain weight, and was associated with significantly increased levels of tau,⁸⁹ suggesting that obesity and type 2 DM may contribute to AD. In both AD and mild cognitive impairment groups, higher BMI was associated with brain volume deficits in frontal, parietal, and occipital lobes.⁹⁰ In addition, central obesity in the elderly individuals is related to late-onset AD.⁹¹ In a meta-analysis of prospective studies, BMI in midlife and late life was shown to increase dementia risk.⁹² In addition, serum 1,25OHD and 25OHD levels were low in diabetic patients,⁹³⁻⁹⁵ and diabetic rats had an increased metabolic clearance rate of 1,25OHD.⁹⁶ Similarly, vitamin 25OHD₃ concentrations in subcutaneous fat tissue and serum were inversely and correlated with body weight.⁹⁷ Decreased 25OHD₃ levels were observed during obesity and may have been secondary to alterations in tissue distribution resulting from increases in adipose mass.⁹⁸ The percentage body fat content was independently inversely related to the serum 25OHD₃ levels in healthy women, regardless of dietary vitamin D intake, season, age, and race.⁹⁹ The association between 25OHD₃ concentrations and adiposity was stronger for visceral than for subcutaneous abdominal adiposity.¹⁰⁰ Interestingly, a significant high prevalence of vitamin D insufficiency has been reported in patients with AD.¹⁰¹ Elderly women with AD have an

increased prevalence of vitamin D deficiency,² which is also associated with low mood and impaired cognitive performance in older adults.¹⁰² There is an association between Mini-Mental State Examination (MMSE) test scores and serum 25OHD levels, vitamin D-sufficient patients had significantly higher MMSE scores compared to vitamin D-insufficient ones.¹⁰³ In another study, vitamin D deficiency was associated with increased odds of cognitive impairment in the elderly population of the United States.¹⁰⁴ A vitamin D-free regimen intensified the spatial learning deficit in Alzheimer's animal models.¹⁰⁵ Conversely, vitamin D₃-enriched diet was correlated with a decrease in the number of amyloid plaque, a decrease in A β peptides, a decrease in inflammation, and an increase in nerve growth factor (NGF) in the brains of APP transgenic mice.¹⁰⁶ Furthermore, long-term treatment with calcitriol resulted in a higher density of CA1 neurons in the middle regions of the hippocampus in aging rats,¹⁰⁷ suggesting that vitamin D can modulate markers of brain aging.

Acetylcholine (ACh) and norepinephrine (NorEpi) are the most common neurotransmitters associated with the pathophysiological conditions observed in AD. It is hypothesized that these neurotransmitters are hypoactive in AD. Alterations in the density of cholinergic and noncholinergic receptors for glutamate, noradrenaline, and serotonin have been reported in transgenic Tg2576 mice with A β plaque pathology.¹⁰⁸ Decreases in the number of NorEpi-containing neurons in the locus coeruleus suggest reduced NorEpi activity in patients with AD.¹⁰⁹ Moreover, Kumar et al¹¹⁰ demonstrated the neuroprotective role of vitamin D in cerebral cortex by normalizing the altered cholinergic synaptic transmission in streptozocin-induced diabetic rats. Altered pressor to NorEpi is also noted in vitamin D-deficient rats^{111,112} and increased in hypotensive response to ACh, L-dopamine, histamine, and 5-hydroxytryptamine.¹¹² The pressor responses to NorEpi and angiotensin II were augmented by vitamin D and its analogs.¹¹³

Normal calcium homeostasis is critical to neuronal survival in AD. Elevated intracellular calcium levels have been observed in neurons in AD. The remaining neurons in the hippocampus were demonstrated to have increased L-type voltage-sensitive calcium channels (L-VSCCs) in patients with AD,¹¹⁴ resulting in increased calcium influx. A β protein is reported to trigger neurodegeneration not only by inducing L-VSCC expression but also by suppressing VDR expression; treatment with vitamin D in this model protected neurons by preventing cytotoxicity and apoptosis and also by downregulating L-VSCCs and upregulating VDRs.¹¹⁵ Calcitriol decreased L-VSCC activity in aged rats and in vulnerable neurons with particularly impact on reducing age-related changes associated with Ca²⁺ dysregulation.^{116,117} 24R, 25 dihydroxyvitamin D₃ also reduced L-VSCC in vascular smooth muscle in rats.¹¹⁸ These findings suggested that calcitriol may have a role in regulating the abnormal intracellular calcium levels in neurons in AD.

Nerve growth factor is a small secreted protein that is important for the growth, maintenance, and survival of certain target neurons (nerve cells). It has been implicated in maintaining and regulating the normal functioning of the septohippocampal

pathway, which is involved in learning and memory¹¹⁹⁻¹²¹ Mature NGF levels are substantially decreased in the forebrain of aged animals and patients with AD.¹²² In vitro, NGF has been shown to modulate *APP* gene expression,¹²³ and its withdrawal induced an increase in APP expression in neuronal PC12 cells.¹²⁴ In in vivo studies, intranasal administration of NGF rescued recognition memory deficits in AD11 anti-NGF transgenic mice.¹²⁵ Moreover, implantation of autologous fibroblasts genetically modified to express human NGF into the forebrain of patients with mild AD demonstrated a marked reduction in the rate of cognitive decline and an increase in cortical glucose metabolic uptake in treated participants.¹²⁶ Interestingly, brains of newborn rats from vitamin D-deficient dams displayed reduced expression of NGF and glial cell-line-derived neurotrophic factor.¹²⁷ In vitro, calcitriol regulated the expression of the *VDR* gene and stimulated the expression of the *NGF* gene in Schwann cells.¹²⁸ In mouse fibroblasts, calcitriol and vitamin D analogs were reported to enhance NGF induction by increasing AP-1 binding activity in the NGF promoter.^{129,130} These findings suggest a protective role for vitamin D in the CNS.

