Beyond Vitamin Status

Is There a Role for Vitamin D in Parkinson Disease?

Two years ago, Newmark and Newmark[1] hypothesized that insufficient vitamin D could play a role in the pathogenesis of Parkinson disease (PD). The study by Knekt et al[2] in this issue of the *Archives* is the first longitudinal analysis of vitamin D status as a risk of incident PD and examines a cohort of more than 3000 participants from the Mini-Finland Health Survey. As an important logical progression from previous epidemiological and animal studies of vitamin D and PD, Knekt and colleagues' study begins to address some of the questions posed by Newmark and Newmark.[1] Furthermore, it provides preliminary data supporting future interventional studies of the role of vitamin D in the pathogenesis of PD.

VITAMIN D AND THE PHYSIOLOGY OF CHRONIC DISEASE

Vitamin D is no longer considered a vitamin, but rather a hormone that has autocrine and paracrine functions well beyond those of regulating calcium absorption and bone health. The association with and possible causal role of insufficient vitamin D in many chronic diseases is becoming more widely appreciated, yet what constitutes an

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optimal blood concentration of vitamin D for humans, and specifically for the human nervous system, remains unknown; UV-B radiation converts 7-dehydrocholesterol to provitamin D_3 in the skin, which is rapidly converted to vitamin D_3 then to 25-hydroxyvitamin D_3 (25[OH]D) in the liver. Because it has a relatively long half-life of 2 to 3 weeks, 25(OH)D is the best indicator of vitamin D status. Analogous to how glycosylated hemoglobin reflects glucose control, 25(OH)D plasma or serum concentration reflects an individual's vitamin D status during the previous 1 to 2 months. Major determinants of 25(OH)D concentration include latitude (or more specifically, UV-B radiation), season, age, skin tone, and body mass index, with dietary and multivitamin or calcium/vitamin D supplement intake providing a relatively small contribution to circulating levels. Older published studies typically use lower cutoffs for vitamin D deficiency (10-20 ng/mL [to convert to nanomoles per liter, multiply by 2.496]) that are based on concentrations needed to avoid rickets and osteopenia. However, the cutoffs for defining vitamin D sufficiency in more recently published literature are higher. Many vitamin D researchers suggest that 25(OH)D concentration should be above 30 to 40 ng/mL based on results of interventional trials for optimal skeletal health and falls prevention that demonstrate a positive benefit from giving either a high dose of vitamin D (>800 IU daily) or obtaining 25(OH)D concentrations above 30 to 40 ng/mL. Other investigators have suggested that optimal levels are even higher, but data supporting this are lacking. Because vitamin D regulates the gamut of physiological processes that go awry in disease states, including cell proliferation, differentiation, and survival, as well as resistance to oxidative stress, regulation of other hormones, and immune modulation, it is not surprising that insufficient or low vitamin D has been associated with increased risk of several cancers and chronic diseases.[3]

VITAMIN D AND NEUROBIOLOGY

Although Stumpf et al[4] reported the presence of vitamin D receptors in the rodent brain and cervical spine in the early 1980s, exploration of the role of vitamin D with respect to neurobiology in humans and the implications of vitamin D insufficiency in neurological disease has burgeoned in the last decade. Eyles et al[5] confirmed that vitamin D receptors and 1-α-hydroxylase (the activating enzyme for vitamin D) are widespread in the human brain and mimic the distribution in several other species. Both basic and clinical evidence suggests that gestational and neonatal vitamin D status affects neurodevelopment, including dopaminergic neuronal development,[6] with some dopaminergic effects of neonatal vitamin D supplementation in rodents persisting into the second-generation (F2) offspring.[7]

Gestational vitamin D deficiency has been hypothesized to be a factor in the genesis of such neurodevelopmental disorders as autism[8] and schizophrenia.[6] Epidemiological evidence in humans also supports the hypothesis that vitamin D deficiency during gestation or early childhood may affect the risk of schizophrenia. Furthermore, active vitamin D appears to have antiepileptic activity in vivo and in vitro.[9,10] However, the role of vitamin D in multiple sclerosis is perhaps the most thoroughly investigated of the neurological diseases. Vitamin D is known to prevent the experimental allergic encephalomyelitis animal model of multiple sclerosis and diminish disease severity once experimental allergic encephalomyelitis is established.[11] With substantial epide-

miological evidence suggesting vitamin D may play a protective role in the risk of multiple sclerosis[12] and open-label pilot trials suggesting benefits, double-blinded pilot safety and efficacy trials are under way to prepare for larger clinical trials to examine vitamin D as a potential disease-modifying treatment.

