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SHORT REVIEW ARTICLE

Vitamin D basis of Alzheimer's disease: from genetics to biomarkers

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Abstract
Alzheimer's disease (AD) is a progressive neurodegenerative disorder seen mostly in the elderly population. While to date AD research has focused on either neurochemical disruptions, genetic studies, or the pathological hallmarks, little has been done to establish a novel approach that would encompass all three aspects, one that would overcome the current barriers in AD research and determine the cause of AD and, eventually, discover a treatment. Meanwhile, there have been strong indications in recent years that vitamin D, a secosteroid hormone, and its receptors are fundamentally involved in neurodegenerative mechanisms. Observational studies have pointed to vitamin D deficiency as a genetic risk factor for AD, Parkinson's disease (PD), vascular dementia, and multiple sclerosis (MS), as well as other neurological disorders, brought about by alterations in genes involved in metabolism, transportation, and actions of vitamin D. Molecular studies have demonstrated that vitamin D treatments prevent amyloid production while also increasing its clearance from the brain in AD. Finally, recent vitamin D intervention studies have reported significant improvement in cognitive performance in subjects with senile dementia, mild cognitive impairment, and AD. This review aims to describe how a vitamin D research strategy, fully integrating all aspects of present-day AD research, would elucidate the genetic, molecular, and biochemical background of the disease.

Keywords Alzheimer's disease · Parkinson's disease · Vitamin D deficiency · Vitamin D receptor · Biomarker

Alzheimer's disease

Alzheimer's disease (AD) is a chronic, slowly progressing neurodegenerative disorder that begins well before its symptoms appear [1]. It is the most common cause of dementia seen in aging individuals, underlying 60–80% of cases [2]. Two major pathological hallmarks of AD involve extracellular and intracellular protein aggregation [3]. Amyloid plaques are extracellular aggregations which include a 4-kDa peptide as the core component. Neurofibrillary tangles are intracellular protein aggregations consisting of hyperphosphorylated tau which is a microtubule-associated protein. A series of adverse events caused by protein aggregation, such as disruption of interneuronal signal transduction, axonal transport and neurotrophic factor synthesis, induction of oxidative stress, and alteration of neuronal calcium homeostasis eventually results in the death of neurons [3].

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Brief history of Alzheimer's disease

Although Alzheimer's disease is named after Dr. Alois Alzheimer and he was the first, in 1906, to identify neurofibrillary tangles in the brain, it was his colleague, Emil Kraepelin, who, in 1910, would coin the term "Alzheimer's disease". Kraepelin stressed that this newly reported disease was not to be classified among other diseases that cause presenile dementia [4]. For a long time subsequently, Alzheimer's disease was considered to be synonymous with early onset presenile dementia, while late onset senile dementia, thought to be caused by vascular abnormalities accompanying the normal aging process, was rarely studied. The senile dementia or sporadic form of the disease was thus unfortunately long disregarded [4].

In 2006, Dr. J. Hardy meticulously reviewed a century of AD research and described the three basic science research tracks for development of understanding of the disease: (1)

the neurochemical approach, which seeks to understand the mechanisms of neurotransmitter loss; (2) the pathological approach, which investigates the role of protein aggregation pathology; and (3) the genetic approach, which focuses on a positional cloning strategy in Mendelian forms of AD to determine what are the causative variants in disease etiology [4]. Thanks to the implementation of these three approaches over the past four decades, many factors concerning brain function, AD pathogenesis, and the genetic risk factors of AD have been brought to light. However, though great progress has been made, the cause of and treatment for AD still remain unresolved [4, 5]. This implies that a novel strategy embracing all three "tracks" or approaches is needed to overcome the current challenges in AD research, thereby determining the ultimate cause of AD and identifying optimal treatment [6].

Where does vitamin D stand?

