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Neuroprotective and immune effects of active forms of vitamin D_3 and docosahexaenoic acid in Alzheimer disease patients

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ABSTRACT:

Neurodegenerative diseases, in particular Alzheimer disease (AD), afflict an increasing proportion of the older population with aging. Decreased exposure to sunlight and decreased consumption of fish, fruits, and vegetables, are two epidemiological factors that appear to be related to the pandemic of AD. In addition to replacing simple with complex carbohydrates and avoiding saturated fat, two nutritional components, vitamin D (acting through the endogenous hormonal form 1α,25 dihydroxyvitamin D, 1,25D) and docosahexaenoic acid (DHA) (acting through the docosanoid lipidic modulators resolvins and neuroprotectins) have high potential for prevention of Alzheimer disease. 1,25D is a neuroprotective, it acts both directly and indirectly in neurons by improving the clearance of amyloid-beta by macrophages/microglia. Resolvins and neuroprotectins inhibit amyloidogenic processing of amyloid-precursor protein, inflammatory cytokines, and apoptosis. It is likely that the increased consumption of vitamin D and fish oil could prevent neurodegeneration in some subjects by maintaining adequate endocrine, paracrine, and/or autocrine production of 1,25D and the DHA-derived lipidic modulators. Before firm recommendations of the dosage can be proposed, however, the in vivo effects of vitamin D_3 and DHA supplementation should be investigated by prospective studies.

Key words: Alzheimer disease, vitamin D3, DHA, fish oil

REVIEW:

Alzheimer disease (AD) is the leading cause of dementia worldwide. The major neuropathology of AD is related to amyloid-β 1-42 (Aβ), a peptide cleaved from the Amyloid precursor protein. The upstream causes of the most common sporadic form of AD are thought to include oxidative stress, dyslipidemia, insulin resistance, physical and psychological stress, and lack of physical

and mental exercise in subjects with the E4 allele of the lipid transport protein apolipoprotein E (ApoE) [1]. The downstream mechanisms of AD are considered to include (a) brain amyloidosis with both fibrillar and oligomeric Aβ with related synapse loss [2], as described by the amyloid hypothesis [3]; (b) hyperphosphorylation of tau leading to neurofibrillar tangles [4]; and (c) brain inflammation [5]. Although no disease-modifying therapy is available, preventive therapy could address the epidemiological factors associated with AD, i.e. decreased exposure to sunlight, and decreased consumption of fish, fruits, and vegetables.

As recommended for optimal health, nutritional prevention of AD should include a diet with a low amount of saturated fat, and high proportion of complex carbohydrates from cereals and vegetables, such as the Mediterranean diet, with the addition of phytochemicals and other functional food components. In fact, greater adherence to the Mediterranean diet and higher physical activity were independently associated with reduced risk of AD [6]. Anti-oxidants, such as vitamin C and vitamin E, should be included in the diet in physiological amounts [7]. A low cholesterol diet is important because the cholesterol oxidation products, i.e. oxysterols, have pro-inflammatory properties [8]. Patients with diabetes mellitus type II have an increased risk of AD, which could be related to a diet high in calories, or to the metabolic complications of diabetes [9].

In principle, phytochemicals could be protective against AD due to their antioxidant, anti-inflammatory and hypolipidemic properties, including inhibition of (a) protein kinases, such as Akt/protein kinase B (Akt/PKB), Janus kinase 1 (JAK1), glycogen synthase kinase 3 (GSK) [10] [11], (b) dysregulated insulin signaling [12], and (c) cytokines stimulating phosphoinositide 3 kinase (PI3K), GSK, and protein kinase C (PKC) [13].

Chronic diseases are complex and regulated by multiple genes mandating careful and multitargeted selection of phytochemicals. Although there was initial excitement about curcuminoids based on epidemiological data in India and Singapore [14], curcuminoids were not effective in a double-blind trial in AD patients at UCLA [15]. It has become clear that molecular and immunological effects of phytochemicals need to be understood before they can be used for therapy. For example, while curcuminoids have beneficial immune effects on Aβ phagocytosis at 0.1 μM, they cause apoptosis at 1 μM [16]. Furthermore, the heterogeneity of AD mandates that therapy should be personalized in patients with macrophages of different types (Type 0, I and II), as discussed below. Nonetheless, because immune cells migrate from the blood into the brain, improvement of immune cell function stands out as a therapeutic target.

