Review

A review of vitamin D and Parkinson's disease

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ABSTRACT

The role of vitamin D in bone health has been known for over a century. More recent research has suggested that vitamin D may play a role in the muscular, immune, endocrine, and central nervous systems. Animal research suggests that vitamin D may have some protective effects against toxic insults that are known to damage dopamine cells, the primary cells to degenerate in PD. Persons with PD tend to have lower vitamin D levels than persons of similar ages without PD. Vitamin D levels are generally associated with bone mineral density (BMD) in persons with PD, but simply giving vitamin D does not appear to improve BMD. Results of genetic studies examining polymorphism of the vitamin D receptor and PD risk, severity, or age at onset have shown variable results, with FokI CC seeming to possibly carry some increased risk of PD. Amount of sun exposure and vitamin D levels in earlier life may influence the risk of developing PD. Cross-sectional research suggests a relationship between vitamin D levels and severity of PD symptoms. A single intervention study did show some improvement in PD with vitamin D supplementation. Vitamin D may have effects on PD symptoms and perhaps even on the risk of disease development or disease progression. More well designed intervention studies are needed to confirm the effect of vitamin D on PD symptoms. Human neuroprotection studies are needed, but probably not feasible until better biomarkers are established.

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Contents

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1. Introduction

The importance of vitamin D in bone health was realized in the early 1900s [1]. More recent research suggests that vitamin D may have effects on the muscular, immune, endocrine, and central nervous systems [2]. The final enzyme to convert vitamin D to the active form and the vitamin D receptor are known to be present throughout the human brain [3].

Vitamin D comes from two main sources – diet and skin [4]. Human skin makes D3 from 7-dehydrocolesterol when exposed to UV-B rays from the sun [4]. For most persons this is the primary source of vitamin D. Vitamin D can also come in the form of D2 and D3 from food sources and supplements [4]. Thirty minutes of full body sun exposure equates to about 10,000 international units (IU's) of vitamin D [5]. The darkness of a person's skin effect how efficiently they make vitamin D with darker skinned persons making less vitamin D with equivalent sun exposure [5]. Common food sources of vitamin D include wild salmon, tuna, and milk with approximately 600–100 IU, 230 IU, and 100 IU respectively per serving [5]. There is some disagreement, but currently defined optimal levels of vitamin D are generally based on bone health, specifically parathyroid hormone levels (PTH). Vitamin D levels lower than 30–40 ng/ml are inversely associated with PTH levels. Vitamin D deficiency is commonly defined as <20 ng/ml, insufficiency as 20–30 ng/ml and, sufficiency as >30 ng/ml [5].

PD is a neurodegenerative disease with four cardinal features: resting tremor, rigidity (stiffness), bradykinesias (slowness), and postural instability. The motor symptoms are thought to largely be due to a loss of dopamine cells in the basal ganglia. A diagnosis of PD is made clinically and disease severity is judged by clinical ratings. There are two major clinical scales used: the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr Scale (H&Y) [6,7]. The motor section of the UPDRS is the most often used section with a maximum of 108 points; with a higher score indicating more severe disease. Each individual piece is scored on a four-point scale with points for the following: speech, facial expression, tremor at rest (face, limbs), action or postural tremor (arms), rigidity (neck, limbs), three types of rapid alternating movements (arms), leg agility, arising from a chair, posture, gait, postural stability, and overall slowness. The H&Y is a scale of 1–5. It is rated on if symptoms are unilateral – 1, bilateral – 2, or how balance/gait is affected. If postural reflexes are affected – 3, severe disability but able to walk or stand unassisted – 4, or confined to bed or wheelchair unless aided – 5.

2. Methods

A Medline search was done using the terms "Parkinson's disease" and "vitamin D." Abstracts for all articles in English were reviewed for relevance with appropriate articles included. All of these articles were read, including reviews. Any primary research from the review references were also included if relevant. Finally a Pubmed search was completed using the search terms "vitamin D" and "Parkinson's or parkinson" and any unique publications in English were included. Not all review articles are presented, but all primary data related to PD and vitamin D is included.