Vitamin D is a secosteroid (i.e., a type of steroid with a "broken" B-ring) hormone with neurosteroid-like properties and is a ligand of vitamin D receptor (VDR) [7]. Although vitamin D is very well known for its role in calcium metabolism and bone mineralization, it is increasingly proposed that greater focus be placed on its lesser known roles, which include modulation of the immune system, the renin-angiotensin system, and cell cycle control, protection against cardiovascular disease and cancer, and regulation of neuromuscular function and cognitive functions [8–10]. Data from our previous studies and research work in the field have indicated that the consequences of long-term vitamin D deficiency, i.e., hypovitaminosis D, and/or inefficient utilization of vitamin D may cause neurons to be vulnerable to aging and neurodegeneration, this hypothesis being substantiated by numerous other publications over the last decade [6, 11–13]. On the basis of these accumulating findings, we have suggested Alzheimer's disease as being an outcome of long-term hormonal imbalance, the crucial hormone being vitamin D [6, 14, 15]. Given that the modern era of AD research has utilized, as mentioned above, the three basic science research tracks as proposed by Hardy, the rest of this review will focus on how a vitamin D research strategy for Alzheimer's disease fully integrating the three approaches of AD research under one umbrella would elucidate the genetic, molecular, and biochemical background of the disease, thus opening the way to a better understanding of the disease mechanisms.

The genetic background

Starting from 1998 and during the first decade of the 2000s, certain loci on chromosome 12 were suggested as constituting additional risk loci for AD [16–20]. The locus is particularly important since the VDR gene is also located in this region. The first evidence of a genetic association between AD and VDR was provided by our study in 2007. The study suggested that a VDR gene polymorphism has the potential to increase the risk of AD 2.3-fold [21]. Since our previous studies indicated that the Turkish population, which is located geographically between Europe and Asia, shows a similar distribution of the genotype and allele frequencies with Caucasian descent samples, but not with Asians [22, 23], our initial data required confirmation from other populations. Beecham et al., through their genome-wide association study including 518 AD cases and 555,000 single nucleotide polymorphisms (SNPs), proposed that, among a number of nearby candidate genes in the 12q13 region, VDR is the most probable genetic risk factor for AD [20], thereby confirming our findings. SNPs in the VDR gene are hypothesized to cause some of the alterations in the vitamin D-VDR pathway [21, 24, 25]. Of note, none of the SNPs in the VDR gene has a functional consequence, with the exception of rs2228570 (FokI site). rs2228570, which is in exon 2 of the VDR gene, produces an elongated form of VDR by three additional amino acids [26]. Intron 8 of the VDR gene includes rs1544410 (BsmI site), rs7975232 (ApaI site), and rs757343 (Tru9I site) SNPs. The other SNP, rs731236 (TaqI site), is located in exon 9 of the VDR gene. The intronic SNPs are thought to be in strong linkage disequilibrium with the SNPs in the 3′ untranslated region, which are involved in the regulation of VDR gene expression [26]. Studies performed over the last 15 years have demonstrated an association between VDR polymorphisms and cognitive decline [27, 28], AD [21, 25, 29], and PD [12, 30]. Due to these findings, the genes related to vitamin D metabolism and transport and the receptors involved in vitamin D action have taken center stage in current research into the genetic background of AD and neurodegeneration.

Recent studies have also reported that SNPs of megalin (low-density lipoprotein receptor-related protein 2-LRP2), a cell membrane vitamin D transporter, are associated with Alzheimer's disease [31, 32] and cognitive decline [28]. Our recent study also indicated, for the first time in the literature, that SNPs in the vitamin D binding protein (VDBP or GC) gene are also associated with PD and its clinical features [12].

Another important issue was a well-known genetic risk factor for sporadic AD, ApoE. Due to the surprising evolutionary juncture of vitamin D and ApoE, we have investigated the genetic background of ApoE and vitamin D deficiency in our cohort and found that well-known genetic risk factors for AD might additionally be related to vitamin D metabolism [11].

Although these studies strongly point to the role in the genetic background of neurodegenerative disorders of the genes related to vitamin D metabolism and transport and the receptors involved in vitamin D action, more studies are needed to fully elucidate the issue.

