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Systematic Review

The Role of Vitamin D in Basal Ganglia Diseases

Carl Nikolaus Homann[1,2,*], Barbara Homann[1]

[1]Department of Neurology, Medical University Graz, 8036 Graz, Austria
[2]Department of Public Health, St. Elisabeth University of Health and Social Schiences, 81000 Bratislava, Slovakia
*Correspondence: nik.homann@medunigraz.at (Carl Nikolaus Homann)
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Abstract

Objective: Vitamin D (VitD) has been shown to influence several cellular processes in the brain. The extent to which VitD plays a role in the pathomechanism of neuronal loss and dysfunction in basal ganglia diseases (BGDs) is still debated. There is yet to be a comprehensive study that provides an overview of all of the most relevant BGDs. **Methods**: PubMed, and Google Scholar were systematically searched for observational studies that investigated the association between serum VitD levels and BGDs up to March 2022. **Results**: We extracted 60 studies, but with a great variety of design and quality. VitD deficiency appears to be common in most BGDs, but only in Parkinson's disease (PD) has a causal association been fully examined. There is some evidence that low VitD serum levels influence symptom severity, most notably in restless legs syndrome (RLS), PD, and tic disorders. The effects of vitamin D supplementation were studied in three BGDs, with results mostly favorable for RLS, ambiguous for tics, and mostly unfavorable for PD. **Conclusions**: There are still various elements of BGDs with insufficient, ambiguous, or altogether absent evidence, and further high-quality research is required. However, there appears to be sufficient scientific justification already to recommend that practitioners treating BGDs check serum VitD levels and supplement as appropriate.

Keywords: basal ganglia diseases; movement disorders; vitamin D; deficiency; insufficiency; disease severity; risk factor; biomarker; supplementation

1. Introduction

Basal ganglia disorders (BGDs) are slowly progressive incurable conditions that impact motor functions such as movement, muscle control, and balance, as well as non-motor functions such as mood, behavior and cognition [1]. BGDs are among the most common neurological diseases, with a prevalence in the 50+ year-olds of 28% [2]. Though psychiatric symptoms can be as troubling and distressing as are abnormal movements, traditionally, the focus has been on motor abnormalities [1]. Accordingly, BGDs are classified into hypokinetic with Parkinson's disease (PD), and hyperkinetic with essential tremor (ET), restless legs syndrome (RLS), dystonia, chorea, and tic disorders (TDs) as its most common representatives [2].

The BG are a set of intricately interconnected subcortical nuclei [3], including the substantia nigra, the dorsal striatum (caudate nucleus and putamen), the ventral striatum (nucleus accumbens and olfactory tubercle), the globus pallidus, the ventral pallidum, and the subthalamic nucleus [4]. Functionally, the BG are recognized as components of parallel, reentrant cortico-subcortical circuits that originate in distinct cortical areas, transit the BG and thalamus, and terminate at their respective areas of origin in the frontal lobe [5]. As mentioned above, these circuits run parallel but separate from one another so that failure of different locations of the BG output nuclei or connected pathways would result in varied patterns of symptomatology [1]. This explains the heterogeneity within the group and the individual disease.

The treatment of BGDs is purely symptomatic, and its effectiveness often diminishes over time. To date, there are no drugs that have prophylactic or progression-retarding properties. This has prompted the search for novel pharmacological and non-pharmacological strategies [6] that can improve brain pathology. VitD has been described as one of the promising candidates. It is a prohormone that, concerning the CNS, performs various pleiotropic tasks, including ensuring healthy neural development, appropriate adult brain trophism, and slowing the aging process [7]. For these tasks, VitD, as recently discovered, may perform both enzymatic activation and inactivation locally within the CNS [8].

VitD receptors (VDRs) are found throughout the embryonic and adult brain, and evidence indicates that both the mRNA encoding the VDR and the protein itself are present in the CNS [9]. VDRs are also abundant in neurons and glia in areas of the BG circuits such as in the substantia nigra, caudate, putamen, thalamus, and hypothalamus [7]. Of the many functions, VitD displays there, the furthering of synaptic plasticity and neurotransmission seems the most essential [10,11]. This is mainly achieved by decreasing the creation of pro-inflammatory cytokines and the oxidative stress load [12]. Neuronal loss and dysfunction are complex, poorly understood processes that can be caused by aggregation of misfolded proteins, mitochondrial dam-

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age, excitotoxicity, and misguided autonomous pathways [13]. VitD is thought to play a role in many of these mechanisms. All these facts support the widespread notion that VitD is a crucial factor in reducing neurodegeneration and other neuropathological processes that lead to the development of BGDs.

Unfortunately, even though abundant surveys are available for PD, there is no systematic investigation of the role of VitD in all of the most important BGDs. Of particular interest should be to provide insight into the prevalence of VitD deficiency, VitD as a risk factor and potential biomarker, the association of VitD and symptom severity, and finally, the effect of VitD supplementation. To clarify for which BGDs there is sufficient evidence, ambiguity, and data are entirely lacking could guide researchers in future investigations and would give physicians a basis for evidence-based decision-making.

2. Materials and Methods

A standard search protocol guided the ascertainment of publications investigating the association of VitD and BGDs until March 1, 2022 in PubMed and Google Scholar. The following Medical Related Subjects (MeSH) were used to specify the literature search: vitamin D or ergocalciferol; AND Parkinson's disease; restless leg syndrome or RLS; tic or Tourette; chorea or Huntington; tremor or essential tremor; dystonia; myoclonus; athetosis; ataxia; stereotypies; and ballism. If there was any uncertainty about whether a recognized article should be included, the text was examined by the second author. If the opinion of the two matched, the publication was in- or excluded accordingly. Where no agreement could be reached, it was omitted.

Furthermore, the bibliographies of the indicated articles were examined for other relevant research. By comparing author names, interventions, publication dates, sample sizes, and findings, dual publications were identified for exclusion.
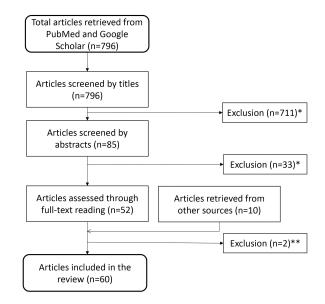
3. Results

3.1 Article Selection

Screening 796 papers, identified using the above-mentioned systematic search technique, by titles and abstracts, we removed 744 that did not match the inclusion criteria. We further deleted two duplicate publication after full-text reading but gained seven from bibliographies and three from other sources. This left us with 60 scientific papers to include for our survey (Fig. 1)

3.2 Parkinson's Disease and Vitamin D

Parkinson's disease (PD) is a disabling, slowly progressive disease characterized by dyskinesia, tremor, rigidity, and postural instability. In addition, nonmotor symptoms such as autonomic, sensory, or psychomotor symptoms also occur in most patients. PD is the second most

Fig. 1. Flow diagram for identification of relevant studies. This diagram depicts the path from the 796 articles retrieved initially, through exclusion and additional inclusion, to the 60 articles used in the survey. Reasons for exclusion: *studies not related to search topic, non-human (i.e., animal) studies, or no new data presented (editorials, reviews etc.) or **duplicate or retracted publications.

frequent neurodegenerative disease, with a 1% prevalence in 60+ years olds [14].