Prostaglandins (PGs) play a role in inflammatory processes.¹³¹ Cyclooxygenase (COX) participates in the conversion of arachidonic acid into PGs. Prostaglandin receptors are found in the hypothalamus, thalamus, and limbic system,¹³² and COX-2 is expressed by excitatory neurons at postsynaptic sites in rat cerebral cortex.¹³³ Overexpression of COX-2 has been demonstrated in the perinuclear, dendritic, and axonal areas of pyramidal neurons as well as in subregions of the hippocampal formation in AD.^{134,135} The COX-2 potentiated A β protein generation through mechanisms that involve γ -secretase activity.^{136,137} Long-term treatment with nonsteroidal anti-inflammatory drugs has been shown to benefit in the improvement of the AD process.^{138,139} Calcitriol has been reported to regulate the expression of several key genes involved in the PG pathways, causing a decrease in PG synthesis.¹⁴⁰ Calcitriol and its analogs have also been shown to selectively inhibit the activity of COX-2.¹⁴¹

Reactive oxygen species (ROS) have been implicated in the pathogenesis of neuronal death in AD. Increased levels of ROS have been reported in AD.^{142,143} Oxygen-free radical injury has been reported to cause some AD-type molecular abnormalities in human neuronal cells.¹⁴⁴ Cultured skin fibroblasts from patients with AD had increased superoxide dismutase (SOD) activity and were more susceptible to free radical damage.^{145,146} Calcitriol has been reported to exert a receptor-mediated effect on the secretion of hydrogen peroxide by human monocytes¹⁴⁷ and regulated adipocyte ROS production.¹⁴⁸ Human monocytes in culture gradually lose their capability to produce superoxide when stimulated; the addition of calcitriol, lipopolysaccharide (LPS), or lipoteichoic acid (LTA) restored the ability of stimulated monocytes to produce superoxide and increased the oxidative capacity compared with unstimulated monocytes.¹⁴⁹ Calcitriol could also protect nonmalignant prostate cells from oxidative stress-induced cell death by eliminating ROS-induced cellular injuries.¹⁵⁰ Vitamin D metabolites and vitamin D analogs were reported to induce lipoxigenase mRNA

expression, lipoxygenase activity, and ROS production in a human bone cell line.¹⁵¹ Vitamin D could also reduce the extent of lipid peroxidation and induce the SOD activity of the hepatic antioxidant system in rats.¹⁵² These findings suggested a role of vitamin D in modulating oxidative stress in AD.

Nitric oxide synthase (NOS) has a role in generating nitric oxide (NO), which has been shown to be a critical signaling molecule involved in synaptic plasticity and memory.^{153,154} Nitric oxide synthase activity was reported to increase significantly in leukocytes and brain microvessels of patients with AD.^{155,156} Moreover, NOS has been suggested to contribute to the pathogenesis of AD. In AD and APP transgenic mice, astrocytes with high NOS levels were associated with A β protein deposits.¹⁵⁷ Nitric oxide synthase deficiency protected the AD-like mice from premature mortality, cerebral plaque formation, increased A β protein levels, astrocytosis, and microgliosis.¹⁵⁸ The activation of macrophages by 1 α -hydroxylase resulted in an increase in 1,25OHD, which inhibited inducible NOS (iNOS) expression and reduces NO production by LPS-stimulated macrophages.¹⁵⁹ This calcitriol production by macrophages may provide protection against oxidative injuries caused by the NO burst. Calcitriol is known to inhibit LPS-induced immune activation in human endothelial cells.¹⁶⁰ In experimental allergic encephalomyelitis, calcitriol inhibited the expression of iNOS in the rat central nervous system (CNS).¹⁶¹ Astrocytes play a pivotal role in CNS detoxification pathways, in which glutathione (GSH) is involved in the elimination of oxygen and nitrogen reactive species, such as nitric oxide. Calcitriol also enhances intracellular GSH pools and significantly reduces nitrite production induced by LPS.¹⁶²

Conclusion

The relationship between vitamin D and AD has been discussed. Vitamin D clearly has a beneficial role in AD and improved cognitive function in some patients with AD. Genetic studies have provided the opportunity to determine what proteins link vitamin D to AD pathology. Vitamin D also exerts its effect on AD through nongenomic mechanisms. It is necessary to check the vitamin D status in patients with AD. Calcitriol is best used for AD because of its active form of vitamin D₃ metabolite, and its receptor in the CNS. Adjusting dose for calcitriol depends on serum calcium and PTH levels. However, monitor of serum 25OHD after taking calcitriol is not necessary because calcitriol inhibits the production of serum 25OHD in the liver.^{163,164} Calcitriol can cause hypercalcemia and also suppress PTH levels in vitamin D deficiency-induced secondary hyperparathyroidism. Further investigation with calcitriol in AD would be needed.

