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Vitamin D and Neurocognitive Dysfunction: Preventing "D"ecline?

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Abstract

A preponderance of evidence supports a role for vitamin D beyond the classical function in mineral homeostasis. Epidemiologic investigations have revealed a beneficial role of vitamin D in muscle function, cardiovascular health, diabetes, and cancer prevention. More recently, studies have suggested a potential beneficial role of vitamin D in cognitive function.

Vitamin D exhibits functional attributes that may prove neuroprotective through antioxidative mechanisms, neuronal calcium regulation, immunomodulation, enhanced nerve conduction and detoxification mechanisms. Compelling evidence supports a beneficial role for the active form of vitamin D in the developing brain as well as in adult brain function. The vitamin D receptor and biosynthetic and degradative pathways for the hydroxylation of vitamin D have been found the rodent brain; more recently these findings have been confirmed in humans. The vitamin D receptor and catalytic enzymes are colocalized in the areas of the brain involved in complex planning, processing, and the formation of new memories. These findings potentially implicate vitamin D in neurocognitive function.

Introduction

Nutritional factors play an important role in promoting health and a preponderance of evidence has linked nutritional deficiencies to exacerbating cognitive deterioration. Elderly individuals with inadequate dietary intake of certain nutrients score lower than average on tests of cognitive function (Riggs, Spiro et al.; Masaki, Losonczy et al. 2000; Cherubini, Martin et al. 2005; Tucker, Qiao et al. 2005). Historically, antioxidative nutrients and B vitamins have been evaluated for neuroprotective effects. Recently other nutrients, such as vitamin D have come under investigation for a role in cognitive preservation.

Vitamin D is a steroid hormone that has long been known for its important role in regulating body levels of calcium, phosphorus, and bone mineralization. Vitamin D can be obtained from the diet or synthesized in the skin from 7-dehydrocholesterol during sunlight exposure. Upon intake, the hormone is biologically inert and requires activation through a two-step enzymatic pathway involving 25-hydroxylase (25OHase) and 1α-hydroxylase (1,α-OHase) for the

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conversion to the active form of vitamin D ($1,25(OH)_2D_3$). Once activated, vitamin D influences a wide range of metabolic systems through both genomic and nongenomic pathways. In addition to regulating intestinal calcium absorption and mineral homeostasis, $1,25(OH)_2D_3$ binds to the vitamin D receptor (VDR) which interacts with the nuclear receptor retinoic acid X receptor (RXR). In the presence of $1,25(OH)_2D_3$ the VDR/RXR complex binds small sequences of DNA known as vitamin D response elements (VDREs) and initiates a cascade of molecular interactions that modulate the transcription of a myriad of genes in tissues throughout the body.

While a role for vitamin D in tissue growth and bone metabolism is well established, the presence of the vitamin D receptor and enzymes involved in the hydroxylation of vitamin D (25OHase and 1,α-OHase) in the brain implicates a role for this hormone in cognitive function and dementia (Garcion, Wion-Barbot et al. 2002; Guyton, TW et al. 2003; DeLuca 2004).

Dementia is the progressive decline in cognitive function due to the presence of disease or damage in the brain. The pathology of dementia is complex and may involve a number of mechanisms including oxidation, inflammation, disease induced neurotoxicity, and genetic vulnerability. Alzheimer's type dementia (AD) is the most common form of age-associated dementia (NIA 2006) affecting approximately half of adults aged over 85 years (NCCDP 1999). Vascular dementia (VaD) is the second most common form of age-associated dementia and comprises over 20% of dementia cases in the United States (Geldmacher and Whitehouse 1996;Roman 2003;Vermeer, Prins et al. 2003).

Alzheimer's disease and vascular dementia, though etiologically distinct frequently coexist. The presence of dementia with concomitant Alzheimer's and vascular features is termed "mixed dementia" and may encompass over 45% of the cases of dementia (Langa, Foster et al. 2004). Other forms of dementia, such as, Lewy body dementia, frontotemporal dementia, and Parkinson's disease, are less common and share unique etiologic and pathologic features.

Vitamin D may help to protect against cognitive deterioration and dementia, specifically, vascular dementia and Alzheimer's disease, through vasculoprotection (Lind, Wengle et al. 1987; Burgess, Hawkins et al. 1990; O'Connell, Berry et al. 1997; Pfeifer, Begerow et al. 2001; Wang, Wu et al. 2001; Zittermann, Schleithoff et al. 2003; Wang, Pencina et al. 2008), preservation of neurons (Sutherland, Somerville et al. 1992; Landfield and Cadwallader-Neal 1998; Brewer, Thibault et al. 2001), and protection against risk factors for cognitive dysfunction (Lind, Wengle et al. 1987; Burgess, Hawkins et al. 1990; Hypponen, Laara et al. 2001; Pfeifer, Begerow et al. 2001; Li, Kong et al. 2002; Zittermann, Schleithoff et al. 2003; Bischoff-Ferrari, Dietrich et al. 2004; Li, Qiao et al. 2004; Wang, Pencina et al. 2008).

In this review, we will discuss the current evidence for the presence of metabolic pathways for vitamin D in the brain, review the biological plausibility of a role of vitamin D in neuronal health, and discuss new evidence of a link between vitamin D, cognitive function, Alzheimer's disease, and vascular dementia in elders.

Alzheimer's Disease and Vascular Dementia

Neurodegenerative diseases involve the loss of neurons involved in cognitive, emotional, motor and sensory functions. Dementia of the Alzheimer's type is characterized by progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perceptions (agnosia) (McKhann, Drachman et al. 1984; American Psychiatric Association 1994). The diagnosis is supported by impaired activities of daily living, altered behavioral patterns, memory loss, and evidence of cerebral atrophy on radiographic or magnetic imaging scans (Geldmacher and Whitehouse 1997; NIA 2006). Histopathologically, AD brains show

synaptic loss and neuronal loss concentrated in the cerebral cortex, hippocampus, and amygdala as well as hallmark amyloid B plaques and neurofibrillary tangles(NIA 2006).