3.2.1 Vitamin D Status and Parkinson's Disease

Fifteen observational studies [15–27] and two meta-analysis [28,29] have investigated the link between VitD and PD and, except for two [18,28], have consistently reported low serum VitD levels in PD patients [15,23,30–35] (Appendix Table 1).

Luo et al. [29] included in his meta-analysis 15 studies with 2436 PD patients and 2567 age matched controls demonstrating a lower serum in patients (WMD –3.96, 95% CI –5.00, –2.92), especially in higher latitude regions (WMD –4.20, 95% CI –5.66, –2.75). There are four studies by Sato et al. [32] that were recently retracted, however when those were removed from the calculation the result did not change (WMD –3.96, 95% CI –5.00, –2.92, I^2 = 82.6%). Rimmelzwaan's meta-analysis, which included 658 PD patients and 1255 controls, likewise indicated that VitD levels in PD were lower than in the control group. His computation yielded a mean difference of 11.6 μg/mL (SD 12.2–10.9) [28]. The prevalence of VitD deficiency in PD ranged from 57% to 71% [28].

3.2.2 Vitamin D and Symptom Severity in Parkinson's Disease

There have been 14 studies on VitD and disease severity, with a total of 1833 PD patients included (Appendix Table 2). The severity of PD motor symptoms was primarily assessed using the motor subscore of the Unified Parkin-

son's Disease Rating Scale (UPDRS III) or the Hoehn and Yahr stage (H&Y). Suzuki, for example, reported a significant inverse relationship between blood VitD levels and UPDRS III scores in 137 PD patients [36]. Accordingly, VitD levels were highest in people with H&Y stages 1–1.5 (mean 23.9 ng/mL) and lowest in participants with H&Y stages 4–5 (mean 14.5 ng/mL), with a dose-response relationship. The Harvard-Biomarker-Study by Ding *et al.* [16] used data from 388 PD patients and found comparable patterns for UPDRS results. After controlling for age, gender, race, and VitD supplementation, the UPDRS total score was negatively associated with serum VitD level ($p = 0.02$). However, there was no correlation between VitD level and H&Y stage in this investigation. In an add-on to a longitudinal study following neuropsychiatric function in PD patients, Peterson *et al.* [37] also included an assessment of VitD serum levels and disease severity. This revealed that in 286 persons with PD, there was a significant association between VitD and both H&Y stage ($r = 0.191$, $p = 0.0013$) and UPDRS III scores ($r = 0.242$, $p = 0.0025$). Peterson *et al.* [30] included 40 PD patients in cross-sectional, observational research on balance and falls. Their VitD concentration exhibited a significant negative connection with the severity of their PD symptoms as measured by the UPDRS III ($r = 0.33$; $p = 0.04$). When age was taken into account, this link was maintained. However, there was no significant correlation between VitD concentration and H&Y stage ($r = 0.39$; $p = 0.69$). Two other studies to assess bone health and VitD status in PD also looked at disease severity. Senel *et al.* [38] found a strong negative link between VitD levels and the H&Y stages in 19 consecutive PD patients ($r = 0.69$, $p = 0.01$). In line with this, VitD levels in 52 PD patients in Serdarolu Beyazal's study had a significant negative correlation with UPDRS II and III scores, as well as H&Y stages [21]. Finally, and in contrast with the previous findings, the prevalence of VitD insufficiency in 108 subjects with early PD of Chitsaz's research project was not associated with H&Y stage or UPDRS III scores even after multivariate adjustment for possible confounders [39].

The little data available linking non-motor symptoms to VitD insufficiency is limited to two investigations on psychiatric, one on sensory and two on autonomic dysfunction. In the aforementioned paper Peterson *et al.* [37] showed in 286 PD patients that higher serum levels are connected with better scores in neuropsychiatric tests, particularly verbal fluency and verbal memory ($t = 4.31$, $p < 0.001$ and $t = 3.04$, $p = 0.0083$), and depression scores ($t = –3.08$, $p = 0.0083$) and Zhang *et al.* [40] that in 182 PD patients lower serum concentration was correlated with higher depression ($p = 0.020$) and anxiety-scores ($p = 0.009$). Gatto [41] investigated the effect of VDR and FokI polymorphism in 190 PD patients suggesting a link with cognitive decline ($p = 0.005$). In the study by Kim *et al.* [42], Vit D levels were associated with the degree of olfactory impairment in 39 PD patients, as evidenced by a reduced odor identifica-

tion score ($\beta = 0.38$, $p < 0.01$). The serum VitD level was also negatively correlated with the score for item number 28 on the Non-Motor Symptoms Scale for PD (NMSS) (Spearman's rho = –0.32, $p < 0.05$).

Orthostatic hypotension (OH), the paper by Jang *et al.* [43] states, was inversely related to lower blood concentrations of Vit D (OR, 0.54; [CI], 0.59–0.86; $p < 0.05$) and calcitriol (OR, 0.69; CI, 0.50–0.91; $p < 0.05$) in 55 PD patients. Furthermore, serum VitD and calcitriol levels were significantly decreased in 27 patients with orthostatic hypotension compared with those 28 without (VitD OH: 19.99 $\pm$ 4.73 ng/mL vs non-OH 26.89 $\pm$ 4.82 ng/mL, $p < 0.01$ and calcitriol OH 20.47 $\pm$ 6.79 vs non-OH 35.50 $\pm$ 9.32, $p < 0.01$). Finally, Kwon *et al.* [44] conclude that low serum VitD levels may also impair gastric motility, resulting in a slower gastric emptying time (GET). The serum VitD levels were decreased in the delayed-GET group compared with the normal-GET and control groups (PD delayed-GET 11.59 $\pm$ 4.90 ng/mL vs. PD non-delayed-GET 19.43 $\pm$ 6.91 ng/mL and Co 32.69 $\pm$ 4.93 ng/mL, respectively, $p < 0.01$). The serum VitD level was independently associated with delayed GET in PD patients in the multivariate model.

3.2.3 Vitamin D as a Risk Factor for Parkinson's Disease

However, data to prove a causal association has been a source of contention. Without this, it is possible that VitD deficiency is a result rather than a cause. Fortunately, there are two longitudinal studies and a genetic investigation to shed more light onto the situation.

Knekt *et al.* [45] investigated the link between VitD levels in midlife and the likelihood of developing PD later in life using the Finnish National Drug-Reimbursement Database. Within the 29-year follow-up period, 1.6% of the 3173 included were diagnosed with PD. Compared to those with insufficient levels, the risk for PD patients with adequate serum VitD was 65% lower. The relative risk of the highest vs. lowest quartiles was 0.33 (95% CI, 0.14–0.80). In contrast, Shrestha *et al.* [46] reported no link between serum VitD concentrations and PD risk in their US population-based prospective cohort analysis of 15,792 people. After a median of 17 years of follow-up, 0.42% of patients developed PD. The mean serum VitD concentrations in individuals who got PD and those who did not were similar (25.6 $\pm$ 8.4 ng/mL vs. 24.2 $\pm$ 8.5 ng/mL; $p = 0.24$). A recent genetic analyses has been conducted to investigate the relationship between VDR polymorphisms and the risk of developing PD. This study by Wang *et al.* [47] reveals that the SNP FokI is associated with a decreased risk of PD in Asian populations but not in Caucasian people.