3. Results/discussion

3.1. Vitamin D appears neuroprotective in animal studies

There are a number of *in vitro* and *in vivo* animals studies in PD examing potential neuroprotective effects of vitamin D. Nissou found that the mRNA of 27 genes was increased by at least 1.9-fold when neuron-glial cell cultures were exposed to 1,25-dihydroxyvitamin D3 [8]. Seventeen of these genes were known to be related to neurodegeneration, psychiatric disease, or brain morphogenesis with three having specific relationships with PD: CBS – involved in hydrogen sulfide production, SLC1A1 – involved in glutathione synthesis, ITGA8 – required for hippocampal long term potentiation.

An *in vitro* study using rat mesencephalic neurons and l-buthionine sulfoximine (BCO) and 1-methyl-4-phenylpyridium ion (MPP+), which are known to cause particular damage to dopamine neurons, showed that pretreatment for 24 h with vitamin D was protective till it reached a toxic threshold at high concentrations [9]. There was also a dose response when looking at glutathione production and vitamin D exposure. A reduction in glutathione is seen in early PD and may be a primary event in the development of PD [10]. Both experiments showed benefit and harm at similar concentrations of vitamin D.

In vivo animal studies include one in rats where vitamin D was given intraventricularly seven days before then one day or up to four weeks after intraventricular injection of 6-hydroxydopamine (6-OHDA), a compound that induces symptoms similar to PD [11]. Benefits were only seen in the group of rats that received vitamin D before and for the longer duration (3.5–4 weeks) after the 6-OHDA. Specifically an increase in strial dopamine, potassium and amphetamine evoked over flow of dopamine, and dopamine metabolites. They also looked at levels of glial derived neurotrophic factor (GDNF) and brain derived neurotrophic factor (BDNF) in animals who received 8 days of vitmain D or saline, but did not undergo lesioning with 6-OHDA. There was an increase in GDNF in the substantia nigra, but not the striatum, in the rats receiving vitamin D. There were no significant difference in levels of BDNF.

Another study in rats gave vitamin D for eight days prior to 6-OHDA and found an increase in tyrosine hydroxylase (TH) labelled cells (presumably dopamine cells) in the rats that received vitamin D [12]. Two other studies, one in rats using 6-OHDA and one in mice using (1-methyl-4-phenyl-1,2,3,6-tetrahydro pyridine (MPTP – another means of inducing a PD model), gave vitamin D for seven days prior to the insult [13]. They looked at inflammation *via* microglial activation and found in both models vitamin D increased TH positive cells and reduced activated microglial cells.

A study using a genetic PD mouse model did find conflicting results. Specifically showing more TH positive cells in the substantia nigra pars compacta and ventral tegmental area, when the mice were vitamin D restricted [14]. Neuroprotection or disease modification is a somewhat controversial topic in PD, but is certainly the hope of any therapy. Animals studies often suggest therapies that offer protection, but when human studies are performed the results are often disappointing.

3.2. Vitamin D is often low in persons with PD

The prevalence of vitamin D deficiency appears to be higher in persons with PD than other populations. Evatt showed in a 2008 paper that 55% of persons with PD were insufficient compared to 41% of person with another neurodegenerative disorder, Alzheimer's disease, and compared to 36% in a control population that was age matched [15]. Numerous studies by Sato have shown insufficient and deficient vitamin D levels are common in PD [16–18]. In a population in the Pacific Northwest United States, we found 40% of persons with PD had insufficient vitamin D levels [19]. The one study that appears in disagreement with these data was done in an Iranian population and did not show significantly lower vitamin D in the PD population compared to controls, however there may have be some confounding issues related to gender [20].