Vascular dementia, conversely, is characterized by cognitive dysfunction secondary to ischemic or hemorrhagic brain lesions due to cerebrovascular disease or cardiovascular disease. The blood vessels may become compromised secondary to concomitant illnesses such as hypertension or diabetes, or injury from a blood clot. Ischemic brain injury is the third leading cause of death in the United States; over 50% of survivors have resultant neurologic disorders and require chronic care (Roman 2003). In addition to this, cerebrovascular disease may lead to cognitive dysfunction even in the absence of stroke (Geldmacher and Whitehouse 1997; Skoog 2000; Kuller, Lopez et al. 2003; Zittermann, Schleithoff et al. 2005).

Cognitive dysfunction in vascular dementia differs from Alzheimer's Disease in that executive dysfunction is impaired and memory impairment is less profound (Roman, Tatemichi et al. 1993). Executive functions are those involved in complex cognitive tasks, such as planning, problem solving or sequencing. Patients with Alzheimer's disease and those with subcortical ischemic vascular disease show selective deficits in these areas (Roman, Tatemichi et al. 1993).

Relevant Risk factors for neurodegeneration

Aging is the most common risk factor for the development of neurodegenerative disease. Age-associated neuropathological changes include reductions in total brain volume and atrophy. Microscopically, age associated neurodegeneration leads to deleterious changes in essential central nervous system structures. These changes include loss of density in nerve synapses, reduction in number and length of dendrites, neuronal atrophy, loss of cortical and hippocampal neurons, and loss of cerebellar perkinje cells and cells within the substantia nigra (Zehnder, Bland et al. 2001).

Oxidative stress may also contribute to the pathophysiology of neurodegenerative disorders (Markesbery 1997). Increases in reactive oxygen species results in cellular damage through the generation of free radicals (hydroxyl radical, superoxide, nitrogen oxide, etc.). These stressors may also impair innate antioxidative mechanisms (Halliwell 1992; Coyle and Puttfarcken 1993). Consistent with these degenerative changes reside behavioral changes and impairments in cognitive function.

Vitamin D and the Brain: Mechanisms of Action

Interest in the relationship between vitamin D and central nervous system function was inspired by the evaluation of the neuroactivity of central nervous system steroids rather than the presence of clinical deficiency syndromes (Luine, Sonnenberg et al. 1987). Evidence for a role of vitamin D in brain function began to accumulate over two decades ago with autoradiographic findings of vitamin D receptors in the brains of experimental animals (Stumpf, Sar et al. 1982) and the demonstration that $1,25(OH)_2D_3$ was present in cerebrospinal fluid (Balabanova, Richter et al. 1984). Animal studies revealed the presence of VDR in the neuroepithelium during early neurogenesis, and in later stages, in an area involved in the maintenance of neural stem cells, the subventricular zone (Veenstra 1998). More recent animal data confirm the expression of VDR in specific brain regions, including but not limited to, the temporal lobe, cingulate cortices, thalamus, cerebellum, amygdala and hippocampal regions (Clemens, Garrett et al. 1988; Stumpf, Clark et al. 1988; Prufer, Veenstra et al. 1999; Langub, Herman et al. 2001; Garcion, Wion-Barbot et al. 2002; Eyles, Brown et al. 2003; McGrath, Feron et al. 2004).

Co-localization of VDR and 1, 25$(OH)_2D_3$ in the brain

While in vitro and animal data confirm the presence of vitamin D in the brain, until recently, little evidence existed to support a ligand mediated VDR pathway in the human brain. An early study of patients with Alzheimer's disease revealed the presence of VDR mRNA in humans (Sutherland, Somerville et al. 1992), yet the presence and accessibility of 1, 25$(OH)_2D_3$, necessary for activation of the nuclear pathway, remained unclear. Previously, brain concentrations of 1, 25$(OH)_2D_3$ were thought to be dependent on plasma concentrations (Taylor 1977; Gascon-Barre and Huet 1983), until biosynthetic and degradative pathways for the hormone were found in neuronal and glial cells (Clemens, Garrett et al.; Neveu, Naveilhan et al.; Neveu, Naveilhan et al.), cerebral perkinje cells, and cells in the cerebral cortex (Zehnder, Bland et al. 2001). These areas are particularly vulnerable to age and disease related degeneration.

It is of particular importance that a novel study in human brains confirmed the presence of the vitamin D receptor as well as genes encoding catalytic enzymes in 1,25$(OH)_2D_3$ metabolism in both neuronal and glial cells within brain structures critical for cognition (Zehnder, Bland et al. 2001; Burne, JJ et al.; Eyles, Smith et al. 2005). Furthermore, the VDR and catalytic enzymes were colocalized in the brain; these findings support a functional role for vitamin D in the human brain.

1, 25$(OH)_2D_3$ and Neuronal protection

The physical and mechanistic evidence of vitamin D in the brain underscored the potential for biologic function. Studies have shown that vitamin D may protect the structure and integrity of neurons through detoxification pathways and neurotrophin synthesis (Neveu, Naveilhan et al. 1994; Kang and Schuman 1995; Kang and Schuman 2000). Similar to the benefits of traditional antioxidant nutrients, 1, 25$(OH)_2D_3$ inhibits inducible nitric oxide synthase (iNOS) (Garcion, Nataf et al. 1997), an enzyme that is upregulated during ischemic events, and in patients with Alzheimer's and Parkinson's disease. 1, 25$(OH)_2D_3$ also enhances innate antioxidant pathways. The hormone upregulates gamma glutamyl transpeptidase (Baas, Prufer et al. 2000) and subsequently increases glutathione. Glutathione is an innate antioxidant which protects oligodendrocytes and the integrity of the nerve conduction pathway critical to mental processing.