3.2.4 Vitamin D as a Biomarker for PD

For PD, there are currently two VitD biomarker studies available. Lawton *et al.* [48] recently evaluated four biomarkers, including VitD, in the baseline blood of 624 participants from the Oxford Discovery prospective cohort

in quest of a PD biomarker as indicator for disease progression. The follow-up time for clinic visits was 3.2 ± 1.9 years. The authors discovered that lower VitD levels, lower apolipoprotein A1 levels, and greater C-reactive protein levels were linked with lower baseline activities of daily living measured by the score of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale part II (MDS-UPDRS II). Santangelo et al. [49] performed a 48-month longitudinal research on 60 untreated, de novo PD patients to investigate the association between VitD and future cognitive decline. According to binary logistic regression analysis, a lower level of VitD at baseline ($p = 0.022$) and lower education ($p = 0.049$) were predictors of the occurrence of mild cognitive impairment (MCI) at the end of the study period. Thus, the authors were confident to have confirmed VitD as a conceivable biomarker for PD-MCI development.

3.2.5 Vitamin D Supplementation

Three prospective PD supplementation trials (Appendix Table 3) and one small meta-analysis have been conducted, however, the findings have been equivocal [50]. Hiller et al. [51] undertook a pilot randomized, double-blind intervention study (n = 58) to assess the effects of 16 weeks of high-dose VitD (10,000 IU/day) on balance and other PD symptoms. Despite a rise in VitD serum concentrations (30.2 ng/mL to 61.1 ng/mL), the Sensory Organization Test (SOT) did not demonstrate a significant improvement in balance in the 27 VitD treated individuals ($p = 0.43$). However, a post hoc analysis comparing treatment effects in younger (age <67 yrs.) and older (age 67+ yrs.) individuals indicated a significant improvement in the SOT in the younger PD group ($p = 0.012$) [51]. Other PD symptoms, however, were unaffected. Habibi et al. [52] randomly assigned 120 PD patients with levodopa-induced dyskinesia to 1000 IU of VitD per day or a placebo. There was no difference in scores for L-dopa-induced dyskinesia (UPDRS IV sub score) or motor function (UPDRS III motor score) at the 3-month follow-up [52]. Suzuki et al. [36] randomly assigned 114 PD patients to receive 1200 IU of VitD daily (n = 58) or placebo (n = 56) for 12 months. The serum VitD level in the intervention group doubled, whereas the level in the placebo group remained steady. Simultaneously, the intervention group's motor scores (H&Y stage, UPDRS) were consistent, but the placebo group's scores dropped dramatically (difference between groups: $p = 0.005$). The authors came to the conclusion that, at least in the short run, VitD administration might help stabilize motor elements of PD [36].

Zou et al. [50] conducted a meta-analysis and concluded that in patients with PD the use of vitamin D supplements was effective in increasing VitD levels (SMD, 1.79; 95% CI, 1.40–2.18; $p < 0.001$) but had no significant effect on motor function (MD, –1.82; 95% CI, –5.10–1.45; $p = 0.275$).

3.3 Restless Legs Syndrome and Vitamin D

Restless legs syndrome (RLS) is a disorder of the sensory-motor system. RLS is characterized by intense, unpleasant sensations, such as paresthesia and dysesthesia, in the extremities, especially the legs, and the urge to move them. Typical is deterioration at rest, in the evening, and at night, and improvement with exercise. RLS affects 5–15% of adults [2,53].

3.3.1 Prevalence of Vitamin D Deficiency in RLS

Multiple studies suggest that VitD deficiency is common in patients with RLS. Wali et al. [54] conducted a population-based case-control study to assess the association between RLS and VitD levels. He discovered when analyzing the data of 78 RLS patients and 123 controls that the likelihood of being diagnosed with RLS was considerably greater in VitD deficient than in sufficient subjects (OR 3.1, $p < 0.002$, 95% CI 1.51–6.38). Furthermore, the mean blood VitD level was significantly lower in patients with RLS than in normal controls (RLS: 12.65 ng/mL vs. Co: 26.12 ng/mL, $p < 0.001$), and the number of deficient cases was greater in the patient group than in the control group (RLS: 75.6% vs. Co: 42.3%, $p < 0.001$). Balaban et al. [55] observed that in 83% of his 36 patients with RLS, serum VitD levels were deficient and that serum levels were substantially lower in female RLS patients than in female control participants. (RLS: 7.31 ± 4.63 ng/mL vs. Co 12.31 ± 5.27 ng/mL; $p = 0.001$). Oran et al. [56] separated 155 consecutive patients, 18–65 years of age, with musculoskeletal symptoms into groups based on their serum VitD level. The 119 patients with VitD levels <20 ng/mL had a significantly higher presence of RLS than those 36 above this threshold (deficient: 50.4% vs. not-deficient: 16.7%; $\chi^2 = 12.87$, $p < 0.001$). Regression analysis showed VitD deficiency (odds ratio [OR] 5.085, $p < 0.0019$) and serum VitD level to be significantly associated with the presence of RLS (OR 1.047, $p = 0.006$). Liu et al. [19] analyzed in their cross-sectional study VitD serum levels in 57 patients with primary RLS and healthy controls and revealed that the serum VitD level was significantly lower in patients with RLS than in healthy controls (RLS: 16.07 vs. Co: 27.0 ng/mL; $p < 0.05$). In addition, the incidence of insufficient serum VitD levels was significantly higher in patients with RLS than in healthy people (RLS: 80.7% vs. Co: 1.57%; $p < 0.05$). Cakir et al. [57] found in 102 consecutive patients with pain in the lower extremities that the prevalence of RLS in the group with VitD deficiency (<20 ng/mL) was significantly higher than in the non-deficient group (deficient: 52.63% vs. non-deficient: 37.78%; $p = 0.034$). The prevalence of insufficient cases was 90.1% in RLS patients and 66.3% in those without RLS. Almeneessier et al. [58] studied 1136 consecutive non-pregnant female patients aged 15–44 years, presenting to a primary care center to assess the prevalence of RLS, as well as its correlates and severity. RLS was more frequent in women with VitD de-

ficiency than in those with normal serum levels (deficient: 64% vs. non-deficient: 45%, $p < 0.001$). Multivariate binary logistic regression analysis identified VitD deficiency as one of the three independent predictors of RLS (OR 2.147 [1.612–2.86], $p < 0.001$). Işıkay et al. [59] looked at the occurrence of RLS in children with celiac disease. The eight out of 226 patients that were diagnosed with RLS according to the International RLS Study Group (IRLSSG) criteria had significantly lower VitD serum levels (RLS: 9.88 ± 4.68 ng/mL vs. non-RLS: 12.48 ± 11.68; ng/mL; $p = 0.03$). Mansourian et al. [60] included a total of 36 studies involving 9590 participants in their meta-analysis. Results revealed that in RLS patients serum VitD levels were significantly lower (WMD –3.39 ng/mL; 95% CI, –5.96 to –0.81; $p = 0.010$; $I^2 = 86.2\%$) and those of phosphorous significantly higher (SMD 0.19; 95% CI, 0.04–0.34; $p = 0.011$; $I^2 = 83.6\%$) compared to the non-RLS individuals [60]. As opposed to all the studies previously mentioned that showed lower Vitamin D levels in patients with idiopathic RLS, Jiménez-Jiménez et al. [61] observed higher serum VitD concentrations in RLS patients than in age and gender-matched controls (RLS: 21.94 ± 9.77 ng/mL vs. Co: 18.63 ± 4.40 ng/mL, $p = 0.0002$). Noteworthy is that both groups were average deficient, but the control group was more so. The authors, who focused primarily on VDR gene polymorphism and measured serum VitD levels only as a sideline, failed to provide an explanation for these surprising findings.

