VITAMIN D
UpDates
2021;4(4):132-135
https://doi.org/10.30455/2611-2876-2021-7e

Vitamin D and dementia

Andrea Giusti[1], Giulia Botticella[2], Dario Camellino[2], Giuseppe Girasole[2], Giuseppina Tramontano[1], Gerolamo Bianchi[2]

[1] Department of Metabolic Bone Diseases and Fracture Prevention in the Elderly, Genoa ASL 3; [2] Rheumatology Unit, Department of Medical Specialities, Genoa ASL 3

Summary

Many findings arising from experimental studies, mostly using in vitro or animal models, seem to indicate that vitamin D plays a role in nervous system physiology and physiopathology with the potential for also determining the pathogenesis of certain degenerative diseases, such as dementia. It appears that vitamin D exerts neurotrophic, neuroprotective and neuroplastic effects, whilst also being involved in the synthesis of certain neurotransmitters. Data drawn from prospective observational studies have clearly confirmed the experimental observations by showing an inverse association between vitamin D status (25-hydroxyvitamin D concentration) and the incidence of dementia, with a dose-response relationship. To date, interventional studies using cholecalciferol to reduce the risk of dementia have not had positive results. This has been mainly due to significant limitations in terms of experimental design, treatment regimens, test population size and follow-up duration. Ad hoc and methodologically more appropriate study designs are needed to define the potential beneficial effect of cholecalciferol in preventing the risk of dementia.

VITAMIN D AND THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM

A large body of scientific evidence has suggested that vitamin D plays a role in the physiology and physiopathology of the central (CNS) and peripheral nervous systems. Indeed, it has been advanced that vitamin D deficiency might play a role in the pathogenesis of some neurodegenerative diseases, including dementia, Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis [1-3]. Many observations support vitamin D's involvement in CNS physiological and physiopathological processes. The vitamin D receptor (VDR) is ubiquitously distributed in the CNS and peripheral nervous system [1]. In fact, the topography of VDR distribution, initially defined in rats and hamsters, was subsequently confirmed and detailed in humans as well [1]. VDR is thought to be expressed in neurons and glia in several areas of the nervous system, including the cortex (e.g., temporal, frontal, parietal), the cerebellum, the spinal cord and in the basal ganglia [1]. 25-hydroxylase and 1α-hydroxylase activity has also been identified in the CNS, which is indicative of paracrine production of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] [1-3]. The same vitamin D metabolites have been identified in cerebrospinal fluid [1-3]. Finally, further evidence for the existence of paracrine production activity of 1,25$(OH)_2$D in the nervous system comes from the observation that the concentration of 1,25$(OH)_2$D in the CNS is in positive correlation with the plasma concentration of 25-hydroxyvitamin D [25(OH)D], whereas it does not correlate with the plasma concentration of 1,25$(OH)_2$D [1-3].

Based on this and other findings, it has therefore been hypothesised that vitamin D may exert several actions in the CNS and peripheral nervous system, which can be summarised in four main effects: neurotrophic support, neurotransmission, neuroprotection and neuroplasticity [1-3].

It is believed that Vitamin D exerts neurotrophic functions related to neuronal differentiation, maturation and growth, through for example stimulating the synthesis of neurotrophic factors such as nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF) or neurotrophin 3 (NT-3) [1-3]. Similar significance is thought to be attached to the effect on levels of *neurotrophin 4* (NT-4) (*downregulation*) and on the regulation of gene expression of the neurotrophic low-affinity NGF receptor

Correspondence
Andrea Giusti
andreagiusti6613@gmail.com

Conflict of interest
The authors state that there are no conflicts of interest.

How to cite this article: Giusti A, Botticella G, Camellino D, et al. Vitamina D e demenza. Vitamin D – Updates 2021;4(4):132-135. https://doi.org/10.30455/2611-2876-2021-7e

(p75NTR) [1-3]. Sustaining these hypotheses as well as the neurotrophic role of vitamin D, morphological studies in healthy elderly people or those suffering from various degrees of cognitive impairment have shown a correlation between vitamin D status (defined by plasma 25(OH)D concentration) and/or vitamin D deficiency, and the volume of grey matter and the hippocampus [4,5].

It also appears that Vitamin D and its metabolites mediate the synthesis of a variety of neurotransmitters, including acetylcholine, catecholamines, serotonin and dopamine [1]. This effect of vitamin D appears to be persistent over time and above all transgenerational. Indeed, early exposure to insufficient or deficient levels of vitamin D seems to induce epigenetic changes, which in turn are believed to influence gene expression and increase susceptibility to many neurodegenerative diseases over time (*metabolic imprinting*) [1,6-10].