Declaration of Conflicting Interests

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References

1. Baker NL, Cook MN, Arrighi HM, Bullock R. Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988-2007. *Age Ageing*. 2011; 40(1): 49-54.
2. Sato Y, Asoh T, Oizumi K. High prevalence of vitamin D deficiency and reduced bone mass in elderly women with Alzheimer's disease. *Bone*. 1998; 23(6): 555-557.
3. Kipen E, Helme RD, Wark JD, Flicker L. Bone density, vitamin D nutrition, and parathyroid hormone levels in women with dementia. *J Am Geriatr Soc*. 1995; 43(10): 1088-1091.
4. Björkman MP, Sorva AJ, Tilvis RS. Does elevated parathyroid hormone concentration predict cognitive decline in older people? *Aging Clin Exp Res*. 2010; 22(2): 164-169.
5. Sato Y, Kanoko T, Satoh K, Iwamoto J. Risk factors for hip fracture among elderly patients with Alzheimer's disease. *J Neurol Sci*. 2004; 223(2): 107-112.
6. Watt F. Nuclear microscope analysis in Alzheimer's and Parkinson's disease: a review. *Cell Mol Biol*. 1996; 42(1): 17-26.
7. Murray FE, Landsberg JP, Williams RJ, Esiri MM, Watt F. Elemental analysis of neurofibrillary tangles in Alzheimer's disease using proton-induced X-ray analysis. *Ciba Found Symp*. 1992; 169: 201-210.
8. McGeer PL, Itagaki S, Tago H, McGeer EG. Reactive microglia in patients with senile dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR. *Neurosci Lett*. 1987; 79(1-2): 195-200.
9. Styren SD, Civin WH, Rogers J. Molecular, cellular, and pathologic characterization of HLA-DR immunoreactivity in normal elderly and Alzheimer's disease brain. *Exp Neurol*. 1990; 110(1): 93-104.
10. Tooyama I, Kimura H, Akiyama H, McGeer PL. Reactive microglia express class I and class II antigens in Alzheimer's disease. *Brain Res*. 1990; 523(2): 273-280.
11. Liew SCK, Penfold PL, Provis JM, Madigan MC, Billson FA. Modulation of MHC class II expression in the absence of lymphocytic infiltrates in Alzheimer's retinae. *J Neurophathol Exp Neurol*. 1994; 53(2): 150-157.
12. Rogers J, Luber-Narod J, Styren SD, Civin WH. Expression of immune system associated antigens by cells of the human central nervous system: relationship to the pathology of Alzheimer's disease. *Neurobiol Aging*. 1988; 9(4): 339-349.
13. Shalit F, Sregni B, Brodie C, Kott E, Huberman M. T lymphocyte subpopulations and activation markers correlate with severity of Alzheimer's disease. *Clin Immunol Immunopathol*. 1995; 75(3): 246-250.
14. Zota V, Nemirovsky A, Baron R, et al. HLA-DR alleles in amyloid β -peptide autoimmunity: a highly immunologic role for the DRB1*1501 allele. *J Immunol*. 2009; 183(5): 3522-3530.
15. Tokuda N, Levy RB. 1,25-hydroxyvitamin D₃ stimulates phagocytosis but suppresses HLA-DR and CD13 antigen expression in human mononuclear phagocytes. *Proc Soc Exp Biol Med*. 1996; 211(3): 244-250.
16. Tokuda N, Mizuki N, Kasahara M, Levy RB. 1,25-hydroxyvitamin D₃ down-regulation of HLA-DR on human peripheral blood monocytes. *Immunol*. 1992; 75(2): 349-354.

17. Takami K, Saitoh A, Kubota Y. 1,25-hydroxyvitamin D₃ decreases the interferon-gamma (IFN-gamma) induced HLA-DR expression but not intercellular adhesion molecule 1 (ICAM-1) on human keratinocytes. *Reg Immunol*. 1990-1991; 3(5): 223–227.
18. Tone T, Eto H, Katsuoka K, Nishioka K, Nishiyama S. Upexpression of gamma-interferon induced HLA-DR antigen expression on normal and transformed keratinocytes by 1,25 (OH)₂ vitamin D₃ [in Japanese]. *Nippon Hifuka Gakkai Zasshi*. 1991; 101(5): 519–525.
19. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *J Chem Neuroanat*. 2005; 29(1): 21–30.
20. Sutherland MK, Somerville MJ, Yoong LKK, Bergeron C, Haussler MR, McLachlan DRC. Reduction of vitamin D hormone receptor mRNA levels in Alzheimer as compared to Huntington hippocampus: correlation with calbindin-28 k mRNA levels. *Mol Brain Res*. 1992; 13(3): 239–250.
21. Gezen-Ak D, Dursun E, Ertan T, et al. Association between vitamin D receptor gene polymorphism and Alzheimer's disease. *Tohoku J Exp Med*. 2007; 212(3): 275–282.
22. Luedeking-Zimmer E, DeKosky S, Nebes R, Kamboh I. Association of the 3'UTR transcription factor LBP-1c/CP2/LSF polymorphism with late-onset Alzheimer's disease. *Am J Med Gene*. 2003; 117B(1): 114–117.
23. Changaris DG, Keil LC, Severs WB. Angiotensin II immunohistochemistry of the rat brain. *Neuroendocrinol*. 1978; 25(5): 257–274.
24. Healy DP, Printz MP. Distribution of immunoreactive angiotensin II, angiotensin I, angiotensinogen, and renin in the central nervous system of intact and nephrectomized rats. *Hypertension*. 1984; 6 (suppl 1): 130–136.