3.3.2 Vitamin D Levels and Symptom Severity in RLS

In addition, VitD seems to have disease-specific beneficial effects regarding the severity of RLS symptoms. Balaban et al. [55] for example, reported on a correlation between low VitD values with increased disease severity. Wali et al. [54] also revealed an association between increased RLS severity ratings (International Restless Legs Syndrome Study Group rating scale (IRLSSG-RS)) and lower serum VitD levels (IRLSSG of deficient cases: 19.4 ± 5.9 vs. sufficient 14.5 ± 4.7, $p < 0.002$). In the aforementioned cross-sectional study, Liu et al. [62] analyzed the relationship between VitD levels and parameters of RLS severity, as well as sleep quality, anxiety, and depression. Pearson's correlation analysis indicated that lower serum VitD levels were related with more severe symptoms of RLS as measured by IRLSSG ratings ($r = –0.395$, $p = 0.002$), worse quality of sleep (Pittsburgh Sleep Quality Index (PSQI) score) ($r = –0.304$, $p = 0.022$), and worse depression scores (Hamilton Depression Rating Scale (HAMD$_{24}$)) ($r = –0.295$, $p = 0.027$). The research of Işıkay et al. [59] on children with celiac disease also looked at the relationship between VitD and RLS severity. In the correlation analysis, the severity of RLS symptoms assessed using the IRLSSG rating scale was significantly negatively correlated with serum VitD levels ($r = –0.67$, $p = 0.04$). Cakir et al. [57] in the study mentioned above,

however, did not detect any statistically significant differences in clinical assessment or IRLSSG Symptom Severity Scale when comparing VitD deficient and non-deficient RLS patients.

3.3.3 Vitamin D as a Biomarker for RLS

Mondello et al. [63] performed comparative proteomic analyses of the blood of RLS patients and healthy persons in search of novel potential RLS biomarkers. When they quantified 272 proteins in 12 patients with RLS and ten healthy controls, they revealed that with eight other proteins, VitD-binding protein was decreased, suggesting that these proteins may have clinical value as biomarkers and as possible treatment targets. Patton et al. [64] conducting a proteomic analysis of cerebrospinal fluid of five RLS patients and five controls with the aim of establishing whether biomarkers in the cerospinal fluid are capable of distinguishing patients with RLS from those with other neurological disorders. Their results revealed a distinctive protein profile in the RLS CSF that included among others an increased VitD binding protein, which could possibly serve as a CSF biomarker for early RLS.

3.3.4 Vitamin D Supplementation in RLS

Aricò et al. [65] studied the effects of VitD supplementing in 5 females with low VitD levels as part of a research to investigate RLS patients with augmentation. At six-month follow-up visits, in parallel with VitD values normalization (pre: 10.3 ng/mL vs. post: 30.4 ng/mL), augmentation had been resolved in two patients, and RLS scores had improved in all (IRLS-RS pre: 19.8 vs. post: 8.6; $p < 0.5$). A small open-label study by Wali et al. [66] showed that after administering VitD supplementation to 12 VitD-deficient RLS patients, the VitD level was successfully corrected to >50 nmol/L. Furthermore, the intensity of RLS symptoms was significantly reduced. A more recent 12-week double-blind placebo-controlled research on 22 completed cases by the same authors, on the other hand, revealed that VitD supplements (7142.85 IU, per os/12 weeks) were unsuccessful in treating RLS symptoms [67]. However, the authors acknowledged that the study's shortcomings, including the short trial period, the small sample size, and the inclusion of patients with mild forms of RLS, could have played a role in this outcome.

3.3.5 Other Aspects of Vitamin D in RLS

There are no investigations on VitD as a risk factor or biomarker for RLS or aspects thereof.

3.4 Tic Disorders and Vitamin D

Tics are characterized by a sudden onset of involuntary, rapid, repetitive, non-rhythmic muscle contractions (motor tics) or sound production (vocal tics). Tic Disorders (TDs) are often transient but can become a life-long chronic disorder [68]. While 10% of all people experience

some form of transient TD at some point in their lives, the prevalence of the Gille de la Tourette syndrome, the most severe manifestation of the spectrum of TDs, is 1% [68].

3.4.1 Vitamin D Status in Tic disorders

So far, two case-control studies on VitD serum levels in TDs have been conducted. In a recent research project, Li *et al*. [69] examined 132 children with TDs and 144 healthy controls. The TD group included 92 patients with transient TDs and 40 with chronic TDs (including eight cases of Gille de la Tourette syndrome). He discovered that the mean serum level of Vit D in the TD group was significantly lower than in the control group ($p < 0.01$) and that the insufficiency or deficiency rate in the TD group was significantly higher than in the control group ($p < 0.01$). In addition, he observed that the mean serum level of Vit D in the transient group was higher than in the chronic TD group ($p < 0.05$), possibly suggesting that adequate VitD levels could protect from conversion from the less debilitating transitory type to the more severe chronic form. In a multicentre cross-sectional study, Bond *et al*. [70] explored 320 children and adolescents with chronic TDs and 31 of their first-degree relatives with and 93 without TDs. The aim was to see whether VitD is associated with the presence or severity of chronic TDs and with respective psychiatric comorbidities. Contrary to what they had expected from the previous studies, lower levels of VitD were not associated with a higher but rather a lower presence of TDs. When comparing their first-degree relatives who did develop TDs with those that did not, the unaffected had a higher insufficiency rate (no-TDs: 37.6% vs. TDs: 25.8%) and a lower median serum level (no-TDs. 21.6 (17.0–27.3) ng/mL vs. TDs: 24.3 (19.6–33.7) ng/mL). Expressed in risk ratios, this translates that a 10 ng/mL increase in VitD was associated with higher odds of having a TD diagnosis when compared to the unaffected cohort (OR 2.08, 95% CI 1.27–3.42, $p < 0.01$).

3.4.2 Vitamin D Levels and Symptom Severity in Tic Disorders

In another case-control study by Li *et al*. [71] designed to expand the previous data, they explored in 179 children with TDs and 189 healthy children the relationship between serum VitD level and tic severity. They discovered a negative correlation between the serum concentration and severity of symptoms. Bond *et al*. [70] however, in their before-mentioned study, found no significant association between VitD levels and tic severity as measured by both Yale Global Tic Severity Scale (YGTSS) ($p = 0.84$) and Clinical Global Impression (CGI) ($p = 0.91$). However, as correctly hypnotized, lower VitD levels were associated with significantly higher presence and severity of comorbid ADHD; in other words, higher VitD levels were somewhat protective, i.e., a ten ng/mL increase in VitD level was associated with lower odds of having comorbid ADHD within the TD cohort (OR

0.55, 95% CI 0.36–0.84, $p = 0.01$) and was inversely associated with ADHD symptom severity ($\beta = -2.52$, 95% CI -4.16–0.88, $p < 0.01$).

3.4.3 Vitamin D Supplementation in Tic disorders

There are two relatively small investigations on the effect of VitD supplementation. A study by Gemawat *et al*. [72] on 34 patients indicated an improvement in frequency, duration, and intensity of tic movements at the 24-week follow-up. In an open-label study by Li *et al*. [73] 36 children with chronic TDs received 300 IU/kg/d (<5000 IU/day) orally. After three months of treatment, serum VitD level and scores of YGTSS total, motor tics, phonic tics, total tic, impairment, and Clinical Global Impression (CGI) improved significantly. In addition, there were no adverse reactions to the treatment.

