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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-1gene). 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, 1α,25-dihydroxyvitamin D_3, is best used for AD because of its active form of vitamin D_3 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 al[2] 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 D_3 (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 postmortem brain of patients with AD and correlates with the number of senile plaques.[12] Shalit et al[13] 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 (Aβ) 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 Aβ 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 1α-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 pattern[19]; VDR was restricted to the nucleus while 1α-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 Aβ plaque load.[27] Increased binding of radioactively labeled ACI 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 Aβ in peripheral blood.[30] The role of ACE in AD remains controversial; ACE has been shown to inhibit Aβ aggregation and to lower the levels of secreted Aβ 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 Aβ levels and plaque deposition in vivo in another study.[33] Although short-term treatment with ACE inhibitors failed to increase Aβ formation in the brain, long-term treatment enhanced Aβ 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 amygdale[38] and to trends toward increased brain Aβ42 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 ϵ4 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 ε4-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 Ecudorian 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 al[52] 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 Aβ 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, LXRα and LXRβ, but only LXRβ is expressed in the brain. Liver X receptor β is known to play a key role in Aβ and cholesterol modulation.[55] In mice, expression of the *LXR* gene causes a decrease in cellular Aβ secretion.[56]

A synthetic LXR agonist is reported to decrease Aβ 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 LXRβ levels were significantly higher than those in wild-type mice.[62] There is crosstalk between LXRα 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 D_3 (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 sites[65] 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 Aβ.[69] $BACE_1$, 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 Aβ.[70] Sp1 and signaling mother 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 Aβ-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 al[88] 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 $25OHD_3$ concentrations in subcutaneous fat tissue and serum were inversely and correlated with body weight.[97] Decreased $25OHD_3$ 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 $25OHD_3$ levels in healthy women, regardless of dietary vitamin D intake, season, age, and race.[99] The association between $25OHD_3$ 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 D_3 -enriched diet was correlated with a decrease in the number of amyloid plaque, a decrease in Aβ 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 Aβ 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 al[110] 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 in calcium influx. Aβ 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 Ca^{2+} dysregulation.[116,117] 24R, 25 dihydroxyvitamin D_3 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 memory[119-121] 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 Aβ 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 monocytes[147] 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 lipoxygenase 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 Aβ protein deposits.[157] Nitric oxide synthase deficiency protected the AD-like mice from premature mortality, cerebral plaque formation, increased Aβ protein levels, astrocytosis, and microgliosis.[158] The activation of macrophages by 1α-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 D_3 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.

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