3.3. Vitamin D is related to bone health in PD

There are a large number of studies related to PD and bone health and details on all studies will not be presented. The overarching theme is that vitamin D levels tend to be lower in persons with PD and that vitamin D and bone mineral density (BMD) generally correlate [16–18,21–29]. Sato's group in Kurume, Japan carried out the majority of these studies. There are numerous reasons why persons with PD would be at risk for low BMD. Levodopa may itself or through homocysteine result in reduced BMD [30]. PD for a variety of reasons may lead to poor nutrition, lower body weight, and decreased muscle strength. Decreased mobility from PD may lead to lower vitamin D and exacerbated related bone loss [30].

Highlighting some of the interesting findings, a paper by Abou-Raya found that at baseline persons with PD had less sun exposure, with 74% having less than 15 min a day compare to 19% in a control group [21]. The PD group took in less calcium and vitamin D with 59% taking in less than 200 IU a day, compared to 4% in the control group [21]. A study by Lorefalt found that lower BMD's were seen in persons with PD who were less active, had lower body weights, and surprisingly those with less rigidity [31].

Sato's group has done two intervention studies with bisphosphonates [16,26]. In these two studies the control groups received 1000 IU of vitamin D along with the placebo. In both studies the vitamin D levels rose considerably in the course of the 2 years, from 11.3 ng/ml to 35.1 ng/ml and from 12.5 ng/ml to 37.5 ng/ml. Somewhat surprisingly however, the BMD's decreased in both control (vitamin D) groups by about 3% over the two year period in spite of the elevation in vitamin D levels. Sato in a 1999 paper looking at an active vitamin D3 analogue, suggesting that there may be a defect in renal synthesis of the active form of vitamin D [32]. With supplementation with the active vitamin D, there was only a 1.2% decrease in BMD over 18 months.

Another means of increasing vitamin D is sunlight. In a 2011 study, again by Sato's group, they tested the effect of increased sun exposure [28]. Participants were followed for two years. Those in the intervention group were asked to spend 15 min outside on clear days. In the sunlight group vitamin D levels increased to 10.8–20.8 ng/ml and BMD increased by over 3%. The other studies with oral vitamin D had larger increases in vitamin D levels but, still had reduction in BMD. This suggests that there is something beyond vitamin D at play, perhaps increased physical activity. The sunlight group also had improved strength and lower risk of hip fracture (OR3.9 in no intervention vs. sunlight). The study design also did not have an active control arm so placebo effect cannot be ruled out.

Yet another study by Sato's group looked at stooped posture and vertebral fractures [25]. Over 120 women over age 50 with PD and without stooped posture at enrollment were followed yearly for five years to evaluate compression fractures. At the end of the study 34 had developed stooped posture. This group had lower vitamin D intake, lower BMD, and higher rates of vertebral fractures at the time of study enrollment. The BMD also decreased more quickly in the stooped posture group.

3.4. The relationship between the vitmain D receptor and PD risk is unclear

The VDR receptor is an intranuclear receptor. It is encoded by a large gene, over 100 kb, on chromosome 12q12-14 [33]. It is made up of two promoter regions, eight protein-coding exons, and six untranslated exons [33]. An animal study knocking out the VDR resulted in rats with muscular and motor impairments, alopecia, short stature, lower body weight, shorter gait, and impairments on rotarod testing (measures gait and balance) [34]. The mice did not appear to have cognitive impairments.

There are over 60 identified polymorphisms for VDR. Polymorphisms are mutations with an allele frequency of at least 1% in a given population. These subtle DNA sequence variation, which occur often in the population, can have a modest but real biological effect. Polymorphisms can effect enhanced/reduced transcription, altered posttranscriptional or posttranslational activity, or the tertiary structure of the gene product [33].

A number of studies have tried to examine if VDR phenotypes relate to PD, primarily looking at either risk of development or age of onset. A fairly large US study was done using two populations, first doing a discovery phase (770 Caucasian families with a history of PD) then a validation phase (267 cases, 267 controls) [35]. In the discovery phase one single nucleotide polymorphism (SNP) met threshold for overall risk, rs4334089. There were five other SNPs that met threshold for early onset risk. In the validation phase however there were no associations with any of these SNPs. There were three other SNPs that met threshold in the validation phase for early age on onset of PD, but none met threshold for PD risk.