3.4.4 Other Aspects of Vitamin D in Tic disorders

There are no investigations on VitD as a risk factor or biomarker for TD or aspects thereof.

3.5 Essential Tremor and Vitamin D

Essential tremor, with a pooled prevalence including patients of all ages of 0.9% [74], is the most widespread movement disorder in Central Europe [2]. According to established diagnostic criteria, Essential tremor is characterized by postural and action tremor of the upper limbs, often also of the head, legs, and trunk.

3.5.1 Vitamin D Status in Essential Tremor

In our literature search, we detected no systematic studies on the VitD status of Essential tremor (ET). All what we found was a case report by Calarge describing tremor as a probable, possibly even indicative symptom of VitD deficiency in children [75].

3.5.2 Causal Relationship between Vitamin D and Essential Tremor

The relationship between ET and VDR polymorphism has been examined in two studies. Chen *et al*. [76] tried to detect genetic risk factors of ET in the Chinese population and investigated in 200 ET patients and 229 controls 12 single nucleotide polymorphisms (SNPs) in seven candidate genes for RLS including VDR. They reported an association of IL1B polymorphism with the risk of ET but, no significant differences either in the frequencies of genotypes or in the frequencies of the allelic variants of other SNPs harbored in VDR or any other of the targeted RLS genes. Sazci *et al*. [77] examined the rs2228570 variant of the human VDR gene in a case-control genetic association project, including 239 sporadic ET patients and 239 healthy controls. He revealed that the rs2228570 mutation of the VitD receptor gene is generally associated with sporadic ET, notably in male patients, making it a genetic risk factor for sporadic ET. Similarly, Agundez *et al*. [78] looked for

a possible association between several common variants in these genes and the risk for ET. Genotyping 272 patients diagnosed with familial ET and 272 age-matched controls, they too confirmed that VDR rs2228570 SNVs is related to ET risk.

3.5.3 Vitamin D Supplementation in Essential Tremor

There are, to date, no investigations on the effect of supplementation of VitD in ET.

3.5.4 Other Aspects of Vitamin D in Essential Tremor

There are no studies on other aspects.

3.6 Huntington's Chorea and Vitamin D

Huntington's Chorea (HC) is an autosomal dominant, currently incurable, progressive and ultimately lethal neurodegenerative disorder caused by polyglutamine (CAG) repeats in the huntingtin protein [79]. The most prominent neurological symptoms are chorea, loss of coordination, and dysphagia. HC's most common psychiatric symptoms include depression, irritability, mood swings, memory and concentration deficits, and full-blown dementia [79]. Prevalence rates among predominantly Caucasian populations in Western countries are especially high, estimated at 9.71 per 100,000 [80].

3.6.1 Vitamin D Status in Huntington's Chorea

Minimal data are available on the status of VitD levels in HC [81]. Chel *et al*. [81] explored VitD status in 28 institutionalized patients with manifest HC in a cross-sectional study. Eight patients (29%) were VitD deficient (<25 nmol/L) and 25 (89%) insufficient (<50 nmol/L), but only three (10%) had adequate serum levels. Mean serum VitD levels were 33 ± 15 nmol/L (6.5–58.2). A positive association was found between serum VitD levels and Functional Ambulation Classification (FAC) scores ($p = 0.023$). However, with more than half of the patients being bedridden, wheelchair-bound, or needing continuous help while walking, and 89% of them having a Huntington's Disease Rating Scale-Total Functional Capacity score (UHDRS-TFC) of "0" (i.e., complete dependence), the study cohort reflects the situation of more advanced disease stages, so that it is uncertain if these findings are generalizable to other patient cohorts.

3.6.2 Other Aspects of Vitamin D in Huntington's Chorea

To date, there have been no VitD supplementation studies in HC patients conducted to explore the effects of VitD administration. There have also been no research of VitD as a risk factor or biomarker for HC or aspects thereof.

3.7 Ataxia and Vitamin D

Hereditary ataxias with predominant cerebellar pathology, leading in a gradually increasing loss of fine motor coordination, are commonly attributed to movement disorders, and there is emerging evidence of basal ganglia involvement for at least some of the spinocerebellar ataxias (SCA) [82–84]. According to a systematic review of prevalence studies, roughly 1:10,000 persons are afflicted by hereditary ataxias [85].

3.7.1 Vitamin D Status in Ataxias

The role of VitD in inherited ataxias has received little attention. The limited research that are available focused primarily on bone health, such as the tiny study on Friedreich's ataxia (FRDA) [86] and a bigger one in patients with spinocerebellar degeneration (SCD) [87]. We presently have no relevant data regarding VitD status to contribute because the latter was recently withdrawn and the former cannot be regarded a BGD.

3.7.2 Other Aspects of Vitamin D and Ataxias

There have been no studies on VitD as a risk factor for ataxia, nor have there been any on VitD supplementation.

3.8 Myoclonus and Vitamin D

Myoclonus is a sudden, brief, jerky, shock-like involuntary movement caused either by a contraction of a single or several agonist and antagonist muscles (positive myoclonus) or by a transient interruption of tonic muscle activity (negative myoclonus) [88]. The lifetime prevalence of myoclonus is estimated to be approximately 10 cases per 100,000 population [89].

3.8.1 Vitamin D Status in Myoclonus

There are no systematic investigations on VitD status in myoclonus. However, we found one historic case report on a 98-year-old woman with myoclonia and low serum concentration of VitD and calcium, in which symptoms disappeared after supplementation [90].

3.8.2 Other Aspects of Vitamin D and Myoclonus

The literature search did not reveal any systematic investigations on VitD supplementation in patients with myoclonus, nor are there any regarding Vit D as a possible risk factor or biomarker.

3.9 Dystonia and Vitamin D

Dystonia is a movement disorder, characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements or postures, or both [91]. The prevalence of dystonia reported by Steeves *et al*. [92] in a systematic review and meta-analysis is 16.43 per 100,000.

3.9.1 Vitamin D Status in Dystonia

There is but one study examining the VitD status in dystonia patients. Serefoglu Cabuk *et al*. [93] investigated 20 patients with benign Blepharospam (BEB), a common form of focal dystonia, and 20 healthy individuals. He

showed that the BEB patients had in comparison significantly lower serum levels of VitD (BEB: 16.58 ± 7.23 ng/mL vs. Co: 19.23 ± 6.37 ng/mL; $p = 0.037$).

3.9.2 Causal relation between Vitamin D and Dystonia

There is no investigation linking low VitD status to the development of dystonia.

3.9.3 Vitamin D and Severity of Dystonia

In the afore mentioned study Serefoglu Cabuk *et al*. [93] calculated that the VitD level of his BEB patients, strongly negatively correlated with the Jankovic severity score ($r = –0.375$, $p = 0.043$).