Neurotrophins are proteins necessary for neuronal survival in aging and neuropathological conditions (Siegel and Chauhan 2000). When neurotrophin synthesis is decreased, spatial navigation is compromised (Siegel and Chauhan 2000). The hippocampus is involved in spatial navigation, processing, and learning, and is especially sensitive to age or pathology related degeneration. 1, 25$(OH)_2D_3$ upregulates neurotrophin factors, such as neurotrophin-3 (NT-3) and glial cell line derived neurotrophic factor (GDNF) (Neveu, Naveilhan et al. 1994).

NT-3, a protein found in the hippocampus and neocortex, protects nerve transmission and synapticity (Kang and Schuman 1995; Kang and Schuman 2000; Siegel and Chauhan 2000). The protein also increases signal transmission in hippocampal cells which are known to have high levels of VDR mRNA (Kang and Schuman 1995; Eyles, Smith et al. 2005). Another protective neurotrophin, GDNF, affects the survival and differentiation of dopaminergic cells. In animal models, treatment with 1, 25$(OH)_2D_3$ increased GDNF concentrations and reduced oxidative stress in Parkinson's disease (Wang, Wu et al. 2001). In support of these findings, vitamin D depletion in utero resulted in reduced levels of NGF and GDNF in addition to morphological brain changes in newborn rodents (Becker, Eyles et al. 2005). These deleterious characteristics remained through adulthood (Becker, Eyles et al. 2005).

Vitamin D and Neuronal Calcium Regulation

Age related changes and, to a greater extent, in neurodegenerative diseases, hippocampal cell loss and neuronal aging have been attributed to elevated L-type voltage calcium channel density and glucocorticoid (GC) neurotoxicity (Kimura, Sawada et al.). Vitamin D is a major calcium regulatory steroid hormone in peripheral tissues and modulates L-type sensitive calcium channels in the periphery. Studies have shown that vitamin D confers regulatory benefits in neuronal calcium homeostasis and protects neurons from excess calcium entry in the brain (Brewer, Thibault et al. 2001). These beneficial changes protect brain neurons during ischemic events or excitotoxic insults.

While excessive calcium levels are deleterious for memory formation and cognitive function (Sattler 2000; Thibault 2001; Veng 2003), Kuningas et al showed that certain variations in VDR polymorphisms contribute to differences in cognitive function that were postulated to be independent of calcium levels (Kuningas, Mooijaart et al.). *BsmI* and *TaqI* carriers experienced impairments in memory and attention--domains most vulnerable to age related deterioration. Interestingly, the haplotype associated with better cognitive performance, *ApaI* in haplotype 1 (baT), is the same haplotype associated with increased risk of fractures (Uitterlinden, Pols et al. 1996; Turner, Chen et al. 2004; Uitterlinden, Fang et al. 2004; Becker, Eyles et al. 2005). Calcium concentrations did not vary across the phenotypes and suggest that vitamin D may be neuroprotective beyond its role in calcium regulation.

Vitamin D, Cerebrovascular Disease, and Vascular Dementia

Vascular related brain damage may result from an influx of excitatory amino acids, inflammatory responses, and changes in cellular polarity which result in excessive calcium entry. In concert with these changes is an increase in intracellular nitric oxide production and increased oxidative stress.

Vitamin D may help ameliorate vascular related brain disease by mediating deleterious effects of inflammation, calcium dysregulation, and increased oxidative stress. During transient ischemic events, transforming growth factor and GDNF are upregulated in hippocampal cells to promote survival (Garcion, Sindji et al. 1999). As discussed earlier, vitamin D augments innate antioxidative defenses by increasing glutathione and GDNF concentrations (Wion, MacGrogan et al. 1991; Naveilhan, Neveu et al. 1996). These particular changes were shown to attenuate ischemic brain disease in rodents (Wang, Wu et al. 2001). In in vitro and animal models of cerebral ischemia, vitamin D inhibits antigen presenting cell maturation (Carthy, Yamashita et al. 1989), down regulates NF-κB activity (Kong, Zhu et al. 1999), and stimulates anti-inflammatory cytokine production (Timms, Mannan et al. 2002). Epidemiological studies show an inverse association between vitamin D and C-reactive protein levels, a marker of inflammation (Timms, Mannan et al. 2002).

In addition to these vasculoprotective benefits, vitamin D may play a role in protection against cardiovascular and cerebrovascular disease secondary to benefits that extend beyond those mentioned above (Zittermann, Schleithoff et al. 2005; Zittermann 2006; Wang, Pencina et al. 2008). Therapeutic intervention with vitamin D regulates blood pressure (Lind, Wengle et al. 1989; Pfeifer, Begerow et al. 2001), cardiac hypertrophy (O'Connell, Berry et al. 1997), and plasma rennin activity (Burgess, Hawkins et al. 1990; Li, Kong et al. 2002). There is an inverse relationship between vitamin D levels and congestive heart failure (CHF) (Zittermann, Schleithoff et al. 2003) and C-reactive protein levels (CRP). A recent study from the Framingham Heart Study revealed that vitamin D insufficiency is associated with incident cardiovascular disease (Wang, Pencina et al. 2008). It is plausible that vitamin D may influence vascular-related dementia via these indirect mechanisms.

Vitamin D and Alzheimer's Disease

Hippocampal neuronal loss is a characteristic finding in Alzheimer 's disease. Information flow through the hippocampus originates in the dentate gyrus to common amuns 3 (CA3) to CA1 to the subiculum. Treatment with 1, $25(OH)_2D_3$ attenuated hippocampal atrophy and protected neuron density (a marker for neuronal health) in aging rats (Landfield and Cadwallader-Neal 1998). Data in human subjects with Alzheimer's disease revealed a reduction in VDR mRNA in specific regions of the hippocampus (CA1 and CA2) compared to controls (Sutherland, Somerville et al. 1992) and a higher frequency of VDR polymorphisms were found in Alzheimer's brains than in age-matched controls (Gezen-Ak, Dursun et al. 2007).