25. Ganten D, Hermann K, Bayer D, Unger T, Lang RR. Angiotensin synthesis in the brain and increased turnover in hypertensive rats. *Science*. 1983; 221(4613): 869–871.
26. Dzau VJ, Ingelfinger J, Pratt RE, Ellison KE. Identification of renin and angiotensinogen messenger RNA sequences in rat brain. *Hypertension*. 1986; 8(6): 544–548.
27. Arregui A, Perry E, Rossor M, Tomlinson BE. Angiotensin converting enzyme in Alzheimer's disease: increased activity in caudate nucleus and cortical areas. *J Neurochem*. 1982; 38(5): 1490–1492.
28. Barnes NM, Cheng CH, Costall B, Naylor RJ, Williams TJ, Wischik CM. Angiotensin converting enzyme density is increased in temporal cortex from patients with Alzheimer's disease. *Eur J Pharmacol*. 1991; 200(2-3): 289–292.
29. Savaskan E, Hock C, Olivieri G, et al. Cortical alterations of angiotensin converting enzyme, angiotensin II and AT1 receptor in Alzheimer's dementia. *Neurobiol Aging*. 2001; 22(4): 541–546.
30. Akatsu H, Ogawa N, Kanetsaka T, et al. High activity of peripheral blood angiotensin-converting enzyme is associated with later-onset of Alzheimer's disease. *J Neurol Sci*. 2011; 300(1-2): 67–73.
31. Hu J, Igarashi A, Kamata M, Nakagawa H. Angiotensin-converting enzyme degrades Alzheimer amyloid β -peptide (A β); retards A β aggregation, deposition, fibril formation; and inhibits cytotoxicity. *J Biol Chem*. 2001; 276(51): 47863–47868.
32. Heming ML, Selkoe DJ. Amyloid β -protein is degraded by cellular angiotensin-converting enzyme (ACE) and elevated by an ACE inhibitor. *J Biol Chem*. 2005; 280(45): 37644–37650.
33. Hemming ML, Selkoe DJ, Farris W. Effects of prolonged angiotensin-converting enzyme inhibitor treatment on amyloid β -protein metabolism in mouse models of Alzheimer disease. *Neurobiol Dis*. 2007; 26(1): 273–281.
34. Zou K, Yamaguchi H, Akatsu H, et al. Angiotensin-converting enzyme converts amyloid beta-protein 1-42 (A β ₁₋₄₂) to A β ₁₋₄₀, and its inhibition enhances brain A β deposition. *J Neurosci*. 2007; 27(32): 8628–8635.
35. Kölsch H, Jessen F, Freymann N, et al. ACE I/D polymorphism is a risk factor of Alzheimer's disease but not of vascular dementia. *Neurosci Lett*. 2005; 377(1): 37–39.
36. Elkins JS, Douglas VC, Johnston SC. Alzheimer disease risk and genetic variation in ACE: a meta-analysis. *Neurology*. 2004; 62(3): 363–368.
37. Lehmann DJ, Cortina-Borja M, Warden DR, et al. Large meta-analysis establishes the ACE insertion-deletion polymorphism as a marker of Alzheimer's disease. *Am J Epidemiol*. 2005; 162(4): 305–317.
38. Slegers K, den Heijer T, van Dijk EJ, et al. ACE gene is associated with Alzheimer's disease and atrophy of hippocampus and amygdala. *Neurobiol Aging*. 2005; 26(8): 1153–1159.
39. Lendon CL, Thaker U, Harris JM, et al. The angiotensin 1-converting enzyme insertion (I)/deletion (D) polymorphism does not influence the extent of amyloid or tau pathology in patients with sporadic Alzheimer's disease. *Neurosci Lett*. 2002; 328(3): 314–318.
40. Pérez-Castrillón JL, Justo I, Sanz A, De Luis D, Dueñas A. Effect of angiotensin converting enzyme inhibitors on 1,25(OH)₂ D levels of hypertensive patients. Relationship with ACE polymorphisms. *Horm Metab Res*. 2006; 38(12): 812–816.
41. Xiang W, Kong J, Chen S, et al. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. *Am J Phys Endocrinol Met*. 2005; 288(1): E125–E132.
42. Higihara H, Furuhashi H, Nakaya K, Nakamura Y. Effects of vitamin D₃ and related compounds on angiotensin converting activity of endothelial cells and on release of plasminogen activator from them. *Chem Pharm Bull*. 1988; 36(12): 4858–4864.
43. Licastro F, Chiappelli M, Thal LJ, Masliah E. α -1-antichymotrypsin polymorphism in the gene promoter region affects survival and synapsis loss in Alzheimer's disease. *Arch Gerontol Geriatr*. 2004;(suppl 9): 243–251.
44. Lane RM, Farlow MR. Lipid homeostasis and apolipoprotein E in the development and progression of Alzheimer's disease. *J Lipid Res*. 2005; 46(5): 949–968.
45. Puchades M, Hansson SF, Nilsson CL, Andreassen N, Blennow K, Davidsson P. Proteomic studies of potential cerebrospinal fluid protein markers for Alzheimer's disease. *Brain Res Mol Brain Res*. 2003; 118(1-2): 140–146.
46. Thal DR, Papassotiropoulos A, Saido TC, et al. Capillary cerebral amyloid angiopathy identifies a distinct APOE ϵ 4-associated subtype of sporadic Alzheimer's disease. *Acta Neuropathol*. 2010; 120(2): 169–183.