3.9.4 Vitamin D Supplementation in Dystonia

VitD supplementation has been studied, although only in one double-blind placebo controlled study conducted by Habibi *et al*. [52] on patients with L-dopa induced dyskinesias, including dystonias. He randomly allocated 120 patients to receive over the course of three months VitD at a dose of 1000 IU/day orally or placebo. Dyskinesia duration improved when compared to placebo (VitD: –0.88 hours/day vs. Placebo: –0.23 hours/day), as did dyskinesia severity (VitD: –0.4 patients vs. Placebo: –0.6 patiens), although the difference did not reach levels of significance. In summary, the overall trial results were mostly unfavorable, and most importantly, there was no mention of the effect on dystonia specifically.

3.9.5 Other Aspects of Vitamin D in Dystonia

There are no studies on other aspects of VitD and the development of dystonia, particularly none on VitD as possible biomarker.

3.10 Other Basal Ganglia Disorders and Vitamin D

There have been no research on the VitD status of other BGDs, such as stereotypies, akathisia, athetosis, and ballism. There are no studies on VitD as a risk factor or biomarker, nor on the impact of supplementing in these situations.

4. Discussion

This study reviewed the available research on VitD and its potential impact on BGDs. In particular, we investigated how VitD blood levels might be associated with BGD symptoms and clinical development and its potential application in improving clinical manifestations in BGD patients.

Specifically (Table 4), we found that VitD deficiency appears to be prevalent in all BGDs, and in addition, to be more prominent both quantitatively and qualitatively when compared to the general population. Only in PD has a causal association been thoroughly examined, with conflicting results; in HC, Myoclonus, and ET, there are some indications that there may be a link. VitD as a biomarker

has been investigated in PD and RLS with promising outcomes. There is evidence that low VitD serum levels influence symptom severity, most notably in RLS and, to a lesser extent, in PD and TDs. The effects of VitD supplementation were studied in three BGDs, with the results being mostly favorable for RLS, ambiguous for TDs, and mostly unfavorable for PD.

Previous evaluations touched on these issues in various ways, covering some of the examined diseases such as PD [29,94] or other movement disorders [35], but none covered BGDs entirely. Furthermore, since their publication, as can be expected in this dynamic field of research, there has been a steep increase in the number of new studies; thus, many of the prior material has become outdated. Fresh discoveries have been made, some of which contradict prior ones [18], but there have also been withdrawals of fraudulently manufactured data that previously supported the assumption of a favorable protective impact [95].

VitD's effect has also been examined in various other neurological diseases [96]. There is general agreement that VitD insufficiency is a risk factor for disease development and poor outcome, as seen by more severe symptoms in most of the disorders studied [97]. Stroke and Alzheimer's disease (AD) have the highest level of evidence, whereas traumatic brain injury, neuro-oncologic processes, multiple sclerosis (MS), and associated disorders have lower quality data [97]. VitD as a supplement has been researched in most neurological illnesses, including high-quality studies for MS and neuro-trauma, medium-quality for stroke and AD, and lower quality for brain tumors and CNS infections, the latter , in addition, having disappointing results [97]. VitD has also been examined as a late-stage therapy for stroke, with conflicting outcomes despite high-quality data [97]. VitD and VitD binding protein have been discussed as potential biomarkers in patients with stroke [98], MS [99], AD [100], glioblastoma [101], traumatic brain injury [102], and meningitis [103].

In the research of other neurological diseases we find similar patterns as with that of BGDs: there is an increasing quantity of articles with heterogeneity in design and quality. However, the quest to implore alternative interventions is more pressing for BGDs, because of more limited treatment options. Therefore, further research is crucial, especially in BGDs. As potential guidance for these future research projects, this survey points out that there are areas where more research is needed and where there are qualitative shortcomings in the existing research.

In this respect we also want to summarize the limitations of our review. These can mainly be divided into three categories: The first and most important challenge was considerable heterogeneity across included studies, which complicated comparisons and interpretations of our findings. There were major disparities in the research populations, including genetic, regional, and cultural background, outcomes and assessment techniques, treatment regimes,

Table 4. Quality and outcome of studies on the role of vitamin D in individual basal ganglia diseases.

Disease	Deficiency	Risk Factor	Biomarker	Symptom	Treatment
Parkinson's disease	A +++/−	B +/−	C +	B ++/−	A +/——
Restless Legs Syndrome	A +++		C +	C ++	C +++/−
Tic Disorders	B ++			C ++/−	C +/−
Huntington's Chorea	D +	D +			
Myoclonus	D +	D +			
Ataxia					
Essential Tremor		D +			

Quality: A: one or more meta-Analysis; B: more than one RCT or RCS; C: one randomized controlled trial (RCT) or one representative cohort study (RCS); D: observational studies only.
Study-outcome: +, Favorable; ++, very favorable; +++, highly favorable; −, unfavorable; —, very unfavorable; ——, highly unfavorable.

duration of study periods, and seasonality of testing. As stated in a recent scientific paper, the latter two may have a significant impact on the study's outcome [104].

Some of the publications considered did not include critical information such as VitD levels, the daily dosage equivalent of current symptomatic BGD therapy, whether disease severity was assessed on or off medication, the type of VitD, and the VitD level evaluation technique. The laboratory assessment procedure, in particular, appears to be an essential element. Some authors even go so far as to suggest that the lack of use of globally approved measuring methodologies and materials in a not insignificant part of VitD investigations potentially undermines their findings' reliability [100].

Finally, there was an overall variability in design and quality and only a relatively small number of studies in some of the BGDs. Also, it should be emphasized that correlations in some of the studies were somewhat low, though still significant. Due to the profound heterogeneity, we were unable to undertake a meta-analysis of the findings, and our interpretation was limited to a qualitative synthesis.

There are strengths in our review that should be highlighted. We used a highly sensitive search strategy, followed a systematic approach in our search and analysis, had a guideline for discerning views during the inclusion process, and followed reporting recommendations. Furthermore, where essential data was missing or full text was not accessible, we contacted the authors, unfortunately, not always successfully.

At this point, the implications of our study deserve some attention. The investigation began with the question of whether VitD can be the preventive or curative treatment for BGDs that has been sought for a long time or whether it can be the decisive risk factor or the reliable biomarker; with the current knowledge, the answer to that question is probably neither.

We discovered that the situation for BGDs is mixed: On the one hand, there is not enough evidence to draw definitive conclusions, and on the other, there is a lot of data suggesting that VitD deficiency can impact disease development and progression, flawed as they might be. Similar to Bivona et al.'s [105] argument for AD research, we in BGD research are also required to remember that, apart

from inaccuracies in study design and execution, we are also dealing with highly complex pathological processes. Bivona's paper elucidates that an influential factor in the evaluation of interventional studies is the lengthy latency period of AD, and most likely also of BGDs, which complicates the interpretation of the potential role of VitD in the disease. Also, in some of the BGDs, including PD and HC, and possibly in other BGDs too, the disease process begins years, if not decades, before they show symptoms. At that stage, the structural damage might be already too extensive for interventions to be successful [106,107]. In addition, the pathological processes, as indicated, for instance, by twin, [108,109] are most likely triggered by a multitude of factors [110,111]. In light of the complexity of this situation, it would be unexpected if one treatment, such as VitD supplementation, could be the sole cure and, at the same time, serve as a biomarker. However, VitD might play a role in ways not yet explored. It is possible, for instance, that VitD may prove most effective when it acts in synergy with one or more other medications, in which one enhances the effect of the other, or that VitD does not exert any direct influence but merely provides the conducive environment to allow other interventions to work.

Therefore, the key implication of this study is that we must acknowledge the complexity and consequently scale back on unrealistic expectations while remaining optimistic and open to further discoveries.