The pathological approach

The molecular basis of vitamin D as related to AD pathogenesis is reviewed in another article dealing with this issue. Briefly, the authors' initial study reported reduced levels of VDR mRNA in the hippocampal cells of AD patients [33]. Meanwhile, our molecular studies provided strong evidence for overlapping mechanisms of amyloid pathology and vitamin D action in hippocampal or cortical neurons [6, 13, 25, 34–42]. Basically, our studies, in addition to others, indicate that vitamin D deficiency or its insufficient utilization may change the brain microenvironment to induce AD-type pathogenesis or directly induce at least one of the neuropathological hallmarks of AD, amyloid aggregations. Subsequently, these pathological changes alter vitamin D-related pathways, creating a complimentary negative feedback loop for decades before AD exerts its symptoms (Fig. 1). On the other hand, researchers have also provided valuable data on the molecular mechanism of vitamin D action in neurodegenerative disorders, in amyloid beta clearance by macrophages and glia, or in neuronal development [43, 47–49].

These novel findings in the field of the molecular basis of vitamin D as related to AD pathogenesis or neurodegeneration have, however, created more questions than answers, particularly from the perspective of neuronal survival and development. Providing answers to these questions is expected to be the focus of the next decade.

The biochemistry and the neurochemical approach

Geographical conditions, seasons, cultural features, and nutrition are suggested as being the primary cause of vitamin D deficiency. Moreover, pigmentation of the skin, geographic latitude, the amount of sunlight present, sunlight exposure, and the age of the individual are additional factors on which the efficiency of vitamin D synthesis in the body depends [50]. Khazai et al. reported that vitamin D deficiency is present in 61% of the white population and 91% of the African-American population of the USA [51]. Since then, similar results have been published regarding different populations [8]. While numerous studies indicate that vitamin D deficiency is common among adults and even among young and healthy individuals of the developed countries, its prevalence is particularly high in elderly persons and institutionalized elderly individuals, resulting in osteopenia, osteoporosis, and hip fractures [51].

Recent studies have reported significantly low levels of serum 25(OH)D in individuals suffering from AD, PD, mood disorders, and cognitive decline [52–58], while the correlation between vitamin D levels and MMSE scores has also been reported [59]. Longitudinal studies, which are at present very limited in number, have suggested that low levels of vitamin D are associated with substantial cognitive decline in the elderly [56]. In addition, they have demonstrated that baseline vitamin D deficiency predicted the onset of dementias of non-AD type