Immunopathology and immunotherapy for Alzheimer disease: Brain amyloidosis is a neuropathological hallmark of AD, and clearance of brain amyloidosis has been the goal of therapies by Aβ vaccine and anti- Aβ antibodies [17]. The vaccine and antibodies are designed to stimulate the adaptive immune system for the enhancement of Aβ phagocytosis by microglia and macrophages. The immunopathology of AD patients also involves the innate immune system, which has not been the prime target of the vaccine. The macrophages of normal subjects are able to phagocytize and degrade Aβ, but the macrophages of AD patients are defective in phagocytosis and degradation, specifically of Aβ (not of bacteria) [18]. Although the Aβ vaccine effectively increased Aβ clearance in animal models, it failed in patients due to pathological

effects related to tau and amyloid angiopathy [19], lack of clinical efficacy, and encephalitis in 6% of patients [20]. Thus, improving the innate immune system of patients is a novel approach to AD.

We have observed that $1,25D_3$, DHA and DHA-derived lipid modulators are effective *in vitro* in recovering dysregulated phagocytosis of Aβ by AD macrophages. However, the benefits of supplementation with vitamin D_3 or DHA *in vivo* have not been uniformly positive in prospective studies, suggesting that the enzymes responsible for the anabolic production of $1,25D_3$ and resolvins by PBMCs/macrophages may be defective in the patients with neurodegenerative diseases. In this respect, we have observed a significant down-regulation of the enzyme 1□-OHase in PBMCs of a patient with amyotrophic lateral sclerosis (treated with SOD-1), when compared to controls treated in an identical manner. Therefore, nutritional therapy may need to be personalized.

Neuroprotective and immune effects of vitamin D and curcuminoids against dementia: Numerous studies have shown an association of vitamin D insufficiency with dementia and cognitive decline [21]. Causal relation to dementia was suggested in two prospective studies: the study of 858 older Italian adults indicated relative risk (RR) of cognitive decline (RR 1.6) in subjects with severe 25 (OH)vitamin D insufficiency (<25nM) [22]; the study of 1136 older US men found increased odds of cognitive decline (OR 1.41) in those with ≤ 49 nM 25 (OH)vitaminD [23].

1,25D has several intra-cranial mechanisms important for brain health. 1,25D modulates, through the nuclear vitamin D receptor (VDR), the transcription of as many as 500-1000 genes [24]. 1,25D3 protects against neurotoxicity of Aβ by downregulating in cortical neurons through VDR L-type voltage-sensitive calcium channels, LVSCC-A1C and LVSCC-A1D, and upregulating nerve growth factor (NGF) and VDR [25]. The role of VDR suppression in AD was highlighted by the demonstration that VDR suppression by siRNA results in an increase of LVSCC-A1C and a decrease of NGF production without a change in LVSCCA1D [26].

As mentioned, the extra-cranial mechanisms of $1,25D_3$ involve, in particular, the innate immune system cells, macrophages, and microglia. Macrophages are immune cells that locally produce 1,25D, given that they, like keratinocytes, contain all components of the vitamin D phytoendocrine system [27]. 1,25D regulates anti-microbial macrophage function through potentiation of interferon-gamma production by T cells [28]. $1,25D_3$ repairs the deficiency in phagocytosis of Aβ by AD macrophages through VDR genomic as well as nongenomic mechanisms [16]. *MGAT3 (GnT3)* is an essential gene for phagocytosis of Aβ by macrophages, as demonstrated using *MGAT3 (GnT3)* siRNA to block Aβ phagocytosis. We have found that the macrophages of AD patients could be distinguished according to *MGAT3 (GnT3)* transcriptional responses to Aβ into Type I, II and 0 as follows: Type I macrophages down regulate *MGAT3* and *TLR-3* but are stimulated by curcuminoids to up regulate these genes; Type II macrophages up regulate *MGAT3* and *TLR-3,* but these genes are down regulated by curcuminoids; Type 0 macrophages are transcriptionally –inhibited and do not respond to stimulation [29]. $1,25D_3$ increased phagocytosis of Aβ by macrophages of both Type I and Type II patients. Bisdemethoxycurcumin had small additive effect only in Type I cells [16].