There is a higher prevalence of falls and fractures in patients with Alzheimer's Disease (Buchner and Larson 1987) and community studies have shown that residents with Alzheimer's Disease and dementia had lower serum concentrations of 25(OH)D (Kipen, Helme et al. 1995; Sato, Asoh et al. 1998). While the temporal association of these findings remains unclear, in a study in patients with Alzheimer 's disease, 25(OH)D concentrations were significantly elevated after year-round sun exposure. Additionally, the sun-exposed cohort had a reduced risk of falls and fractures compared to the unexposed (Sato, J et al. 2005).

Data from the Nutrition and Memory in Elderly study (NAME) (Scott, Tucker et al. 2004) supported these findings. In subjects who completed a full neurological and psychiatric examination, in addition to magnetic resonance imaging (n=275), we observed that vitamin D concentrations were lower in patients with dementia than those without (19.5 vs. 16.5; P=0.03). In addition vitamin D concentrations <50nmol/L were associated with a higher prevalence of a diagnosis of possible or probable Alzheimer's Disease (17.1% vs 6.9%;$p<0.01$).

Vitamin D and Neurocognitive function: Deciphering the evidence

Deficiency studies in animal models and epidemiologic investigations have supported a role of vitamin D in neuropsychiatric and neurodegenerative disorders. The behavioral characterization of the VDR knock-out (VDR-KO) mouse revealed changes consistent with diminished musculoskeletal development and motor impairment (reduced stride length, hyperlocomotion, and reduced habituation in the open field test) (Burne, JJ et al. 2005). While some studies reported no observed impairments in working memory or anxiety in the VDR-KO model (Burne, JJ et al. 2005), others showed anxiety-like behavior and behavioral impairment (Kalueff, Lou et al. 2004; Kalueff, Keisala et al. 2006). In embryonic animal models, vitamin D deficiency during fetal development resulted in morphological brain changes (Eyles, Brown et al. 2003), motor impairments (Burne, Becker et al. 2004) and memory and learning impairments (McGrath, Eyles et al. 2003; Becker, Eyles et al. 2005).

While in vitro and animal models suggest neuroprotective benefits from vitamin D upon exposure, there are inconsistencies in the clinical literature related to vitamin D and cognitive function in the elderly. In a small case control study (n=84) in subjects in the Tromso study, subjects with secondary hyperparathyroidism (SHPT) (n=21) performed worse on cognitive tests associated with working memory (digit span)(Wechsler 1987), processing speed (Stroop test)(Golden 1978), language (controlled oral word association) (Spreen and Strauss 1998) and mood (Becks Depression Inventory) compared to subjects without SHPT (n=63). While the authors also revealed that low serum 25(OH)D concentrations were significantly associated with mood, they were unable to detect an association with 25(OH)D and cognitive function; this may in large part be due to the limited cognitive battery implemented as well as the small sample size under study.

In a much larger cross-sectional investigation of NHANES III data, McGrath et al. found no association between 25(OH)D and cognitive function in adolescence (16–19y) and adults (20–

59y), but revealed an inverse association between 25(OH)D and a test of learning and memory in older adults (60–90y) (McGrath, Scragg et al. 2007). This finding was somewhat surprising, but should be carefully evaluated in the context of the detected difference. Subjects in the highest quintile of vitamin D had the lowest score on this test (6.5 (0.1), compared to scores in the highest quintile (6.4 (0.1) (n=4809). This detected difference is very small and the clinical relevance is questionable. Additionally, the evaluation of an association between 25(OH)D and one test of cognition is not representative of cognitive function.

More recent positive associations between vitamin D and cognitive function in older adults have been revealed. In a cross-sectional study of eighty ambulatory elders (40 with mild dementia and 40 non-demented elders >60yrs), Wilkins et al. reported that vitamin D deficiency (<50nmol/l) was associated with poorer performance on global tests of cognitive function such as the Short Blessed Test (Katzman, Brown et al. 1983) and a higher score (indicative of poorer cognition) on the Clinical Dementia Rating Sum of Box Scores (CDR)(Morris 1993) (Wilkins, Sheline et al. 2006). The authors were not able to detect an association with vitamin D and the cognitive factor score, which is likely due to the small sample size under study (Wilkins, Sheline et al. 2006). Another positive association between vitamin D and a measure of global cognition was reported by Pryzbesky et al. In a retrospective chart review of thirty-two subjects over 60 years of age that were being evaluated in a memory clinic, the authors reported positive correlations between 25(OH)D concentrations and performance on the Mini-Mental State Examination (MMSE) (r=0.23;P=0.01) (Przybelski and Binkley 2007).

In the cases above, the studies were limited in the sample size as well as the outcome evaluation tools used to explore 25(OH)D and cognitive function in older adults. For example, McGrath et al. evaluated cognition in the elderly group using only one cognitive tool, a learning and memory tool. Given the preponderance of evidence of vitamin D in hippocampal health, a more sophisticated cognitive evaluation battery designed to evaluate multiple facets of cognitive performance is necessary. While thestudy by Jorde et al. had a more detailed cognitive battery, the study was limited by its size (n=84). Additionally, the authors did not adjust for multiple testing in their analyses and are thereby limited in the interpretation of their findings.