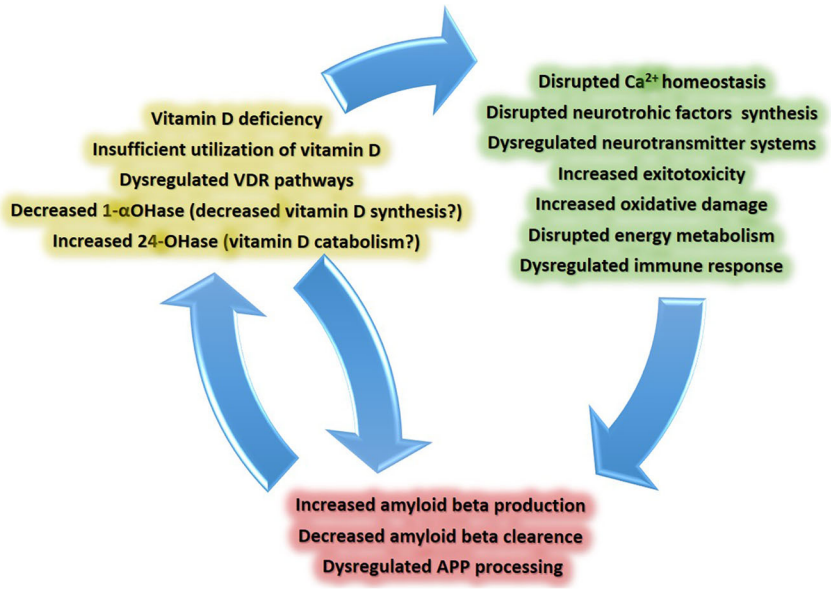

Fig. 1 The relation between vitamin D and amyloid pathology in Alzheimer's disease. Recent studies have indicated that vitamin D directly regulates the production and clearance of amyloid beta peptide in addition to amyloid precursor protein processing in AD [13, 39, 43, 44]. Conversely, amyloid beta peptide itself directly suppresses vitamin D receptor and 1-αOHase (the enzyme involved in synthesis of vitamin D), and induces 24OHase (the enzyme involved in catabolism of vitamin D) [34, 35, 42]. Moreover, vitamin D is involved in certain aspects of cell maintenance and cell fate, like neurotrophic factor synthesis, neurotransmitter regulation, energy metabolism, or/and immune response, all of which indirectly modulate amyloid pathology in AD [36–38, 40, 41, 45, 46]

[60]. Moreover, Annweiler et al. reported that hypovitaminosis D may be involved in the process of dementia from the prodromal stages [61] and may predict executive dysfunction, especially with regard to mental shifting, information updating, and processing speed [62]. A meta-analysis suggested that AD patients have lower serum 25(OH)D levels than healthy subjects [63]. Afzal et al. reported an association of low levels of plasma 25(OH)D with increased risk of the combined endpoint of AD and vascular dementia in a prospective cohort study with a follow-up of 30 years [64]. Finally, vitamin D strongly stimulated phagocytosis and clearance of Aβ [43, 65].

Another important issue that should be emphasized is the evolutionary relationship between vitamin D and ApoE. Recent studies surprisingly revealed the presence of an evolutionary juncture of vitamin D and ApoE, which encompasses latitude UVB radiation, the immune system, and dietary habits. Based on this relationship, our recent study suggested that reduced 25OHD levels in serum, originating only from *ApoEε4* non-carrier AD patients, has the potential to cover almost 60% of phenotype that has no known genetic risk factor for sporadic Alzheimer's cases [11]. Fiala and Mizwicki have suggested that the maintenance of an adequate production of vitamin D and docosahexaenoic acid-derived lipidic modulators has the potential to prevent neurodegeneration, at least in some individuals [66]. Finally, Annweiler and Beauchet combined vitamin D and memantine (a commonly used AD drug) in a novel AD treatment protocol (AD-IDEA) and observed improved results compared to memantine alone [67]. In addition, hypovitaminosis D is also thought to be associated with cerebrovascular changes in the brain. Buell et al. demonstrated a relationship between 25(OH)D levels and diagnoses of AD and stroke (with and without symptoms of dementia) and vascular pathogenesis, observed on MRI [68]. An inverse correlation between 25(OH)D levels and risk of stroke has also been suggested in a recent meta-analysis [69, 70].

Biomarkers

The proposal for new criteria and guidelines for AD diagnosis set the stage for the most significant advances in AD management over the last 30 years. The 1984 criteria required a decline in cognitive functions and loss of memory severe enough to affect daily life before a diagnosis of could be established. By 2011, however, the criteria included a presymptomatic or preclinical stage, this being the principal change in AD diagnosis which, in the present era, takes into consideration the knowledge that AD creates alterations in the brain as many as 20 years before the patient presents any symptoms [5]. This radical change in diagnosis made inevitable the need for additional biomarker research to enable diagnosis of the early stages of AD [5]. For over a decade now, Aβ 1–42, total tau, and hyperphosphorylated tau in cerebrospinal fluid (CSF) have been known to be the CSF biomarkers of AD, capable of indicating the presence of the disease [5, 71, 72]. Nevertheless, little has been done to assess the potential of vitamin D or its metabolites, or any molecule that is related to vitamin D metabolism or its transport troughs system, as a biomarker for any kind of neurodegenerative disorder, despite the fact that a small number of studies suggest that CSF GC levels have the potential to be used as a biomarker for AD [73–75]. Our unpublished data points to the possible positive correlation of CSF 25OHD levels and CSF Aβ 1–42 levels.