The *in vitro* mechanisms of $1,25D_3$ involve potentiation of the currents of the chloride channel named ClC-3 in both Type I and II macrophages. Furthermore, $1,25D_3$ elicits a stronger up-regulation of ClC-3 and VDR mRNA's in Type II cells than Type I cells, and possibly has a stronger effect on Aβ phagocytosis (Mizwicki, Fiala et al, JAD in press). Although there is no firm data on the differences between patients with Type I and II macrophages *in vivo*, anecdotal observations suggest that patients differ in responses to vitamin D_3 supplementation [29].

Regarding the dosage and adverse effects of vitamin D, hypercalcemia has been of concern, however, this has not been documented with administration of vitamin D_3 < 10,000 IU/day (1 IU= 25 ng vitamin D_3) or whole body sunlight exposure (equivalent to 10,000 -20,000 IU vitamin D_3). The dose of vitamin D_3 recommended by the Institute of Medicine is 600 IU before the age 70 years and 800 IU after the age 70 years. To the subjects at risk of deficiency because of race, pregnancy, disease states, obesity, medications, or old age, a higher dose of vitamin D_3 should be administered [30]. In these subjects, at least 1,500 - 2000 IU per day are necessary to maintain vitamin D sufficiency (25-hydroxyvitamin D_3 serum level $\geq$ 30 ng/ml), but higher doses may be beneficial. In our experience, an AD patient with Type II macrophages has been relatively cognitively stable (Mini-Mental State Examination score (MMSE), 19-20) for 3 years on daily supplementation with 5,000 I.U. of vitamin D_3 and 1 gm DHA [29].

Neuroprotective mechanisms of docosahexaenoic acid, resolvin D1 andneuroprotectin D1: Docosahexaenoic acid (DHA; 4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*-docosa-4,7,10,13,16,19-hexaenoic acid) 22:6(n-3) is a major omega-3 fatty acid in neurons, which are essential for brain growth and development. In the brain, DHA has effects on membrane fluidity, synaptic function, and structural integrity and has anti-inflammatory activity [31] via inhibition of calcium channels excitotoxicity [32], and activation of selective gene transcription [33]. In an observational study, high intake of DHA increased gray matter in corticolimbic circuitry [34]. DHA is a precursor for the anti-inflammatory lipid mediators called resolvins, protectins, and neuroprotectins, which have recently been reviewed [35-37]. The E series resolvins, e.g resolvin E1 (RvE1; 5S,12R,18R-trihydroxy-6Z, 8E, 10E, 14Z, 16E eicosapentaenoic acid) are biosynthesized from the omega-3 fatty acid eicosapentaenoic acid (EPA) 20:5(n-3), and the D series resolvins, e.g. resolvin D1 (RvD1; 7S,8R,17S-trihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid) from DHA by transcellular synthesis facilitated by aspirin in vascular, leukocytic, and neural cells [38]. Neuroprotectin D1 (NpD1; 10R,17S-dihydroxy-docosa-4Z,7Z,11E,15E,19Z hexaenoic acid) is a potent lipidic mediator induced in the brain after injury, oxidative stress, or stimulation by neurotrophins, which release DHA through phospholipase A2 (PLA2) from neuronal membrane phospholipids. NPD1 is generated from DHA by 15-lipoxygenase-1, epoxidation and hydrolysis. NPD1 has multiple neuroprotective activities, such as down regulation of inflammatory genes, attenuation of leukocyte infiltration, inhibition of apoptosis, and neurotrophic effects through amyloid-β precursor protein (APP)-derived peptide called sAPPα via a non-amyloidogenic, α-secretase–mediated pathway [39] [40]. On the other hand, arachidonic acid (omega-6) in neuronal membranes generates through cyclooxygenase-2 (COX-2) the pro-inflammatory mediators prostaglandin E_2 (PGE_2), prostaglandin I_2 (PGI_2), and thromboxane A_2 [41]. The binding of PGE_2 to the E1 receptor is neurotoxic through disruption of

calcium homeostasis, whereas binding of PGE_2 to the EP2 receptor is neuroprotective [42]. Other mechanisms of DHA include reducing Aβ production by increasing transthyretin and suppression of phosphorylation of tau [43].