Contrary to the findings in the NHANES III and Tromso study, and consistent with the findings from Wilkins et al. and Przybelski et al., we recently reported findings of a positive association between 25(OH)D and cognitive function. Using data from the NAME study, (Scott, Peter et al. 2006), a large cross-sectional study (n=1200) with a comprehensive neuropsychological battery, 25(OH)D was associated with both global and specific aspects of cognitive function (Buell JS et al, manuscript in review). These associations were not consistent across all cognitive domains. Our results showed positive associations between 25(OH)D and primarily measures of executive functioning. These findings suggest that 25(OH)D may play a role in subcortical health and are consistent with vasculoprotective mechanisms of vitamin D. Further, these results may help to explain the null association with 25(OH)D and cognition in the earlier studies (Jorde, Waterloo et al. 2006; McGrath, Scragg et al. 2007) and help elucidate a potential mechanism through with vitamin D may exert neuroprotective effects.

Vitamin D and Brain Morphology

To date, we are not aware of any published findings of 25(OH)D and morphological measures in humans without schizophrenia. In our analyses of the NAME study, after adjusting for intracranial volume, there were no observed associations between vitamin D concentrations and hippocampal or amygdala volume (Buell JS et al. Manuscript in preparation). However, we did observe an inverse association between 25(OH) D concentration and presence of white matter hyperintensities and large vessel infarcts; indicators of cerebrovascular disease (Buell JS et al, Manuscript in preparation). Consistent with this finding, we observed a positive

association between vitamin D concentrations and the integrity and structural arrangement of white matter fibers using diffuser tensor imaging. Further studies designed to provide information on the temporal relationship of 25(OH)D and brain morphology are warranted.

Conclusions

While the extent to which vitamin D deficiency and cognitive function are related remains unclear, the biological plausibility of this relationship is well supported. The quality of life of aging individuals depends profoundly on functional capacity and dementia is one of the most common causes of institutionalization, morbidity, and mortality among the elderly.

The benefits of vitamin D on physical function in elders are well established. Vitamin D enhances skeletal integrity, muscle strength, as is associated with a reduction in falls and fractures. In addition to the physical benefits; the neurocognitive benefits of vitamin D are becoming clearer. The presence of VDR protein and catabolic enzymes in the parts of the brain most vulnerable to aging is compelling. The growing evidence of clinical associations between vitamin D status and both global and specific areas of cognitive function is of great importance. The potential modulation of risk factors and pathologic processes in vascular dementia and Alzheimer's disease underscore the importance of vitamin D status in the elderly.

Nutritional deficiencies in the elderly are common. Despite fortification, nutritional inadequacies in elders continue to be a problem (Posner, Smigelski et al. 1987; Buell, Arsenault et al. 2007). The elderly population is particularly at risk for vitamin D insufficiency because of sunlight deprivation, in addition to other age-associated risk factors for vitamin D insufficiency, such as, inadequate nutriture, age-related dermatological changes, and impairments in renal function.

Worldwide studies of vitamin D status in healthy community dwellers have shown that 40–100% of elders have vitamin D inadequacy (Chapuy, Preziosi et al. 1997; Holick 2006) and these elders usually have year-round insufficient concentrations (Bhattoa, Bettembuk et al. 2004).

While there are currently no standards for optimal vitamin D concentrations, concentrations ≥ 75nmol/L are recommended to optimize skeletal health. Without adequate sun exposure, dietary intakes of at least 800–1000 IU are necessary to achieve this concentration (Dawson-Hughes, Heaney et al. 2005; Bischoff-Ferrari, Giovannucci et al. 2006), and intakes this high are rarely seen in elders. In a cross-sectional investigation of over 1000 community dwelling elders in Boston, MA, fewer than 10% of non-supplement users, had vitamin D intakes greater than 400 IU and fewer than 5% had intakes over 600 IU/d (Buell et al. manuscript in review).

The health care costs and public health burden of institutionalization of the elderly are significant. Current estimates are that those ≥85 years have the highest risk for dementia and represent the fastest growing segment of the population. U.S. Census Bureau estimates that nearly 19 million Americans will be age 85 by 2050 and over half of those will have some form of dementia (Evans 1990). The prevalence of Alzheimer's disease is even higher in offspring of parents with the disease. A recent report in Archives of Neurology revealed a prevalence of AD in children when both parents have had AD of 31% in those over 60 and 42% in those over 70 years (Jayadev, Steinbart et al. 2008). The costs associated with care of dementia are staggering with annual national direct and indirect costs estimated to be as high as $100 billion (Ernst and Hay 1997).

The need for well designed longitudinal investigations of vitamin D and cognitive function are critical. The aging global population and escalating healthcare costs impose a sense of urgency for cost-effective interventions. If these current positive associations are validated, vitamin D

intervention would prove a cost effective means to mediate cognitive dysfunction and delay institutionalization; significantly off-setting healthcare costs.

References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV). Washington D.C.: American Psychiatric Association; 1994.

Baas D, Prufer K, et al. Rat oligodendrocytes express the vitamin D(3) receptor and respond to 1,25-dihydroxyvitamin D(3). Glia 2000;31(1):59–68. [PubMed: 10816607]

Balabanova S, Richter HP, et al. 25-Hydroxyvitamin D, 24, 25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D in human cerebrospinal fluid. Klin Wochenschr 1984;62(22):1086–1090. [PubMed: 6334780]

Becker A, Eyles DW, et al. Transient prenatal vitamin D deficiency is associated with subtle alterations in learning and memory functions in adult rats. Behav Brain Res 2005;161(2):306–312. [PubMed: 15922058]

Bhattoa HP, Bettembuk P, et al. Prevalence and seasonal variation of hypovitaminosis D and its relationship to bone metabolism in community dwelling postmenopausal Hungarian women. Osteoporos Int 2004;15(6):447–451. [PubMed: 15205715]

Bischoff-Ferrari HA, Dietrich T, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. Am J Clin Nutr 2004;80(3):752–758. [PubMed: 15321818]

Bischoff-Ferrari HA, Giovannucci E, et al. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006;84(1):18–28. [PubMed: 16825677]