What about intervention studies?

A limited number of valuable studies have demonstrated the beneficial effects of vitamin D supplementation in affected subjects. In an aforementioned study, Annweiler et al. demonstrated that combined treatment with both vitamin D and memantine (a well-known AD drug) yielded significantly better results compared with treatment of patients with memantine alone [67]. Another study showed that vitamin D supplementation for 6 months is beneficial in patients with mild cognitive impairment (MCI) [76]. Lemire et al. observed that memantine may prevent the cognitive decline that accompanies the onset of vitamin D deficiency, which finding suggests that AD patients should be given a regimen combining both memantine and vitamin D supplements [77]. One of the two recent intervention studies showed that vitamin D supplementation caused significant improvement in cognitive performance in subjects with senile dementia [78], while the second observed that treatment with vitamin D may be an independent protecting factor in the progression of Alzheimer's disease [79]. These intervention studies, in addition to several genetic and observational studies, are summarized in Table 1.

Immune system modulation

Alzheimer's disease is also hypothesized to be caused, or worsened, by an inflammatory brain disorder [87]. Especially the amyloid plaques which are surrounded by the reactive astrocytes and microglia in the brains of AD patients induce locally elevated levels of cytokines and chemokines around these amyloid aggregations [88–90]. Vitamin D is a major regulator of a number of cytokines [91, 92] in various cell types of the immune system and for the treatment of such disorders as MS, PD, epilepsy, and depression. The effects of vitamin D on neuroimmunomodulatory systems have been meticulously reviewed by Fernandes de Abreu et al. and Landel et al. [49, 93]. AD mouse models that were supplemented with vitamin D for 5 months showed improvements

Table 1 Selected observational and intervention studies related to vitamin D and AD-type dementia

	Study type	Significance
Selected observational studies		
Sutherland et al. [33]	Case-control brain tissue	The hippocampi of AD patients have decreased VDR mRNA expression
Wilkins et al. [58]	Cross-sectional study	Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults
Annweiler et al. [52]	Cross-sectional study	Vitamin D deficiency is associated with cognitive impairment
Llewellyn et al. [55]	Cross-sectional study	Low serum 25-hydroxyvitamin D concentration is associated with cognitive impairment
Annweiler et al. [62]	Meta-analysis	Serum 25OHD levels of AD patients are significantly lower
Afzal et al. [64]	Longitudinal study	Vitamin D deficiency increases the risk of developing AD and vascular dementia
Masoumi et al. [65]	In vitro studies including human samples	Vitamin D induces amyloid beta clearance of macrophages in AD patients
Mizwicki et al. [43]	In vitro studies including human samples	1,25(OH)2-vitamin D3 promotes the recovery of amyloid- phagocytosis by Alzheimer's disease macrophages
Littlejohns et al. [80]	Longitudinal study	Mild vitamin D deficiency increases the risk of developing dementia by 53%. Severe vitamin D deficiency increases the risk of developing dementia by 125%
Dursun et al. [11]	Cross-sectional study	Vitamin D deficiency might pose a greater risk for ApoEe4 non-carrier Alzheimer's disease patients
Licher et al. [81]	Longitudinal study	Lower serum 25OHD levels are associated with higher incidence of dementia
Jayedi et al. [82]	Meta-analysis of dose response	The lower risk of dementia was observed at serum 25(OH)D of ~ 25 ng/ml, whereas the risk of AD decreased continuously along with the increase of serum 25(OH)D up to ~ 35 ng/ml.
Amadieu et al. [83]	Longitudinal study	Low levels of plasma vitamin D, carotenoids, and polysaturated fats are associated with significantly high risk of dementia
Selected genetic studies		
Paduslo et al. [16]	Linkage study	There is a novel AD risk locus on chromosome 12q
Gezen-Ak et al. [21]	SNP study	VDR polymorphisms increase the risk of developing AD 2.3-fold
Beecham et al. [20]	GWA study	A novel locus on chromosome 12q13 is associated with AD
Lehmann et al. [29]	SNP study	VDR is associated with AD
Gezen-Ak et al. [25]	SNP study	VDR "TaubF" haplotype is more frequently seen in AD patients
Wang et al. [84]	SNP study	VDR is associated with Alzheimer's disease
Lee et al. [85]	Meta-analysis	VDR SNPs and susceptibility to Parkinson's disease and Alzheimer's disease
Vargas et al. [31]	SNP study	Megalin (a membrane transporter of vitamin D polymorphism) is associated with AD
Beydoun et al. [86]	SNP study	VDR and megalin SNPs are associated with longitudinal cognitive change in adults
Gezen-Ak et al. [12]	SNP study	GC and VDR SNPs and Vitamin D levels are associated with Parkinson's disease with some clinical features such as progression or stage of the disease
Selected intervention studies		
Annweiler et al. [67]	Intervention study	Vitamin D and memantine (a well-known AD drug) combination yielded significantly better results compared with memantine alone treated patients
SanMartin et al. [76]	Intervention study	Six months of vitamin D supplementation is beneficial for MCI
Lemire et al. [77]	Intervention study	Memantine may prevent the cognitive decline that accompanies the onset of vitamin D deficiency, this suggesting that AD patients be given a regimen combining both memantine and vitamin D supplements
Gangwar et al. [78]	Intervention study	Vitamin D supplementation caused significant improvement in cognitive performance in subjects with senile dementia
Chaves et al. [79]	Intervention study	Vitamin D supplementation may be an independent protection factor in the progression of Alzheimer's disease