47. Wolk DA, Dickerson BC; the Alzheimer's disease neuroimaging initiative. Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. *PNAS*. 2010; 107(22): 10256–10261.
48. Paz-y-Miño C, Carrera C, López-Cortés A, et al. Genetic polymorphisms in apolipoprotein E and glutathione peroxidase 1 genes in the ecuadorian population affected with Alzheimer's disease. *Am J Med Sci*. 2010; 340(5): 373–377.
49. Jouni ZE, McNamara DJ. Lipoprotein receptors of HL-60 macrophages. Effect of differentiation with tetramyristic phorbol acetate and 1,25-dihydroxyvitamin D₃. *Arterioscler Thromb*. 1991; 11(4): 995–1006.
50. Husain K, Suarez E, Isidro A, Ferder L. Effects of paricalcitol and analapril on atherosclerotic injury in mouse aortas. *Am J Nephrol*. 2010; 32(4): 296–304.
51. Becker LE, Koleganova N, Piecha G, et al. Effects of paricalcitol and calcitriol on aortic wall remodeling in uninephrectomized ApoE knockout mice. *Am J Physiol Renal Physiol*. 2011; 300(3): F772–F782.
52. Ullrich C, Pirchl M, Humpel C. Hypercholesterolemia in rats impairs the cholinergic system and leads to memory deficits. *Mol Cell Neurosci*. 2010; 45(4): 408–417.
53. Buxbaum JD, Cullen EI, Friedhoff LT. Pharmacological concentrations of the HMG-CoA reductase inhibitor lovastatin decrease the formation of the Alzheimer beta-amyloid peptide in vitro and in patients. *Front Biosci*. 2002; 7: a50–a59.
54. Refolo LM, Malester B, LaFrancois J, et al. Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. *Neurobiol Dis*. 2000; 7(4): 321–331.
55. Murphy S, Born E, Mathur SN, Field J. LXR/RXR activation enhances basolateral efflux of cholesterol in CaCo-2 cells. *J Lipid Res*. 2002; 43(7): 1054–1064.
56. Sun Y, Yao J, Kim TW, Tall AR. Expression of liver X receptor target genes decreases cellular amyloid beta peptide secretion. *J Biol Chem*. 2003; 278(30): 27688–27694.
57. Koldamova RP, Lefterov IM, Staufienbiel M, et al. The liver X receptor ligand T0901317 decreases amyloid beta production in vitro and in a mouse model of Alzheimer's disease. *J Biol Chem*. 2005; 280(6): 4079–4088.
58. Jorde R, Figenschau Y, Hutchinson M, Emaus N, Grimnes G. High serum 25-hydroxyvitamin D concentrations are associated with a favorable serum lipid profile. *Eur J Clin Nutr*. 2010; 64(12): 1457–1464.
59. Karhapää P, Pihlajamäki J, Pörsti I, et al. Diverse associations of 25-hydroxyvitamin D and 1,25-dihydroxy-vitamin D with dyslipidaemias. *J Intern Med*. 2010; 268(6): 604–610.
60. Riek AE, Oh J, Bernal-Mizrachi C. Vitamin D regulates macrophage cholesterol metabolism in diabetes. *J Steroid Biochem Mol Biol*. 2010; 121(1-2): 430–433.
61. Gupta AK, Sexton RC, Rudney H. Effect of vitamin D₃ derivatives on cholesterol synthesis and HMG-CoA reductase activity in cultured cells. *J Lipid Res*. 1989; 30(3): 379–386.
62. Wang J-H, Keisala T, Salakivi T, Minasyan A, Kalueff AV, Tuohimaa P. Serum cholesterol and expression of ApoA1, LXRβ and SREBP2 in vitamin D receptor knock-out mice. *J Steroid Biochem Mol Biol*. 2009; 113(3-5): 222–226.
63. Jiang W, Miyamoto T, Kakizawa T, et al. Inhibition of LXRα signaling by vitamin D receptor: possible role of VDR in bile acid synthesis. *Biochem Biophys Res Commun*. 2006; 351(1): 176–184.
64. Tashiro K, Ishii C, Ryoji M. Role of distal upstream sequence in vitamin D-induced expression of human CYP24 gene. *Biochem Biophys Res Commun*. 2007; 358(1): 259–365.
65. Jehan F, DeLuca HF. The mouse vitamin D receptor is mainly expressed through and Sp1-driven promoter in vivo. *Arch Biochem Biophys*. 2000; 377(2): 273–283.
66. Chen HT, Chen JY, Huang YC, Chang HC, Hung WC. Function role of VDR in the activation of p27Kip1 by the VDR/Sp1 complex. *J Cell Biochem*. 2006; 98(6): 1450–1456.
67. Santpere G, Nieto M, Puig B, Ferrer I. Abnormal Sp1 transcription factor expression in Alzheimer disease and tauopathies. *Neurosci Lett*. 2006; 397(1-2): 30–34.
68. Citron BA, Dennis JS, Zeitlin RS, Echeverria V. Transcription factor Sp1 dysregulation in Alzheimer's disease. *J Neurosci Res*. 2008; 86(11): 2499–2506.
69. Brock B, Basha R, DiPalma K, et al. Co-localization and distribution of cerebral APP and Sp1 and its relationship to amyloidogenesis. *J Alzheimer's Dis*. 2008; 13(1): 71–80.
70. Christensen MA, Zhou W, Qing H, Lehman A, Philipsen S, Song W. Transcriptional regulation of BACE1, the β-amyloid precursor protein β-secretase, by Sp1. *Mol Cell Biol*. 2004; 24(2): 865–874.
71. Docagne F, Gabriel C, Lebeurrier N, et al. Sp1 and Smad transcription factors co-operate to mediate TGF-β-dependent activation of amyloid-β precursor protein gene transcription. *Biochem J*. 2004; 383(pt 2): 393–399.
72. Love S, Barber R, Wilcock GK. Increased poly(ADP-ribosyl)ation of nuclear proteins in Alzheimers's disease. *Brain*. 1999; 122(pt 2): 247–253.
73. Kassner SS, Bonaterra GA, Kaiser E, et al. Novel systemic markers for patients with Alzheimer disease?—A pilot study. *Current Alzheimer Res*. 2008; 5(4): 358–366.
74. Abeti R, Abramov AY, Duchon MR. β-amyloid activates PARP causing astrocytic metabolic failure and neuronal death. *Brain*. 2011; 134(pt 6): 1658–1672.
75. Infante J, Llorca J, Mateo I, et al. Interaction between Poly(ADP-Ribose) Polymerase 1 and Interleukin 1A genes is associated with Alzheimer's disease risk. *Dement Geriatr Cogn Disord*. 2007; 23(4): 215–218.
76. Liu HP, Lin WY, Wu BT, et al. Evaluation of the poly(ADP-ribose) polymerase-1 gene variants in Alzheimer's disease. *J Clin Lab Anal*. 2010; 24(3): 182–186.
77. Bhatia M, Kirkland JB, Mecking-Gill KA. Modulation of poly(ADP-ribose) polymerase during neurophilic and monocytic differentiation of promyelocytic (NB4) and myelocytic (HL-60) leukaemia cells. *Biochem J*. 1995; 308(pt 1): 131–137.
78. Mabley JG, Wallace R, Pacher P, Murphy K, Szabó C. Inhibition of poly(ADP-ribose) polymerase-1 by the active form of vitamin D. *Int J Mol Med*. 2007; 19(6): 947–952.
79. Shen M, Yen A. Nicotinamide cooperates with retinoic acid and 1,25-dihydroxyvitamin D₃ to regulate cell differentiation and cell cycle arrest of human myeloblastic leukemia cells. *Oncology*. 2009; 76(2): 91–100.