Brewer LD, Thibault V, et al. 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. [PubMed: 11150325]

Buchner DM, Larson EB. Falls and fractures in patients with Alzheimer-type dementia. Jama 1987;257 (11):1492–1495. [PubMed: 3820464]

Buell JS, Arsenault LN, et al. Multivitamin use and B vitamin status in a homebound elderly population. J Nutr Health Aging 2007;11(4):299–303. [PubMed: 17653485]

Burgess ED, Hawkins RG, et al. Interaction of 1,25-dihydroxyvitamin D and plasma renin activity in high renin essential hypertension. Am J Hypertens 1990;3(12):903–905. [PubMed: 2081010]

Burne T, JJ M, et al. Behavioural characterization of vitamin D receptor knockout mice. [Journal Article] Behavioural Brain Research 2005;157(2):299–308. [PubMed: 15639181]

Burne TH, Becker A, et al. Transient prenatal Vitamin D deficiency is associated with hyperlocomotion in adult rats. Behav Brain Res 2004;154(2):549–555. [PubMed: 15313044]

Carthy EP, Yamashita W, et al. 1,25-Dihydroxyvitamin D3 and rat vascular smooth muscle cell growth. Hypertension 1989;13(6 Pt 2):954–959. [PubMed: 2786849]

Chapuy MC, Preziosi P, et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 1997;7(5):439–443. [PubMed: 9425501]

Cherubini A, Martin A, et al. Vitamin E levels, cognitive impairment and dementia in older persons: the InCHIANTI study. Neurobiol Aging 2005;26(7):987–994. [PubMed: 15748776]

Clemens TL, Garrett KP, et al. Immunocytochemical localization of the 1,25-dihydroxyvitamin D3 receptor in target cells. Endocrinology 1988;122(4):1224–1230. [PubMed: 2831024]

Coyle JT, Puttfarcken P. Oxidative stress, glutamate, and neurodegenerative disorders. Science 1993;262 (5134):689–695. [PubMed: 7901908]

Dawson-Hughes B, Heaney RP, et al. Estimates of optimal vitamin D status. Osteoporos Int 2005;16(7): 713–716. [PubMed: 15776217]

DeLuca HF. Vitamin D and Health in the 21st Century: Bone and Beyond. Am J Clin Nutr 2004;80(6): 1689S–1696S. [PubMed: 15585789]

Ernst RL, Hay JW. Economic research on Alzheimer disease: a review of the literature. Alzheimer Dis Assoc Disord 1997;(11 Suppl 6):135–145. [PubMed: 9437458]

Evans DA. Estimated prevalence of Alzheimer's disease in the United States. Milbank Q 1990;68(2): 267–289. [PubMed: 2233632]

Eyles D, Brown J, et al. Vitamin D3 and brain development. Neuroscience 2003;118(3):641–653. [PubMed: 12710973]

Eyles DW, Smith S, et al. Distribution of the Vitamin D receptor and 1[alpha]-hydroxylase in human brain. Journal of Chemical Neuroanatomy 2005;29(1):21–30. [PubMed: 15589699]

Garcion E, Nataf S, et al. 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. [PubMed: 9149100]

Garcion E, Sindji L, et al. 1,25-dihydroxyvitamin D3 regulates the synthesis of gamma-glutamyl transpeptidase and glutathione levels in rat primary astrocytes. J Neurochem 1999;73(2):859–866. [PubMed: 10428085]

Garcion E, Wion-Barbot N, et al. New clues about vitamin D functions in the nervous system. Trends in Endocrinology and Metabolism 2002;13(3):100–105. [PubMed: 11893522]

Gascon-Barre M, Huet PM. Apparent [3H]1,25-dihydroxyvitamin D3 uptake by canine and rodent brain. Am J Physiol 1983;244(3):E266–E271. [PubMed: 6687510]

Geldmacher DS, Whitehouse PJ. Evaluation of dementia. N Engl J Med 1996;335(5):330–336. [PubMed: 8663868]

Geldmacher DS, Whitehouse PJ Jr. Differential diagnosis of Alzheimer's disease. Neurology 1997;48(5 Suppl 6):S2–S9. [PubMed: 9153154]

Gezen-Ak D, Dursun E, et al. Association between vitamin D receptor gene polymorphism and Alzheimer's disease. Tohoku J Exp Med 2007;212(3):275–282. [PubMed: 17592215]

Golden, C. Stroop Color and word test. Chicago: Stoelting; 1978.

Guyton K, TW K, et al. Vitamin D and vitamin D analogs as cancer chemopreventive agents. Nutr Rev 2003;61(7):227–238. [PubMed: 12918875]

Halliwell B. Reactive oxygen species and the central nervous system. J Neurochem 1992;59(5):1609–1623. [PubMed: 1402908]

Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006;81(3):353–373. [PubMed: 16529140]

Hypponen E, Laara E, et al. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001;358(9292):1500–1503. [PubMed: 11705562]

Jayadev S, Steinbart EJ, et al. Conjugal Alzheimer Disease: Risk in Children When Both Parents Have Alzheimer Disease. Arch Neurol 2008;65(3):373–378. 10.1001/archneurol.2007.61. [PubMed: 18332250]

Jorde R, Waterloo K, et al. Neuropsychological function in relation to serum parathyroid hormone and serum 25-hydroxyvitamin D levels. The Tromso study. J Neurol 2006;253(4):464–470. [PubMed: 16283099]

Kalueff AV, Keisala T, et al. Behavioural anomalies in mice evoked by "Tokyo" disruption of the Vitamin D receptor gene. Neurosci Res 2006;54(4):254–260. [PubMed: 16427152]

Kalueff AV, Lou YR, et al. Increased anxiety in mice lacking vitamin D receptor gene. Neuroreport 2004;15(8):1271–1274. [PubMed: 15167547]