mostly in their inflammatory and immune gene expression profiles [94]. Vitamin D was reported to stimulate cytokines and macrophages to increase clearance of Aβ in AD patients [43, 95] and in aged rats [96]. Inducible nitric oxide synthase (iNOS) immunoreactivity was observed in the neurons and astrocytes of AD patients [97, 98]. It has moreover been suggested that increased levels of interleukin 1 beta (IL1β) and tumor necrosis factor alpha (TNFα) cause an Aβ-mediated iNOS induction in glial cells [99], while there is evidence that iNOS and Aβ induce the production of each other [87].

Vitamin D was reported to attenuate iNOS in immune system cells, such as monocytes, macrophages, and reactive microglia, and to reduce the immune response in a brain inflammation model [100, 101]. Lastly, one of our studies indicated that vitamin D prevents Aβ-induced iNOS expression and that iNOS expression is regulated by the vitamin D-VDR pathway in cortical neurons [40].

Conclusions

As pointed out by Dr. J. Hardy in 2006, the modern era of AD research is based on three basic "tracks," these constituting the neurochemical, the pathological, and the genetic approaches. Looking beyond, all the evidence today confirms that what is essentially needed is a vitamin D research strategy for AD that will fully integrate these three approaches of research under one single umbrella. Such a scheme would elucidate the genetic, molecular, and biochemical background of the disease, thus opening up the way to earlier diagnosis and definitive treatment. More specifically, this would be accomplished not only by means of thorough investigation into vitamin D's specific molecular mechanism, but also via exploration of its role in the most basic aspects of AD-type pathology and neurodegenerative mechanisms.

Vitamin D deficiency is widespread among young and old alike today [51], and, as shown above, this state of deficiency has been closely linked to neurological disorders. It appears likely that small changes in the brain microenvironment due to lack of this hormone over decades of a person's life could well have the potential to trigger various neurodegenerative diseases. Current knowledge indicates that such a long-range perspective is crucial for the diagnosis and management of many disease conditions. However, it is particularly so in the case of AD, given that long-term preventive medicine is of vital importance for this insidious neurodegenerative disease. It is thus evident that early diagnosis is of utmost importance, while aging individuals with AD should be strongly advised to avoid vitamin D deficiency and be supplemented when necessary in order to preserve their levels of cognitive reserve and performance longer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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