Vitamin D's neuroprotective effect has been the subject of many experimental studies in animal models, where the administration of vitamin D or its metabolites has been shown to exert a protective effect on neurons by reducing cell damage and neurotoxicity mediated by certain substances known to be neurotoxic [1,11,12].

In one *in vitro* study, conducted on cortical neuronal cell cultures, Annweiler et al. showed that the combination of memantine (a drug used in the treatment of cognitive impairment) and vitamin D (but also vitamin D alone) was able to attenuate and prevent axonal degeneration produced by beta-amyloid and glutamate [11]. The mechanisms underlying vitamin D's neuroprotective effect have only been partially clarified and are still under discussion (e.g., regulation of calcium flow, anti-inflammatory effect and anti-oxidant effect) [11,12].

It seems that Vitamin D is able to influence neuroplasticity by regulating genes that have a significant impact on neuronal development and many neuronal functions (most likely already during pregnancy) [1,13]. For example, it appears that Vitamin D deficiency might alter the transcriptional profile of genes involved in cytoskeleton maintenance, mitochondrial function, neuronal plasticity, cell proliferation and growth [1]. Furthermore, as already detailed, during certain stages of pregnancy, vitamin D deficiency may lead to alterations in the regulation of neuronal function (on a molecular basis), which may influence susceptibility to certain degenerative diseases in adulthood [13].

IS THERE A RELATIONSHIP BETWEEN 25(OH)D CONCENTRATION AND THE RISK OF DEMENTIA?

Epidemiological data on the relationship between vitamin D status and neurodegenerative diseases, in particular dementia, seem to fully support the animal model findings described. A recent *overview* (Table I) analysed the results of the main review/meta-analysis studies on the relationship between vitamin D status and the risk of dementia and/or Alzheimer's disease (AD) [3]. Although the results of the different studies taken into consideration were not always easy to interpret, mainly due to the lack of standardisation of serological and clinical evaluations, overall, two important points emerged with significant uniformity and consistency [3,14-19]:

- there is an inverse relationship between the concentration of 25(OH)D and the risk of dementia or AD.
- It appears that this inverse relationship between 25(OH)D concentration and the risk of dementia or AD follows the "dose-response" principle.

For example, Chen et al. [14], undertook a meta-analysis of 10 cohort studies that included approximately 28,000 patients. The authors identified an inverse correlation between 25(OH)D concentration and the risk of dementia [relative risk 0.72 comparing the category with the highest 25(OH)D concentration with the category with the lowest 25(OH)D concentration] and AD [relative risk 0.78, comparing the category with the highest 25(OH)D concentration with the category with the lowest 25(OH)D concentration]. Furthermore, by analysing the dose effect [25(OH)D concentration] response, the authors also showed that the risk of dementia or AD decreased by 5 and 7% respectively for each 10 nmol/L increase in 25(OH)D concentration [14].

Consistent with the findings of Chen et al. and other similar studies (Table I) [14-19], a

TABLE I. Meta-analysis of cohort studies 14-19 that investigated the relationship between vitamin D status [defined by serum 25(OH)D concentration] and cognitive decline (from Maretzke et al., 2020, mod.) [3].

Reference	Studies included	No. of patients (age)	Cut-off 25(OH)D (nmol/L)	Outcome	Main results (95% CI)
Chen (2018) [14]	10 prospective	28,640 (56-85 y.o.)	High *vs* low concentration 25(OH)D	Dementia and AD	RR Dementia 0.72 (0.59-0.88) RR AD 0.78 (0.60-1.00)
Jayedi (2018) [15]	7 prospective + 1 retrospective	28,354 (≥ 18 y.o.)	Insufficiency: 25-50 Deficiency: < 25	Dementia and AD	HR Dementia due to deficiency 1.33 (1.08-1.58) HR AD due to deficiency 1.31 (0.98-1.65)
Goodwill (2017) [16]	14 prospective	30,000 (≥ 18 y.o.)	High *vs* low concentration 25(OH)D	Cognitive decline	OR cognitive decline 1.14 (1.06-1.23)
Cao (2016) [17]	3 prospective	12,702 (≥ 20 y.o.)	High *vs* low concentration 25(OH)D	Cognitive decline	RR cognitive decline 1.52 (1.17-1.98)
Shen (2015) [18]	2 prospective	8,086 (mean 74 y.o.)	Deficiency: < 50	Dementia and AD	OR Dementia 1.63 (1.09-2.16) or AD 1.21 (1.01-1.40)
Annweiler (2013) [19]	3 prospective	4095 (mean 75 y.o.)	High *vs* low concentration 25(OH)D	Executive functions	OR due to incident decline 1.25 (1.05-1.48)

RR: relative risk; 95% CI: 95% confidence interval; HR: hazard ratio; OR: odd ratio; 25(OH)D: Serum 25-hydroxyvitamin D; AD: Alzheimer's disease; y.o.: years old.