80. Moore M, Piazza A, Nolan Y, Lynch MA. Treatment with dexamethasone and vitamin D₃ attenuates neuroinflammatory age-related changes in rat hippocampus. *Synapse*. 2007; 61(10): 851–861.
81. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the Rotterdam study. *Neurology*. 1999; 53(9): 1937–1942.
82. Kroner Z. The relationship between Alzheimer's disease and diabetes: type 3 diabetes? *Altern Med Rev*. 2009; 14(4): 373–379.
83. Takeda S, Sato N, Uchio-Yamada K, et al. Diabetes-accelerated memory dysfunction via cerebrovascular inflammation and Aβ_{25–35} deposition in an Alzheimer mouse model with diabetes. *Proc Natl Acad Sci U S A*. 2010; 107(15): 7036–7041.
84. Fishel MA, Watson GS, Montine TJ, et al. Hyperinsulinemia provokes synchronous increases in central inflammation and β-amyloid in normal adults. *Arch Neurol*. 2005; 62(10): 1539–1544.
85. de la Monte SM. Insulin resistance and Alzheimer's disease. *BMB Reports*. 2009; 42(8): 475–481.
86. Vanhanene M, Koivisto K, Moilanen L, et al. Association of metabolic syndrome with Alzheimer disease: a population-based study. *Neurology*. 2006; 67(5): 843–847.
87. Garcia-Lara JM, Aguilar-Navarro S, Gutiérrez-Robledo LM, Avila-Funes JA. The metabolic syndrome, diabetes, and Alzheimer's disease. *Rev Invest Clin*. 2010; 62(4): 343–349.
88. Pasinetti GM, Zhao Z, Qin W, et al. Caloric intake and Alzheimer's disease. Experimental approaches and therapeutic implications. *Interdiscip Top Gerontol*. 2007; 35: 159–175.
89. Moroz N, Tong M, Longato L, Xu H, de la Monte SM. Limited Alzheimer-type neurodegeneration in experimental obesity and type 2 diabetes mellitus. *J Alzheimers Dis*. 2008; 15(1): 29–44.
90. Ho AJ, Raji CA, Becker JT, et al; Cardiovascular Health Study; ADNI. Obesity is linked with lower brain volume in 700 AD and MCI patients. *Neurobiol Aging*. 2010; 31(8): 1328–1339.
91. Luchsinger JA, Cheng D, Tang MX, Schupf N, Mayeux R. Central obesity in the elderly is related to late-onset Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2011; June 9. Epub ahead of print.
92. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obes Rev*. 2011; 12(5): e426–e437.
93. Aksoy H, Akçay F, Kurtul N, Baykal O, Avci B. Serum 1,25 dihydroxyvitamin D (1,25(OH)₂D₃), 25 hydroxyvitamin D (25(OH)D) and parathormone levels in diabetic retinopathy. *Clin Biochem*. 2000; 33(1): 47–51.
94. Kaur H, Donaghue KC, Chan AK, et al. Vitamin D deficiency is associated with retinopathy in children and adolescents with type 1 diabetes. *Diabetes Care*. 2011; 34(6): 1400–1402.
95. Yiu YF, Chan YH, Yiu KH, et al. Vitamin D deficiency is associated with depletion of circulating endothelial progenitor cells and endothelial dysfunction in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011; 96(5): E830–E835.
96. Verhaeghe J, Suiker AM, Van Bree R, et al. Increased clearance of 1,25(OH)₂D₃ and tissue-specific responsiveness to 1,25(OH)₂D₃ in diabetic rats. *Am J Physiol*. 1993; 265(2 pt 1): E215–E223.
97. Chen S, Massaro JM, Fox CS, et al. Adiposity, cardiometabolic risk, and vitamin D status: the Framingham heart study. *Diabetes*. 2010; 59(1): 242–248.
98. Liel Y, Ulmer E, Shary J, Hollis BW, Bell NH. Low circulating vitamin D in obesity. *Calcif Tissue Int*. 1988; 43(4): 199–201.
99. Arunabh S, Pollack S, Yeh J, Aloia JF. Body fat content and 25-hydroxyvitamin D levels in healthy women. *J Clin Endocrinol Metab*. 2003; 88(1): 157–161.
100. Blum M, Dolnikowski G, Seyoum E, et al. Vitamin D₃ in fat tissue. *Endocrine*. 2008; 33(1): 90–94.
101. Evatt ML, DeLong MR, Khazai N, Triche S, Tangpricha V. Prevalence of vitamin D insufficiency in patients with Parkinson disease and Alzheimer disease. *Arch Neurol*. 2008; 65(10): 1348–1352.
102. Wilkins CH, Sheline YI, Roe CM, Birge SJ, Morris JC. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatr Psychiatry*. 2006; 14(12): 1032–1040.
103. Oudshoorn C, Mattace-Raso FUS, van der Velde N, Colin EM, van der Cammen TJM. Higher serum vitamin D₃ levels are associated with better cognitive test performance in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2008; 25(6): 539–543.
104. Llewellyn DJ, Lang IA, Langa KM, Melzer D. Vitamin D and cognitive impairment in the elderly U.S. population. *J Gerontol A Biol Sci Med Sci*. 2011; 66(1): 59–65.
105. Taghizadeh M, Djazayeri A, Salami M, Eshraghian MR, Zavareh SA. Vitamin-D-free regimen intensifies the spatial learning deficit in Alzheimer's disease. *Int J Neurosci*. 2011; 121(1): 16–24.
106. Yu J, Gattoni-Celli M, Zhu H, et al. Vitamin D₃-enriched diet correlated with a decrease of amyloid plaques in brain of AβPP transgenic mice. *J Alzheimer Dis*. 2011; 25(2): 295–307.
107. Landfield PW, Cadwallader-Neal L. Long-term treatment with calcitriol (1,25(OH)₂ vit D₃) retards a biomarker of hippocampal aging in rats. *Neurobiol Aging*. 1998; 19(5): 469–477.
108. Klingner M, Apelt J, Kumar A, et al. Alterations in cholinergic and non-cholinergic neurotransmitter receptor densities in transgenic Tg2576 mouse brain with beta-amyloid plaque pathology. *Int J Dev Neurosci*. 2003; 21(7): 357–369.
109. Heneka MT, Nadrigny F, Regen T, et al. Locus ceruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. *Proc Natl Acad Sci U S A*. 2010; 107(13): 6058–6063.
110. Kumar PT, Antony S, Nandhu MS, Sadanandan J, Najil G, Paulose CS. Vitamin D₃ restores altered cholinergic and insulin receptor expression in the cerebral cortex and muscarinic M₃ receptor expression in pancreatic islets of streptozotocin induced diabetic rats. *J Nutr Biochem*. 2011; 22(5): 418–425.
111. Baski SN. Altered pressor response to norepinephrine in calcium- and vitamin D-deficient rats. *Clin Exp Hypertens A*. 1988; 10(5): 811–832.
112. De Novellis V, Loffreda A, Viagliano S, et al. Effects of dietary vitamin D deficiency on the cardiovascular system. *Re Comm Chem Pathol Pharmacol*. 1994; 83(2): 125–144.
113. Shimosawa T, Ando K, Fujita T. Enhancement of vasoconstrictor response by a noncyclic analogue of vitamin D₃. *Hypertension*. 1993; 21(2): 253–258.