RELEVANCE OF VITAMIN D TO PD

Interestingly, basic and clinical research on vitamin D also nicely connects in the context of PD and lends biologic plausibility to the hypothesis that vitamin D may offer neuroprotective benefit for patients with PD or could improve clinical PD symptoms. Neurotoxin models of PD generally show evidence that vitamin D may offer neuroprotection for dopaminergic neurons. Pretreatment with active 1,25-dihydroxyvitamin D ameliorates toxin-induced dopaminergic cell death in both 6-hydroxydopamine dopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine models, with concomitant increases in glial cell line–derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF),[13] and glutathione (GSH) levels[14] and decreased levels of proinflammatory cytokines and microglial activation.[15] As with many pharmacologic phenomena, these neuroprotective effects exhibit a U-shaped curve, with loss of neuroprotection or even detriment at higher, presumably supraphysiological, doses. Furthermore, vitamin D may also be a necessary cofactor or augment the neuroprotective effects of other compounds such as progesterone.[16] However, while gestational vitamin D deficiency appears to have deleterious effects in newborn and adult rodents and supplemental vitamin D improves dopaminergic survival in rodents, it is not clear whether vitamin D deficiency in mature animals leads to increased susceptibility to neurodegenerative disease or whether supplemental vitamin D administered after a toxic insult (but before morphological or behavioral sequela become apparent) could offer neuroprotection.

Epidemiologic studies in the mid-1980s by Lux and Kurtzke[17] and Lanska[18] suggest a latitudinal north-south gradient for PD mortality, similar to that seen in multiple sclerosis. Other studies have not confirmed this gradient,[19] but variations in methodology make comparisons between studies difficult, and no studies have collected data in sufficient detail to take into account all factors that can affect vitamin D status (latitude/UV-B radiation, skin tone, cultural variations, body mass index, et cetera). To date, human studies of vitamin D status in patients with PD have consistently reported lower vitamin D levels in cases compared with matched control subjects.[20-22] One obvious explanation is that PD is a chronic disease, and as patients with PD become more severely affected, they have less UV-B exposure and are less likely to have adequate intake of vitamin D. Although Sato's[21] studies suggest that the prevalence of vitamin D insufficiency correlates with disease duration and severity, we could not confirm this,[20] and the Mini-Finland study[2] also calls this explanation into doubt with lower quartiles of 25(OH)D (measured decades before clinical diagnosis of PD) predicting increased risk of PD. Decreased vitamin D intake in PD cases might also explain the relatively high prevalence of insufficiency, yet vitamin D intake in cases and controls appears to be comparable.[21-23] Interestingly, as Knekt et al[2] point out, there appeared to be a correlation between 25(OH)D concentration and decreased risk of incident PD, but mean 25 (OH)D concentrations in the entire cohort (both cases and controls) reported in this issue were suboptimal. Thus, it remains unknown whether concentrations above 30 ng/mL would predict further PD risk reduction. Similar studies in populations with optimal vitamin D status would be informative.

A growing body of basic research lends plausibility to a role for adequate vitamin D status protecting against development of PD. Knekt and colleagues' study provides the first promising human data to suggest that inadequate vitamin D status is associated with the risk of developing PD, but further work is needed in both basic and clinical arenas to elucidate the exact role, mechanisms, and optimum concentration of vitamin D in PD. With the animal data showing a U-shaped curve for neuroprotective effects of vitamin D, it seems prudent to confirm the findings presented in this issue and investigate whether the apparent dose-response relationship observed in the current study maintains its slope, levels off, or becomes negative with higher 25(OH)D concentrations. In the interim, data from interventional studies of fractures and falls appear to justify optimizing vitamin D levels to greater than 30 to 40 ng/mL.