The rs4334089 has also been studied in other populations. Lv examined this SNP along with rs731236 in a Chinese Han population (483 persons with PD, 498 controls) [36]. The Han population makes up 92% of the Chinese population and is considered the largest ethnic group in the world. Lv's study found no associations to PD risk or age of onset with either rs4334089 or rs721236 [36]. In a Taiwanese population no association was seen with rs 4334089 or five other SNPs examined [37]. Another study in a Han population examined FokI(rs10735810) and BsmI(rs1544410), polymorphisms that may be associated with risk of MS [38]. FokI involves the presence of a cytosine (C) or thymine (T) allele. Han found increased frequency of C allele in PD group and late-onset PD group when compared to controls. There were no relationships seen with the BsmI polymorphism. A Hungarian study also found an association between PD and the FokI C allele [39]. No associations were seen with BsmI, ApaI, or TaqI in the Hungarian population.

Kim examined polymorphisms in a Korean population (85 cases and 231 controls) [40]. Looking at BsmI, specifically the absense (B) or the presense (b) of a restriction site, there was an increased frequency of bb genotype in the PD group (84.7% vs. 72.7%; p = 0.043) and increased frequency of b allele (91.2% vs. 85.7%, p = 0.069). Also the bb genotype and b allele were more common in persons with postrual instability, gait deficits predominant PD (PIDG) vs. the tremor predominant form of PD.

In a Japanese population, Suzuki examined PD severity, vitamin D levels, five VDR polymorphisms, and two vitamin D binding protein (VDBP) polymorphism in 137 persons with PD [41]. There was an association between polymorphisms and vitamin D levels. Specifically the vitamin D bindging protein polymorphisms, TT genotype of GC1 and AA genotype of GC2, were associated with lower 25OHD levels. In regard to the polymorphisms and disease severity, the FokI CC genotype for VDR polymorphism was associated with a milder form of PD. In a Faroe Island populations no associtaions were seen with the polymorphisms assessed, ApaI, BsmI, and TaqI, but there was an association between vitamin D levels and Apal/AC genotype [42].

In regard to polymorphisms, the FokI CC genotype is associated with PD risk in multiple studies. VDR and VDBP themselves are potential biomarkers for PD. VDR expression in the blood may be increased in persons with PD [43]. VDBP protein in the CSF may help to predcit PD when used as part of a multianalyte profile [44,45].

3.5. Vitmain D exposure may predict the risk of developing PD

There have been a few studies looking at diet and PD risk with varying results. Some have shown an increase risk of PD in men who consumed more dairy [46–48]. One of these studies however, did not show any increase risk in PD when looking at overall vitamin D

intake [47]. A study by Anderson did find a relationship with vitamin D rich foods, but this relationship disappeared when correcting for animal fat intake [49]. A final study found no relationship of PD risk with diary, calcium, or vitamin D consumption [50]. Considering the variable results and the amount of vitamin D that is often obtained from non-food sources it is unclear how to interpret this data.

In regard to sun exposure and risk of PD, two using the same 1960s US data set, demonstrated a north-south gradient for PD mortality similar to those seen in multiple sclerosis [51,52]. A study using US data from 1981 found a west-east gradient [53]. A final study, using US data from 1988, showed a north-south gradient, but only in a white population [54]. A large Danish study (3819 men with PD and 19,282 controls) found decreased risk of PD in persons who had occupations associated with outdoor work [55]. The OR was 0.72 (95% CI 0.63–0.82) when comparing persons with maximal outdoor work to persons with exclusive indoor work. A US study with a much smaller sample (447 persons with PD and 578 controls) showed a trend towards decreased risk in persons who did only outdoor work compared to only indoor work with an OR of 0.74 (95% CI 0.44–1.25) [56].

A 2010 looked at vitamin D in 3173 people 29 years prior and compared the 50 people who developed PD. Those with PD had a borderline significance lower mean vitamin D level of 11.5(5.8) ng/mL vs. 13.1(6.1) ng/mL ($p = 0.05$) [57]. When breaking the PD group into quartiles there was a significant trend ($p = 0.006$) for higher relative risk of PD as vitamin D levels decreased.