114. Coon AL, Wallace DR, Mactutus CF, Booze RM. L-type calcium channels in the hippocampus and cerebellum of Alzheimer's disease brain tissue. *Neurobiol Aging*. 1999; 20(6): 597–603.
115. Dursun E, Gezen-Ak D, Yilmazer S. A novel perspective for Alzheimer's disease: vitamin D receptor suppression by amyloid- β and preventing the amyloid- β induced alterations by vitamin D in cortical neurons. *J Alzheimers Dis*. 2011; 23(2): 207–219.
116. Brewer LD, Porter NM, Kerr DS, Landfield PW, Thibault O. Chronic $1\alpha, 25\text{-}(\text{OH})_2$ vitamin D_3 treatment reduces Ca^{2+} -mediated hippocampal biomarkers of aging. *Cell Calcium*. 2006; 40(3): 277–286.
117. Brewer LD, Thibault O, Chen KC, Langub MC, Landfield PW, Porter NM. Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. *J Neurosci*. 2001; 21(1): 98–108.
118. Shan JJ, Li B, Taniguchi N, Pang PK. Inhibition of membrane L-type calcium channel activity and intracellular calcium concentration by 24R, 25-dihydroxyvitamin D_3 in vascular smooth muscle. *Steroids*. 1996; 61(11): 657–663.
119. Wu CK, Yeh HH. Nerve growth factor rapidly increases muscarinic tone in mouse medial septum/diagonal band of Broca. *J Neurosci*. 2005; 25(17): 4232–4242.
120. Poucet B, Herrmann T. Septum and medial frontal cortex contribution to spatial problem-solving. *Behav Brain Res*. 1990; 37(3): 269–280.
121. Olton DS, Walker JA, Gage FH. Hippocampal connections and spatial discrimination. *Brain Res*. 1978; 139(2): 295–308.
122. Calissano P, Matrone C, Amadoro G. Nerve growth factor as a paradigm of neurotrophins related to Alzheimer's disease. *Develop Neurobiol*. 2010; 70(5): 372–383.
123. Mobley WC, Neve RL, Prusiner SB, McKinley MP. Nerve growth factor increases mRNA levels for the prion protein and the β -amyloid protein precursor in developing hamster brain. *Proc Natl Acad Sci U S A*. 1998; 85(24): 9811–9815.
124. Araki W, Wurtman RJ. Increased expression of amyloid precursor protein and amyloid precursor-like protein 2 during trophic factor withdrawal-induced death of neuronal PC12 cells. *Brain Res Mol Brain Res*. 1998; 56(1-2): 169–177.
125. De Rosa R, Garcia AA, Braschi C, et al. Intranasal administration of nerve growth factor (NGF) rescues recognition memory deficits in AD11 anti-NGF transgenic mice. *Proc Natl Acad Sci U S A*. 2005; 102(10): 3811–3816.
126. Tuszynski MH, Thal L, Pay M, et al. A phase I clinical trial of nerve growth factor gene therapy for Alzheimer disease. *Nat Med*. 2005; 11(5): 551–555.
127. Féron F, Burne THJ, Brown J, et al. Developmental vitamin D_3 deficiency alters the adult rat brain. *Brain Res Bull*. 2005; 65(2): 141–148.
128. Cornet A, Baudet C, Neveu I, Baron-Van Evercooren A, Brachet P, Naveilhan P. 1,25-dihydroxyvitamin D_3 regulates the expression of VDR and NGF gene in Schwann cells in vitro. *J Neurosci Res*. 1998; 53(6): 742–746.
129. Musiol IM, Feldman D. 1,25-dihydroxyvitamin D_3 induction of nerve growth factor in L929 mouse fibroblasts: effect of vitamin D receptor regulation and potency of vitamin D_3 analogs. *Endocrinology*. 1997; 138(1): 12–18.
130. Veenstra TD, Fahnestock M, Kumar R. An AP-1 site in the nerve growth factor promoter is essential for 1,25-dihydroxyvitamin D_3 -mediated nerve growth factor expression in osteoblasts. *Biochemistry*. 1998; 37(17): 5988–5994.
131. Ricciotti E, Fitzgerald GA. Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol*. 2011; 31(5): 986–1000.
132. Wanatabe Y, Hamada K, Bommelaer-Bayt MC, et al. Distinct localization of prostaglandin D₂, E₂, and F_{2 α} binding sites in monkey brain. *Brain Res*. 1989; 478(1): 142–148.
133. Kaufmann WE, Worley PF, Pegg J, Bremer M, Isakson P. COX-2, a synaptically induced enzyme, is expressed by excitatory neurons at postsynaptic sites in rat cerebral cortex. *Proc Natl Acad Sci U S A*. 1996; 93(6): 2317–2321.
134. Yasojima K, Schwab C, McGeer EG, McGeer PL. Distribution of cyclooxygenase-1 and cyclooxygenase-2 mRNA and proteins in human brain and peripheral organs. *Brain Res*. 1999; 830(2): 226–236.
135. Ho L, Pironi L, Winger D, Purohit DP, Aisen PS, Pasinetti GM. Regional distribution of cyclooxygenase-2 in the hippocampal formation in Alzheimer's disease. *J Neurosci Res*. 1999; 57(3): 295–303.
136. Xiang Z, Ho L, Yemul S, et al. Cyclooxygenase-2 promotes amyloid plaque deposition in a mouse model of Alzheimer's disease neuropathology. *Gene Expr*. 2002; 10(5-6): 271–278.
137. Qin W, Ho L, Pompl PN, et al. Cyclooxygenase (COX)-2 and COX-1 potentiate beta-amyloid peptide generation through mechanisms that involve gamma-secretase activity. *J Biol Chem*. 2003; 278(51): 50970–50977.
138. Rich JB, Rasmussen DX, Folstein MF, Carson KA, Kawas C, Brandt J. Nonsteroidal anti-inflammatory drugs in Alzheimer's disease. *Neurology*. 1995; 45(1): 51–55.
139. McGeer PL, Schulzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease; a review of 17 epidemiologic studies. *Neurology*. 1996; 47(2): 425–432.
140. Moreno J, Krishnan AV, Swami S, et al. Regulation of prostaglandin metabolism by calcitriol attenuates growth stimulation in prostate cancer cells. *Cancer Res*. 2005; 65(17): 7917–7925.
141. Apama R, Subhashini J, Roy KR, et al. Selective inhibition of cyclooxygenase-2 (COX-2) by 1 $\alpha, 25$ -dihydroxy-16-ene-23-yne-vitamin D_3 , a less calcemic vitamin D analog. *J Cell Biochem*. 2008; 104(5): 1832–1842.
142. Bains JS, Shaw CA. Neurodegenerative disorders in humans: the role of glutathione in oxidative stress-mediated neuronal death. *Brain Res Rev*. 1997; 25(3): 335–358.
143. Butterfield DA, Howard B, Yatin S, et al. Elevated oxidative stress in models of normal brain aging and Alzheimer's disease. *Life Sci*. 1999; 65(18-19): 1883–1892.
144. de la Monte SM, Ganju N, Feroz N, et al. Oxygen free radical injury is sufficient to cause some Alzheimer-type molecular abnormalities in human CNS neuronal cells. *J Alzheimers Dis*. 2000; 2(3-4): 261–281.
145. Zemlan FP, Thienhaus OJ, Bosmann HB. Superoxide dismutase activity in Alzheimer's disease: possible mechanism for paired helical filament formation. *Brain Res*. 1989; 476(1): 160–162.