TABLE II. Incidence of dementia or Alzheimer's disease as a function of baseline 25(OH)D concentration (from Littlejohns et al., 2014, mod.) [20].

Dementia	No. Participants	No. cases	Serum 25(OH)D (nmol/L)			P
			≥ 50	≥ 25 - < 50 HR (95% CI)	< 25 HR (95% CI)	
Dementia (any type)						
Model A*	1658	171	1	1,51 (1,06-2,16)	2,22 (1,23-4,02)	,002
Model B**	1615	168	1	1,53 (1,06-2,21)	2,25 (1,23-4,13)	,002
Alzheimer's Disease						
Model A*	1589	102	1	1,67 (1,06-2,62)	2,27 (1,06-4,84)	,006
Model B**	1547	100	1	1,69 (1,06-2,69)	2,22 (1,02-4,83)	,008

25(OH)D: serum 25-hydroxyvitamin D; HR: hazard ratio; 95% CI: 95% confidence interval.
* Model A: correction (C*ox proportional hazards regression model*) by age and season in which 25(OH)D was dosed. ** Model B: correction (Cox proportional hazards regression model) by age and season in which 25(OH)D was dosed, schooling, gender, body mass index, smoking, alcohol consumption and depressive symptoms.

less recent longitudinal study (Table II) [20], which considered 1,658 elderly outpatients who did not have (at the time of enrolment) dementia, cardiovascular disease or cerebrovascular disease and who showed a higher incidence of dementia and/or AD (during a mean observation period of 5.6 years, range 0.1-8.4 years) in subjects with deficient (< 50 nmol/L) or severely deficient (< 25 nmol/L) vitamin D status at the time of enrolment, compared to subjects deemed to have 25(OH)D concentration in the sufficiency range [20]. Other studies have confirmed these findings, showing consistent results especially for 25(OH)D values < 25 nmol/L (severe vitamin D deficiency) [3]. For levels above this cut-off (e.g. between 25 nmol/L and 50 nmol/L) the results in favour of 25(OH)D seem to be less uniform and consistent.

CHOLECALCIFEROL SUPPLEMENTATION

In light of the experimental data (animal models) and data from epidemiological studies, the role, obviously not primary, of cholecalciferol supplementation in the prevention of neurodegenerative diseases especially dementia [3]. Neither did the randomised controlled trials, pre-post observational studies nor their meta-analyses demonstrate that cholecalciferol supplementation significantly affected the main cognitive parameters examined. Nevertheless, these studies presented significant and determining limitations in the interpretation of the results [3]. Both the randomised controlled trials and the pre-post observational studies were extremely heterogeneous in terms of experimental design and the treatment regimen used: the cholecalciferol dosages used varied from 400 IU per day (a dosage that is probably too low) to 5,000 IU per day, even with boluses of 600,000 IU (inappropriate). Most of these studies had rather short supplementation durations and follow-up periods. They were not at all sufficient in view of the complexity of the physiopathology of dementia/AD and therefore inappropriate for testing the potential protective effect of cholecalciferol on the risk of dementia/AD.

Lastly, in some trials the small number of patients was inadequate to test the hypothesis under study.

In view of the foregoing limitations, there is currently no solid evidence to support a preventive effect, or in any event the beneficial effect of cholecalciferol supplementation in dementia/AD. This potential benefit should not be completely ruled out. *Ad hoc* designed randomised controlled trials will be needed in future to clarify the potential of cholecalciferol supplementation in neurodegenerative diseases and especially in dementia.

In conclusion, one last consideration deserves to be emphasised: elderly patients are at the highest risk of cognitive impairment/dementia and are also the population with the highest prevalence of hypovitaminosis D. Therefore, this category of frail patients are always worth treating with cholecalciferol in view of its low cost, total safety and tolerability, and of its great efficacy in preventing falls and fractures, besides its potential, but likely, extra-skeletal benefits. A daily maintenance dose of 1,000 IU or 2,000 IU of cholecalciferol preceded, where indicated, by a loading dose, would appear to be the most natural strategy for optimising the skeletal and extra-skeletal effects of cholecalciferol [21].