DHA may alter amyloidogenic processing by facilitating the interaction of α-secretase with APP and processing of APP through the nonamyloidogenic pathway [44]. DHA activates pro-survival signaling of Akt by membrane translocation [45]. DHA interacts with the nuclear receptors called retinoid X receptors (RXRs) and peroxisome proliferator-activated receptor-γ (PPAR-γ). RXR/PPAR-γ heterodimers inhibit multiple inflammatory mediators [46].

In some clinical studies, DHA has been shown to be neuroprotective,includingtraumatic brain injury [47], stroke [48], and cognitive decline in 14 of 17 observationalstudies [49]. Supplementation with omega-3 fatty acids for 6 months reduced release of IL-1β and IL-6 from PBMC's of AD patients [50], but this was refuted in a subsequent study [51]. In randomized, double blind clinical trials the overall results of DHA supplementation vs. placebo have been negative, but suggestive of efficacy in early cases and especially in Apoε4 non-carriers. However, in a recent 18-month prospective study algal DHA supplementation, however without attention to n-6/n-3 ratio, did not slow the rate of cognitive and functional decline in patients with mild to moderate AD (MMSE scores, 14-26), although restricted effect on the ADAS-cog and MMSE was observed in Apoε4 non-carriers [52]. Thus, the confounding factors in the studies of omega-3 fatty acids are believed to be related to: (a) the degree of neurodegeneration , (b) high dietary n-6 intake, (c) Apo E4 status, (d) oxidation status of the omega-3 fatty acids [49]. The source and stability of the omega 3 fatty acids may be of importance. The company Smartfish (Oslo, Norway) have tested their drink composion which contains omega 3 from fresh locally harvested fish, and found no oxidation products for as long as 1 year after expiration.

Nutritional supplementation with DHA has had greatest impact on cardiovascular prevention, especially prevention of arrhytmias, when the n-6/n-3 ratio was lowered to 1 [41]. The dietary recommendations for lowering the ratio include eliminating N-6 (linoleic acid)-rich foods (e.g. corn, peanut, soybean, sunflower and safflower oils, margarine, and meats), and increasing N-3 (alpha-linolenic)-rich foods (canola oil, linseed oil) and especially N-3 and EPA+DHA-rich foods, (herring, salmon, and tuna with low mercury content). There have been caveats of high serum DHA level association with increased risk of high-grade prostate cancer [53] and with dementia [54]. However, DHA serum levels do not determine the health consequences, because the derivation of pro- and anti-inflammatory mediators from DHA depends on local enzymes in tissues. Nevertheless, administration of polyunsaturated fatty acids, in particular omega-6 but also omega-3, is not without problems: non-enzymatic oxidation of EPA and DHA leads to the formation of isoprostanes and further chain cleavage yields aldehydes, such as malondialdehyde (MDA), acrolein, and hydroxyalkenals, such as 4-hydroxynonenal, which can impair the function of nervous cells [8].

Clinical use of vitamin D_3 and DHA: Although the effects in animal models provide perspective on biochemical mechanisms, such mechanisms have to be shown to be relevant to human patients. As mentioned, AD patients have defects in the innate immune system for Aβ phagocytosis, which have not been reproduced in animal models. In addition a mouse VDR

responds differently to VDR transcriptional modulators than does the human VDR [55]. For example the MK analogue that blocks $1,25D_3$ transactivation in a number of different cell types and 1,25D3-induced phagocytosis of Aβ by AD macrophages, does not block $1,25D_3$-VDR transactivation in rodent cells [56]. Furthermore, it has been demonstrated that regulation of the cathelicidin antimicrobial peptide (CAMP) gene by VDR and its ligand $1,25D_3$ is not evolutionarily conserved in mice, rats, or dogs, because the promoters of their CAMP genes lack a VDR response element (VDRE) [57]. Therefore, it is quite clear that the results in mouse model cannot be applied to AD patients and must be determined in prospective studies of persons at risk.

CONCLUSIONS:

The combined use of vitamin D_3 and DHA is an emerging novel strategy to enhance direct and immune protection of neurons against brain amyloidosis and other brain insults. These two compounds will likely have preventive effects in the early stage of neurodegeneration, rather than therapeutic effects.

Competing interests:

Milan Fiala, M.D: Meeting support by Smartfish, Inc.

Authors' contributions:

Both authors contributed equally to this work

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