146. Tesco G, Latorraca S, Piersanti P, Sorbi S, Piacentii S, Amaducci L. Free radical injury in skin cultured fibroblasts from Alzheimer's disease patients. *Ann NY Acad Sci.* 1992; 26: 49–153.
147. Cohen MS, Mesler DE, Snipes RG, Gray TK. 1,25-dihydroxyvitamin D₃ activates secretion of hydrogen peroxide by human monocytes. *J Immunol.* 1986; 136(3): 1049–1053.
148. Sun X, Zemel MB. 1 α ,25-dihydroxyvitamin D₃ modulation of adipocyte reactive oxygen species production. *Obesity.* 2007; 15(8): 1944–1953.
149. Levy R, Malech HL. Effect of 1,25-dihydroxyvitamin D₃, lipopolysaccharide, or lipoteichoic acid on the expression of NADPH oxidase components in cultured human monocytes. *J Immunol.* 1991; 147(9): 3066–3071.
150. Bao BY, Ting HJ, Hsu JW, Lee YF. Protective role of 1 α ,25-dihydroxyvitamin D₃ against oxidative stress in nonmalignant human prostate epithelial cells. *Int J Cancer.* 2008; 122(12): 2699–2706.
151. Somjen D, Katzburg S, Grafi-Cohen M, Knoll E, Sharon O, Posner GH. Vitamin D metabolites and analogs induce lipoyxygenase mRNA expression and as well as reactive oxygen species (ROS) production in human bone cell line. *J Steroid Biochem Mol Biol.* 2011; 123(1-2): 85–89.
152. Sardar S, Chakraborty A, Chatterjee M. Comparative effectiveness of vitamin D₃ and dietary vitamin E on peroxidation of lipids and enzymes of the hepatic antioxidant system in Sprague-Dawley rats. *Int J Vitam Nutr Res.* 1996; 66(1): 39–45.
153. Schuman EM, Madison DV. A requirement for the intercellular messenger nitric oxide in long-term potentiation. *Science.* 1991; 254(5037): 1503–1506.
154. Zorumski CF, Izumi Y. Nitric oxide and hippocampal synaptic plasticity. *Biochem Pharmacol.* 1993; 46(5): 777–785.
155. De Servi B, La Porta CAM, Bontempelli M, Comolli R. Decrease of TGF- β 1 plasma levels and increase of nitric oxide synthase activity in leukocytes as potential biomarkers of Alzheimer's disease. *Exper Gerontol.* 2002; 37(6): 813–821.
156. Dorheim MA, Tracey WR, Pollock JS, Grammas P. Nitric oxide synthase activity is elevated in brain microvessels in Alzheimer's disease. *Biochem Biophys Res Commun.* 1994; 205(1): 659–665.
157. Lüth HJ, Holzer M, Gärtner U, Staufenbiel M, Arendt T. Expression of endothelial and inducible NOS-isoforms is increased in Alzheimer's disease, in APP23 transgenic mice and after experimental brain lesion in rat: evidence for an induction by amyloid pathology. *Brain Res.* 2001; 913(1): 57–67.
158. Nathan C, Calingasan N, Nezezon J, et al. Protection from Alzheimer's-like disease in the mouse by genetic ablation of inducible nitric oxide synthase. *J Exp Med.* 2005; 202(9): 1163–1169.
159. Chang JM, Kuo MC, Kuo HT, et al. 1 α ,25-dihydroxyvitamin D₃ regulates inducible nitric oxide synthase messenger RNA expression and nitric oxide release in macrophage-like RAW 264.7 cells. *J Lab Clin Med.* 2004; 143(1): 14–22.
160. Garcion E, Nataf S, Berod A, Darcy F, Brachet P. 1,25-dihydroxyvitamin D₃ inhibits the expression of inducible nitric oxide synthase in rat central nervous system during experimental allergic encephalomyelitis. *Brain Res Mol Brain Res.* 1997; 45(2): 255–267.
161. Equils O, Naiki Y, Shapiro AM, et al. 1,25-dihydroxyvitamin D₃ inhibits lipopolysaccharide-induced immune activation in human endothelial cells. *Clin Exper Immunol.* 2005; 143(1): 58–64.
162. Garcion E, Sindji L, Leblondel G, Brachet P, Darcy F. 1,25-dihydroxyvitamin D₃ regulates the synthesis of γ -glutamyl transpeptidase and glutathione levels in rat primary astrocytes. *J Neurochem.* 1999; 73(2): 859–866.
163. Bell NH, Shaw S, Turner RT. Evidence that 1,25-dihydroxyvitamin D₃ inhibits the hepatic production of 25-hydroxyvitamin D in man. *J Clin Invest.* 1984; 74(4): 1540–1544.
164. Luong VQK, Nguyen THL. Coexisting hyperparathyroidism and primary hyperparathyroidism with vitamin D-deficient osteomalacia in a Vietnamese immigrant. *Endocr Pract.* 1996; 2(4): 250–254.