Kang H, Schuman EM. Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. Science 1995;267(5204):1658–1662. [PubMed: 7886457]

Kang H, Schuman EM. Intracellular Ca(2+) signaling is required for neurotrophin-induced potentiation in the adult rat hippocampus. Neurosci Lett 2000;282(3):141–144. [PubMed: 10717411]

Kang HJ, Schuman EM. Neurotrophin-induced modulation of synaptic transmission in the adult hippocampus. J Physiol Paris 1995;89(1):11–22. [PubMed: 7581294]

Katzman R, Brown T, et al. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. Am J Psychiatry 1983;140(6):734–739. [PubMed: 6846631]

Kimura M, Sawada K, et al. Role of Glutamate Receptors and Voltage-Dependent Calcium and Sodium Channels in the Extracellular Glutamate/Aspartate Accumulation and Subsequent Neuronal Injury Induced by Oxygen/Glucose Deprivation in Cultured Hippocampal Neurons. J Pharmacol Exp Ther 1998;285(1):178–185. [PubMed: 9536008]

Kipen E, Helme RD, et al. Bone density, vitamin D nutrition, and parathyroid hormone levels in women with dementia. J Am Geriatr Soc 1995;43(10):1088–1091. [PubMed: 7560696]

Kong XF, Zhu XH, et al. Molecular cloning, characterization, and promoter analysis of the human 25-hydroxyvitamin D3-1alpha-hydroxylase gene. Proc Natl Acad Sci U S A 1999;96(12):6988–6993. [PubMed: 10359826]

Kuller LH, Lopez OL, et al. Risk factors for dementia in the cardiovascular health cognition study. Neuroepidemiology 2003;22(1):13–22. [PubMed: 12566949]

Kuningas M, Mooijaart SP, et al. VDR gene variants associate with cognitive function and depressive symptoms in old age. Neurobiol Aging. 2007

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. [PubMed: 9880049]

Langa K, Foster N, et al. Mixed Dementia: Emerging Concepts, Therapeutic Implications. JAMA 2004:2901–2908. [PubMed: 15598922]

Langub MC, Herman JP, et al. Evidence of functional vitamin D receptors in rat hippocampus. Neuroscience 2001;104(1):49–56. [PubMed: 11311530]

Li YC, Kong J, et al. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002;110(2):229–238. [PubMed: 12122115]

Li YC, Qiao G, et al. Vitamin D: a negative endocrine regulator of the rennin-angiotensin system and blood pressure. J Steroid Biochem Mol Biol 2004;89–90(1–5):387–392.

Lind L, Wengle B, et al. Blood pressure is lowered by vitamin D (alphacalcidol) during long-term treatment of patients with intermittent hypercalcaemia. A double-blind, placebo-controlled study. Acta Med Scand 1987;222(5):423–427. [PubMed: 3321926]

Lind L, Wengle B, et al. Reduction of blood pressure during long-term treatment with active vitamin D (alphacalcidol) is dependent on plasma renin activity and calcium status. A double-blind, placebo-controlled study. Am J Hypertens 1989;2(1):20–25. [PubMed: 2643969]

Luine VN, Sonnenberg J, et al. Vitamin D: is the brain a target? Steroids 1987;49(1–3):133–153. [PubMed: 3331845]

Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. Free Rad Biol Med 1997;23:134–147. [PubMed: 9165306]

Masaki KH, Losonczy KG, et al. Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. Neurology 2000;54(6):1265–1272. [PubMed: 10746596]

McGrath J, Eyles D, et al. Low maternal vitamin D as a risk factor for schizophrenia: a pilot study using banked sera. Schizophr Res 2003;63(1–2):73–78. [PubMed: 12892860]

McGrath J, Scragg R, et al. No association between serum 25-hydroxyvitamin D3 level and performance on psychometric tests in NHANES III. Neuroepidemiology 2007;29(1–2):49–54. [PubMed: 17898524]

McGrath JJ, Feron FP, et al. Vitamin D3-implications for brain development. J Steroid Biochem Mol Biol 2004;89–90(1–5):557–560.

McKhann G, Drachman D, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34(7):939–944. [PubMed: 6610841]

Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43 (11):2412–2414. [PubMed: 8232972]

Naveilhan P, Neveu I, et al. 1,25-Dihydroxyvitamin D3, an inducer of glial cell line-derived neurotrophic factor. Neuroreport 1996;7(13):2171–2175. [PubMed: 8930983]

NCCDP, NCfCDPaHP. Chronic disease notes and reports: special focus. Healthy Aging 1999;12(3) CDC.

Neveu I, Naveilhan P, et al. 1,25-dihydroxyvitamin D3 regulates NT-3, NT-4 but not BDNF mRNA in astrocytes. Neuroreport 1994;6(1):124–126. [PubMed: 7703399]

Neveu I, Naveilhan P, et al. 1,25-dihydroxyvitamin D3 regulates the synthesis of nerve growth factor in primary cultures of glial cells. Brain Res Mol Brain Res 1994;24(1–4):70–76. [PubMed: 7968379]

NIA. Azlheimer's Disease Education and Referral Center. NIA; 2006.

O'Connell TD, Berry JE, et al. 1,25-Dihydroxyvitamin D3 regulation of cardiac myocyte proliferation and hypertrophy. Am J Physiol 1997;272(4 Pt 2):H1751–H1758. [PubMed: 9139959]

Pfeifer M, Begerow B, et al. Effects of a Short-Term Vitamin D3 and Calcium Supplementation on Blood Pressure and Parathyroid Hormone Levels in Elderly Women. J Clin Endocrinol Metab 2001;86(4): 1633–1637. [PubMed: 11297596]

Posner BE, Smigelski CG, et al. Dietary characteristics and nutrient intake in an urban homebound population. J Am Diet Assoc 1987;87(4):452–456. [PubMed: 3559003]

Prufer K, Veenstra TD, et al. Distribution of 1,25-dihydroxyvitamin D3 receptor immunoreactivity in the rat brain and spinal cord. J Chem Neuroanat 1999;16(2):135–145. [PubMed: 10223312]

Przybelski RJ, Binkley NC. Is vitamin D important for preserving cognition? A positive correlation of serum 25-hydroxyvitamin D concentration with cognitive function. Archives of Biochemistry and Biophysics Highlight Issue: Vitamin D 2007;460(2):202–205.