5. Conclusions

When it comes to contentious matters, more data always seems helpful. However, we have learned that for such a survey, it is not so much the number as the quality. To better understand the situation and produce a valuable meta-analysis, there is a need for adequately powered trials with the state of the art study designs and standardized cut-off levels for deficiency and insufficiency. Nevertheless, more than that, standardized laboratory conditions must be observed to ensure reliable and comparable outcome measures.

It is yet to be determined if VitD reintegration could be an effective adjunct to pharmaceutical and rehabilitative therapy in BGD patients. However, given the high prevalence of VitD deficiency, that BGDs are commonly linked with falls and fractures [112], and the good side effect

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Appendix Table 1. Characteristics of observational vitamin D prevalence studies in patients with basal ganglia diseases.

Authors	Year	Country	Subjects (n)	Study design	Serum Vitamin D ng/mL, mean ± SD	Prevalence of deficiency	Correlated with	Compared to Co
Parkinson's disease (PD)								
Abou-Raya [15]	2009	Egypt	PD (82), Co (68)	case control	PD:40.5 ± 11.4 vs. Co 49.1 ± 12.5; $p = 0.05$	not specified	not specified	sign.
Ding [16]	2013	USA	PD (388), Co (283)	longitudinal	PD: 28.0 ± 11.0 vs. Co 30.6 ± 11.1; $p = 0.0031$	PD: 17.6% vs. Co: 9.3%	UPDRS (total)	sign.
Evatt [17]	2008	USA	PD (100), AD (100), Co (100)	Survey (database): VitD blinded	PD 31.9 ± 13.6 ng/mL vs AD 34.8 ± 15.4 ng/mL vs Co 37.0 ± 14.5 ng/mL; $p = 0.03$	PD 55% vs. Co 36% or vs. AD 41%; $p = 0.02$	not with disease duration or symptoms	sign.
Kuhn [18]	2021	Germany	PD (60), Co (60)	case control	PD 17, 59 ± 9, 28 μg/L, Co 15, 69 ± 8, 43	not specified	none (UPDRS; MOCA)	not sign.
Liu [114]	2014	China	PD (229), Co (120)	case control	PD: 20.6 ± 5.5 vs. Co 22.9 ± 5.6; $p < 0.001$	PD: 43.4% vs. Co: 26.7%; $p = 0.010$	disease duration (r (spearman) = −0.124, $p = 0.041$). H&Y ($p = 0.030$) and UPDRS ($p = 0.000$))	sign.
Ozturk [20]	2014	Turkey	PD (115), Co (117)	case control	mPD: 12.6 ± 7.6 vs. mCo 20.6 ± 11.2 ng/dL; $p < 0.001$. fPD: 11.7 ± 6.8 vs. fCo 18.6 ± 11.4 ng/dL; $p < 0.001$.	Deficient mPD: 89.4% vs. mCo 61.7%; $p < 0.05$. fPD: 92.6% vs. fCo 71.4%; $p < 0.05$.	not applicable	sign.
Beyazal [21]	2016	Turkey	PD (52), Co (39)	case control	PD vs. Co significantly lower	not specified	UPDRS part II, UPDRS part III, and HY stage	sign.
Sleeman [22]	2017	UK	PD (145), Co (94)	Longitudinal	PD 44.1 ± 21.7 vs. Co 52.2 ± 22.1 nmol/L; $p < 0.05$	PD 66.9% vs. Co 45.7%; $p < 0.01$	disease motor severity at 36 months.	sign.
van den Bos [23]	2013	Netherlands	PD (186), Co (802)	case control	PD 48.3 ± 20.2 vs. Co 56.7 ± 22.9; $p = 0.000$	PD 56.2% Co 43.2%	not applicable	sign.
Wang [25]	2016	China	PD (201), Co (199)	case control	PD 20.6 ± 6.5 ng/mL; Co 22.8 ± 5.5; $p < 0.05$	PD 91.0% vs. Co 89.9%	not applicable	sign.
Wang [24]	2015	China	PD 478) Co (431)	case control	PD 25.59 ± 0.56 vs. Co 30.14 ± 0.56; $p < 0.0001$	PD : 71% vs. C0 54% ; <0.0001	not applicable	sign.
Yakşi [26]	2022	Turkey	PD (34) vs. Co (31)	case control	PD 16.0 ± 5.1 vs. Co 17.7 ± 9.2; $p = 0.161$	not specified	H&Y I, II (16.4 ± 5.3 vs. H&Y III, IV 15.1 ± 5.0, $p = 0.475$)	not sign.
Yoon [27]	2015	South Corea	PD (81), Co (52)	case control	PD 21.8 ± 9.5 vs. Co 25.2 ± 9.3 ng/mL, $p = 0.05$	PD 55.5% vs. Co 37.2%; $p = 0.02$	UPDRS III not significant	sign.
Restless Legs Syndrome (RLS)								
Wali [54]	2018	Saudi Arabia	RLS (78), Co (123)	case control	RLS: 12.65 ng/mL vs. Co: 26.12 ng/mL, $p < 0.001$	RLS: 75.6% vs. Co: 42.3%, $p < 0.001$	disease severity IRLSSG deficient cases: 19.4 ± 5.9 vs. sufficient 14.5 ± 4.7, $p < 0.002$	sign.
Oran [56]	2014	Turkey	RLS def (119.); not-def. (36) (out of 155 pts with musculoskeletal symptoms)	case control	Not specified	VitD deficiency (odds ratio [OR] 5.085, $p < 0.0019$)	Disease severity	sign.
Balaban [55]	2012	Turkey	f. RLS (36), f. Co (38)	cross sectional study	RLS: 7.31 ± 4.63 ng/mL vs. Co 12.31 ± 5.27 ng/mL; $p = 0.001$	higher deficiency prevalence 83%	disease severity: IRLS scores in females ($p = 0.01$, $r = 0.47$) 10 -item International Restless Legs Syndrome (IRLS) Rating Scale	sign.
Liu [62]	2021	China	RLS (57), Co (57)	cross sectional study	RLS: 16.07 vs. Co: 27.0 ng/mL; $p < 0.05$	RLS: 80.7% vs. Co: 1.57%; $p < 0.05$	Disease severity: IRLSSG ratings ($r = −0.395$, $p = 0.002$)	sign.
Cakir [57]	2015	Turkey	RLS def. (57); not-def. (45) (out of 102 pts with lower extremity pain)	cross sectional study	not specified	RLS 90.1% vs. Co 66.3%; deficient: 52.63% vs. non-deficient: 37.78%, $p = 0.034$	Disease severity IRLSSG rating scale: No significant correlation	sign.
Almeneessier [58]	2020	Suadi Arabia	RLS def. (173); not-def. (390) (out of 1,136 non-pregnant women at primary health care)	cross sectional study	not specified	RLS 64% vs. non-RLS: 45%, $p < 0.001$ VitD deficiency independent predictor of RLS (OR 2.147 (1.612–2.86), $p < 0.001$)	not specified	sign.
Işıkay [59]	2018	Turkey	RLS (8), non RLS (218) (out of 226 children with celiac disease)	Cross sectional study	RLS: 9.88 ± 4.68 ng/mL vs. non-RLS: 12.48 ± 11.68; ng/mL; $p = 0.03$	not applicable	Symptom severity IRLSSG ($r = −0.67$, $p = 0.04$)	sign.