Bibliography

1. DeLuca GC, Kimball SM, Kolasinski J, et al. Review: the role of vitamin D in nervous system health and disease. Neuropathol Appl Neurobiol 2013;39:458-484. https://doi.org/10.1111/nan.12020
2. Bivona G, Agnello L, Bellia C, et al. Non-skeletal activities of vitamin d: from physiology to brain pathology. Medicina (Kaunas) 2019;55:341. https://doi.org/10.3390/medicina55070341
3. Maretzke F, Bechthold A, Egert S, et al. Role of vitamin D in preventing and treating selected extraskeletal diseases-an umbrella review. Nutrients 2020;12:969. https://doi.org/10.3390/nu12040969
4. Ali P, Labriffe M, Navasiolava N, et al. Vitamin D concentration and focal brain atrophy in older adults: a voxel-based morphometric study. Ann Clin Transl Neurol 2020;7:554-558. https://doi.org/10.1002/acn3.50997
5. Al-Amin M, Bradford D, Sullivan RKP, et al. Vitamin D deficiency is associated with reduced hippocampal volume and disrupted structural connectivity in patients with mild cognitive impairment. Hum Brain Mapp 2019;40:394-406. https://doi.org/10.1002/hbm.24380
6. Wjst M, Heimbeck I, Kutschke D, et al. Epigenetic regulation of vitamin D con-

verting enzymes. J Steroid Biochem Mol Biol 2010;121:80-83. https://doi.org/10.1016/j.jsbmb.2010.03.056

7 Barker DJ. The fetal origins of diseases of old age. Eur J Clin Nutr 1992;46(Suppl 3):S3-S9.

8 Waterland RA, Garza C. Potential mechanisms of metabolic imprinting that lead to chronic disease. Am J Clin Nutr 1999;69:179-197. https://doi.org/10.1093/ajcn/69.2.179

9 Tekes K, Gyenge M, Folyovich A, et al. Influence of neonatal vitamin A or vitamin D treatment on the concentration of biogenic amines and their metabolites in the adult rat brain. Horm Metab Res 2009;41:277-280. https://doi.org/10.1055/s-0028-1103287

10 Tekes K, Gyenge M, Hantos M, et al. Transgenerational hormonal imprinting caused by vitamin A and vitamin D treatment of newborn rats. Alterations in the biogenic amine contents of the adult brain. Brain Dev 2009;31:666-670. https://doi.org/10.1016/j.braindev.2008.10.007

11 Annweiler C, Brugg B, Peyrin JM, et al. Combination of memantine and vitamin D prevents axon degeneration induced by amyloid-beta and glutamate. Neurobiol Aging 2014;35:331-335. https://doi.org/10.1016/j.neurobiolaging.2013.07.029

12 Annweiler C, Dursun E, Féron F, et al. 'Vitamin D and cognition in older adults': updated international recommendations. J Intern Med 2015;277:45-57. https://doi.org/10.1111/joim.12279

13 Levenson CW, Figueirôa SM. Gestational vitamin D deficiency: long-term effects on the brain. Nutr Rev 2008;66:726-729. https://doi.org/10.1111/j.1753-4887.2008.00122.x

14 Chen H, Xue W, Li J, et al. 25-Hydroxyvitamin D Levels and the risk of dementia and Alzheimer's disease: a dose-response meta-analysis. Front Aging Neurosci 2018;10:368. https://doi.org/10.3389/fnagi.2018.00368

15 Jayedi A, Rashidy-Pour A, Shab-Bidar S. Vitamin D status and risk of dementia and Alzheimer's disease: a meta-analysis of dose-response. Nutr Neurosci 2019;22:750-759. https://doi.org/10.1080/1028415X.2018.1436639

16 Goodwill AM, Szoeke C. A systematic review and meta-analysis of the effect of low vitamin D on cognition. J Am Geriatr Soc 2017;65:2161-2168. https://doi.org/10.1111/jgs.15012

17 Cao L, Tan L, Wang HF, et al. Dietary patterns and risk of dementia: a systematic review and meta-analysis of cohort studies. Mol Neurobiol 2016;53:6144-154. 10.1007/s12035-015-9516-4

18 Shen L, Ji HF. Vitamin D deficiency is associated with increased risk of Alzheimer's disease and dementia: evidence from meta-analysis. Nutr J 2015;14:76. https://doi.org/10.1186/s12937-015-0063-7

19 Annweiler C, Montero-Odasso M, Llewellyn DJ, et al. Meta-analysis of memory and executive dysfunctions in relation to vitamin D. J Alzheimers Dis 2013;37:147-171. https://doi.org/10.3233/JAD-130452

20 Littlejohns TJ, Henley WE, Lang IA, et al. Vitamin D and the risk of dementia and Alzheimer disease. Neurology 2014;83:920-928. https://doi.org/10.1212/WNL.0000000000000755

21 Rossini M, Adami S, Bertoldo F, et al. Guidelines for the diagnosis, prevention and management of osteoporosis. Reumatismo 2016;68:1-39. https://doi.org/10.4081/reumatismo.2016.870