Riggs KM, Spiro A 3rd, et al. Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the Normative Aging Study. Am J Clin Nutr 1996;63(3):306–314. [PubMed: 8602585]

Roman GC. Stroke, cognitive decline and vascular dementia: the silent epidemic of the 21st century. Neuroepidemiology 2003;22(3):161–164. [PubMed: 12739527]

Roman GC, Tatemichi TK, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43(2):250–260. [PubMed: 8094895]

Sato Y, Asoh T, et al. High prevalence of vitamin D deficiency and reduced bone mass in elderly women with Alzheimer's disease. Bone 1998;23(6):555–557. [PubMed: 9855465]

Sato Y, J I, et al. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in hospitalized, elderly women with Alzheimer's disease: a randomized controlled trial. Journal of Bone & Mineral Research 2005;20(8):1327–1333. [PubMed: 16007329]

Scott TM, Peter I, et al. The Nutrition, Aging, and Memory in Elders (NAME) study: design and methods for a study of micronutrients and cognitive function in a homebound elderly population. Int J Geriatr Psychiatry 2006;21(6):519–528. [PubMed: 16645938]

Scott TM, Tucker KL, et al. Homocysteine and B vitamins relate to brain volume and white-matter changes in geriatric patients with psychiatric disorders. Am J Geriatr Psychiatry 2004;12(6):631–638. [PubMed: 15545331]

Siegel G, Chauhan N. Neurotrophic factors in Alzheimer’s and Parkinson’s disease brain. Brain Research Reviews 2000;33(2–3):199–227. [PubMed: 11011066]

Skoog I. Vascular aspects in Alzheimer's disease. J Neural Transm Suppl 2000;59:37–43. [PubMed: 10961416]

Spreen, O.; Strauss, E. A compendium of neuropsychological tests. new York: Oxford University Press; 1998.

Stumpf WE, Clark SA, et al. 1,25(OH)2 vitamin D3 sites of action in spinal cord and sensory ganglion. Anat Embryol (Berl) 1988;177(4):307–310. [PubMed: 2833133]

Stumpf WE, Sar M, et al. Brain target sites for 1,25-dihydroxyvitamin D3. Science 1982;215(4538): 1403–1405. [PubMed: 6977846]

Sutherland MK, Somerville MJ, et al. Reduction of vitamin D hormone receptor mRNA levels in Alzheimer as compared to Huntington hippocampus: correlation with calbindin-28k mRNA levels. Brain Res Mol Brain Res 1992;13(3):239–250. [PubMed: 1317496]

Taylor AN. Chick brain calcium binding protein: response to cholecalciferol and some developmental aspects. J Nutr 1977;107(3):480–486. [PubMed: 191581]

Timms PM, Mannan N, et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? Qjm 2002;95(12):787–796. [PubMed: 12454321]

Tucker KL, Qiao N, et al. High homocysteine and low B vitamins predict cognitive decline in aging men: the Veterans Affairs Normative Aging Study. Am J Clin Nutr 2005;82(3):627–635. [PubMed: 16155277]

Turner A, Chen TC, et al. Testosterone increases bone mineral density in female-to-male transsexuals: a case series of 15 subjects. Clin Endocrinol (Oxf) 2004;61(5):560–566. [PubMed: 15521957]

Uitterlinden AG, Fang Y, et al. Vitamin D receptor gene polymorphisms in relation to Vitamin D related disease states. J Steroid Biochem Mol Biol 2004;89–90(1–5):187–193.

Uitterlinden AG, Pols HA, et al. A large-scale population-based study of the association of vitamin D receptor gene polymorphisms with bone mineral density. J Bone Miner Res 1996;11(9):1241–1248. [PubMed: 8864898]

Veenstra T. 1,25-Dihydroxyvitamin Ds receptors in the CNS of the rat embryo. Brain Res 1998;804:193–205. [PubMed: 9757035]

Vermeer SE, Prins ND, et al. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348(13):1215–1222. [PubMed: 12660385]

Wang JY, Wu JN, et al. Vitamin D(3) attenuates 6-hydroxydopamine-induced neurotoxicity in rats. Brain Res 2001;904(1):67–75. [PubMed: 11516412]

Wang TJ, Pencina MJ, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117(4):503–511. [PubMed: 18180395]

Wang TJ, Pencina MJ, et al. Vitamin D Deficiency and Risk of Cardiovascular Disease. Circulation 2008;117(4):503–511. [PubMed: 18180395]

Wechsler, D. Wechsler memory Scale-Revised. New York: The Psychological Corporation; 1987.

Wilkins CH, Sheline YI, et al. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. Am J Geriatr Psychiatry 2006;14:1033–1040.

Wion D, MacGrogan D, et al. 1,25-Dihydroxyvitamin D3 is a potent inducer of nerve growth factor synthesis. J Neurosci Res 1991;28(1):110–114. [PubMed: 1904101]

Zehnder D, Bland R, et al. Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. J Clin Endocrinol Metab 2001;86(2):888–894. [PubMed: 11158062]

Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. Prog Biophys Mol Biol 2006;92(1):39–48. [PubMed: 16600341]

Zittermann A, Schleithoff SS, et al. Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr 2005;94(4):483–492. [PubMed: 16197570]

Zittermann A, Schleithoff SS, et al. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? J Am Coll Cardiol 2003;41(1):105–112. [PubMed: 12570952]