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REFERENCES

1. Newmark HL, Newmark J. Vitamin D and Parkinson's disease: a hypothesis. *Mov Disord*. 2007;22(4):461-468.
2. Knekt P, Kilkkinen A, Rissanen H, Marniemi J, Sääksjärvi K, Heliövaara M. Serum vitamin D and the risk of Parkinson disease. *Arch Neurol*. 2010;67(7):808-811.
3. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr*. 2008;87(4):1080S-1086S.
4. Stumpf WE, Sar M, Clark SA, DeLuca HF. Brain target sites for 1,25-dihydroxyvitamin D3. *Science*. 1982;215(4538):1403-1405.
5. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *J Chem Neuroanat*. 2005;29(1):21-30.
6. Eyles DW, Feron F, Cui X, et al. Developmental vitamin D deficiency causes abnormal brain development. *Psychoneuroendocrinology*. 2009;34(suppl 1):S247-S257.
7. Tekes K, Gyenge M, Hantos M, Csaba G. 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(9):666-670.
8. Cannell JJ. Autism and vitamin D. *Med Hypotheses*. 2008;70(4):750-759.
9. Siegel A, Malkowitz L, Moskovits MJ, Christakos S. Administration of 1,25-dihydroxyvitamin D3 results in the elevation of hippocampal seizure threshold levels in rats. *Brain Res*. 1984;298(1):125-129.

10. Kalueff AV, Minasyan A, Keisala T, Kuuslahti M, Miettinen S, Tuohimaa P. Increased severity of chemically induced seizures in mice with partially deleted Vitamin D receptor gene. *Neurosci Lett*. 2006;394(1):69-73.
11. Cantorna MT. Vitamin D and multiple sclerosis: an update. *Nutr Rev*. 2008;66(10) (suppl 2):S135-S138.
12. Ascherio A, Munger K. Epidemiology of multiple sclerosis: from risk factors to prevention. *Semin Neurol*. 2008;28(1):17-28.
13. Smith MP, Fletcher-Turner A, Yurek DM, Cass WA. Calcitriol protection against dopamine loss induced by intracerebroventricular administration of 6-hydroxydopamine. *Neurochem Res*. 2006;31(4):533-539.
14. Shinpo K, Kikuchi S, Sasaki H, Moriwaka F, Tashiro K. Effect of 1,25-dihydroxyvitamin D(3) on cultured mesencephalic dopaminergic neurons to the combined toxicity caused by L-buthionine sulfoximine and 1-methyl-4-phenylpyridine. *J Neurosci Res*. 2000;62(3):374-382.
15. Kim J-S, Ryu S-Y, Yun I, et al. 1α,25-Dihydroxyvitamin D3 protects dopaminergic neurons in rodent models of Parkinson's disease through inhibition of microglial activation. *J Clin Neurol*. 2006;2(4):252-257.
16. Cekic M, Sayeed I, Stein DG. Combination treatment with progesterone and vitamin D hormone may be more effective than monotherapy for nervous system injury and disease. *Front Neuroendocrinol*. 2009;30(2):158-172.
17. Lux WE, Kurtzke JF. Is Parkinson's disease acquired? Evidence from a geographic comparison with multiple sclerosis. *Neurology*. 1987;37(3):467-471.
18. Lanska DJ. The geographic distribution of Parkinson's disease mortality in the United States. *J Neurol Sci*. 1997;150(1):63-70.
19. de Rijk MC, Tzourio C, Breteler MM, et al. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1997;62(1):10-15.
20. Evatt ML, Delong MR, Khazai N, Rosen A, Triche S, Tangpricha V. Prevalence of vitamin D insufficiency in patients with Parkinson disease and Alzheimer disease. *Arch Neurol*. 2008;65(10):1348-1352.
21. Sato Y, Kikuyama M, Oizumi K. High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease. *Neurology*. 1997;49(5):1273-1278.
22. Lorefält B, Ganowiak W, Wissing U, Granerus AK, Unosson M. Food habits and intake of nutrients in elderly patients with Parkinson's disease. *Gerontology*. 2006; 52(3):160-168.
23. Evatt ML, Hebbar G, Quirk ME, Ziegler TR. Nutrient intake in Parkinson's disease compared to age-matched controls. Paper presented at: American Academy of Neurology Annual Meeting; April 30, 2009; Seattle, WA. Abstract A457.

Announcement

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