3.6. Vitamin D appears to be related to the severity of PD symptoms

A number of studies have looked at the relationship between PD symptoms and vitamin D levels. In Sato's 2005 paper he showed a correlation between the mUPDRS score and 1,25-dihydroxy vitamin D levels [17]. In his 2007 paper which included a lot of advanced stage persons with PD, he found that the mean level of person with H&Y's 3–4 was 8.9 (3.2) compared to 21.7(8.5) in H&Y 1–2 and 21.6 (3.1) in person without PD [16]. Suzuki in another Japanese populations found significant relationships between 25-hydroxyvitamin D (No Reference Selected) and H&Y scores ($p = .002$) and 25-hydroxyvitamin D and UPDRS scores using linear regression ($p = 0.004$) [41]. We also found a relationship between UPDRSm and vitamin D in two of our studies, $r = -0.33$, $p = 0.04$ and $r = -0.242$, $p = 0.0025$ [19,58]. A 2011 paper, used data from DATATOP, examined vitamin D levels and disease progression [59]. No relationship was found between vitamin D concentrations and disease progression but the follow up time averaged only 18 months and patients had generally mild disease (mean H&Y 1.7 at start 2.1 at completions) [59]. A study with slightly more advanced patients did show a relationship between vitamin D level and UPDRS motor at baseline and with progression of symptoms in follow-up [60]. A case report in 1997, describes a person with PD for 10 years who developed hypophosphoremia, hypocalcium, and low vitamin D and with 4000 IU of D3 and 1000 mg of calcium had some improvement in his PD symptoms and was able to lower his levodopa dose to about half of his previous dose [61].

We have also looked at vitamin D concentrations and balance, cognition, and mood. One of our pilot studies showed a relationship with some measures of balance and vitamin D levels [19]. This was an exploratory study and data was not corrected for multiple comparisons. An Iranian study did not find a relationship between overall disease severity and vitamin D levels, but did find an association between lower vitamin D and more severe postural instability, freezing of gait, and abnormal postures [62]. In looking at neuropsychological function in a different PD population we found an association between vitamin D levels and verbal fluency, verbal memory, and depression in persons without dementia [58].

There is one published vitamin D intervention study. It was conducted in Tokyo and enrolled 114 persons aged 45–85 with a diagnosis of PD [63]. It was a double-blinded, randomized, placebo controlled study compairing 1200 IU vitamin D3 daily for three months. Measures included disease severity, quality or life, cognition (MMSE), laboratory testing (calcium, parahyroid hormone, BUN, creatinine, and 25-OHD), and genotyping (VDR and vitamin D binding protein). H&Y stage increased significantly in the control vs. vitamin D group – 0.33 vs. 0.02 ($p = 0.005$) and the number needed to treat was calculated as six. They also examined vitamin D polymorphisms and found that FokI TT geneotype were the most improved by vitamin D, CT intermediately so, and CC not at all.

4. Conclusion

The data that seems most consistent is the relationship between vitamin D levels and symptom severity. Most of this research however is cross-sectional and causation cannot be infered. The one intervention study looking at PD symptoms did show improvement in PD symptoms. These data are certainly hopeful that vitamin D therapy may be benefiial. More well randomized, placebo-controlled intervention studies are needed to confirm an effect of vitamin D on PD symptoms. The area with the most publications, bone health, suggests that vitamin D alone is not enough to prevent bone loss in persons with PD. Interestingly however, recommendation to spend as little as 15 min outside on sunny days did result in increases in bone mineral density, possibly related to increased physical activity. The possibility of neuroprotection is the most exciting aspect of vitamin D therapy, but it is also the most complicated area of research. Animal studies show some promising data, but translation to humans is always difficult. Without better biomarkers in the field of PD examining vitamin D's effect on disease progression or its potential neuroprotective effects seems unlikely.

Contributors

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