Appendix Table 1. Continued.

Authors	Year	Country	Subjects (n)	Study design	Serum Vitamin D ng/mL, mean ± SD	Prevalence of deficiency	Correlated with	Compared to Co
Tic Disorder (TD)								
Li [69]	2017	China	Tics	cross-sectional study	TD: 23 ± 9 vs. Co: 32 ± 8 ng/mL; $p < 0.01$	TD 80.3% vs. Co 43.8%	not specified	sign.
Li [71]	2018	China	Tics	cross-sectional study	TDs: 22.9 ± 7.5 vs. Co: 28.9 ± 8.3 ng/mL, $p < 0.001$	TDs: 81.6% vs. Co: 55.6%	tic severity, after adjusting for age and BMI (adj. OR = 0.94; 95% CI 0.897–0.989; $p = 0.02$)	sign.
Li [73]	2019	China	Tics	cross-sectional study	TDs: 22.9 ± 7.5 vs. Co: 28.9 ± 8.3 ng/mL, $p < 0.001$	TDs: 81.6% vs. Co: 55.6%	not specified	sign.
Bond [70]	2020	UK	Tics	cross-sectional study	TDs: 24.3 ± 19.6–33.7 vs. no-TDs-Co 21.6 ± 17.0–27.3 vs.	TD: 31.1% vs. Co 39.8%	higher ADHD presence and severity trend with tic severity: Yale Global Tic Severity Scale (YGTSS) ($p = 0.84$) and Clinical Global Impression (CGI) ($p = 0.91$)	REVERSED sign.
Huntington's Chorea (HC)								
Chel [81]	2013	Netherlands	HC inst. (28)	survey	33 ± 15 ng/mL	89%	walking disability	not applicable

Co, control subjects (healthy or stated otherwise); PD, Parkinson's disease; HC, Huntington's chorea; RLS, Restless legs syndrome; ET, Essential Tremor; TD, tic disorder; inst, institutionalized; f, female; m, male; sign., significant.

Appendix Table 2. Vitamin D and disease severity in patients with basal ganglia disorder.

Authors	Year	Country	Patients (n)	Study design	Correlation of vitamin D serum levels with:	Study outcome
Parkinson's disease (PD)						
Suzuki [36]	2013	Japan	137	cross-sectional	UPDRS III scores sign difference H&Y stages 1,2 vs. 3,4	Confirmative for PD motor symptoms
Ding [16]	2013	USA	388	cross-sectional	UPDRS total score ($p = 0.02$) not for H&Y stage	Partly confirmative for PD motor symptoms
Peterson [37]	2013	USA	286	longitudinal	H&Y stage ($r = 0.191$, $p = 0.0013$) and UPDRS III scores ($r = 0.242$, $p = 0.0025$)	Confirmative for PD motor symptoms
Peterson [30]	2013	USA	40	cross-sectional	UPDRS III ($r = 0.33$; $p = 0.04$) not for H&Y stage	Partly confirmative for PD motor symptoms
Senel [38]	2011	Turkey	19	cross-sectional	H&Y stages ($r = 0.69$, $p = 0.01$).	Confirmative for PD motor symptoms
Beyazal et al. [21]	2016	Turkey	52	cross-sectional	UPDRS II and III scores, as well as H&Y stage	Confirmative for PD motor symptoms and activities of daily living
Chitsaz et al. [39]	2013	Iran	108	cross-sectional	Not for H&Y stage and not for UPDRS III scores	Not Confirmative for PD motor symptoms
Peterson [37]	2013	USA	286	longitudinal	verbal fluency and verbal memory ($t = 4.31$, $p < 0.001$ and $t = 3.04$, $p = 0.0083$), and depression scores ($t = -3.08$, $p = 0.0083$)	Confirmative for neuropsychiatric symptoms
Zhang [40]	2019	China	182	cross-sectional	higher depression ($p = 0.020$) and anxiety-scores ($p = 0.009$)	Confirmative for neuropsychiatric symptoms
Gatto [41]	2016	USA	190	Cross sectional genetic alalysis	VDR- and FokI polymorphism linked to cognitive decline ($p = 0.005$)	Confirmative for neuropsychiatric symptoms
Kim [42]	2020	Korea	39	Cross sectional	Reduced odor identification score ($\beta = 0.38$, $p < 0.01$)	Confirmative for sensory symptoms (olfactory impairment)
Jang [43]	2015	Korea	55	Cross sectional	Presence of OH (OR, 0.54; [CI], 0.59–0.86; $p < 0.05$) ; sign. group differences (VitD OH: 19.99 ± 4.73 ng/ mL vs. non-OH 26.89 ± 4.82 ng/mL, $p < 0.01$)	Confirmative for autonomic symptoms (Orthostatic hypotension (OH))
Kwon [44]	2016	Korea	51 (+20)	Cross sectional	slower gastric emptying time (GET); sign. group differences (PD delayed-GET 11.59 ± 4.90 ng/mL vs. PD non-delayed-GET 19.43 ± 6.91 ng/mL and Co 32.69 ± 4.93 ng/mL, respectively, $p < 0.01$)	Confirmative for autonomic symptoms (impaired gastric motility)

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Appendix Table 2. Continued.

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Authors	Year	Country	Patients (n)	Study design	Correlation of vitamin D serum levels with:	Study outcome
Restless Legs Syndrome (RLS)						
Wali [54]	2018	Saudi Arabia	78	case control study	International Restless Legs Syndrome Study Group rating scale (IRLSSG-RS) increased disease severity; sign. group differences (IRLSSG of deficient cases: 19.4 ± 5.9 vs. sufficient 14.5 ± 4.7, $p < 0.002$)	Confirmative for motor symptoms
Balaban [55]	2012	Turkey	36	cross sectional	increased disease severity	Confirmative for motor symptoms
Liu [62]	2021	China	57	cross sectional	IRLSSG ratings ($r = -0.395$, $p = 0.002$), Pittsburgh Sleep Quality Index (PSQI) score ($r = -0.304$, $p = 0.022$), and Hamilton Depression Rating Scale (HAMD$_{24}$) ($r = -0.295$, $p = 0.027$)	Confirmative for motor and neuropsychiatric symptoms
Işıkay [59]	2018	Turkey	8	cross sectional	IRLSSG ($r = -0.67$, $p = 0.04$)	Confirmative for motor symptoms
Cakir [57]	2015	Turkey	66	cross sectional	not with IRLSSG	Not confirmative for motor symptoms
Tic Disorder (TD)						
Li [73]	2019	China	179	cross-sectional	Yale Global Tic Severity Scale (YGTSS) total scores (rs $= -0.32$, $p < 0.001$), motor tics scores (rs $= -0.18$, $p = 0.01$), phonic tics scores (rs $= -0.15$, $p = 0.045$), YGTSS total tic scores (rs $= -0.27$, $p < 0.001$), impairment scores (rs $= -0.31$, $p < 0.001$)	Confirmative for motor symptoms
Bond [70]	2020	UK	320	cross-sectional	Not with Yale Global Tic Severity Scale (YGTSS) ($p = 0.84$) not with Clinical Global Impression (CGI) ($p = 0.91$); Reduced ADHS risk with increased in VitD levels (OR 0.55, 95% CI 0.36–0.84, $p = 0.01$) and inverse correlation with ADHD symptom severity ($\beta = -2.52$, 95% CI -4.16–0.88, $p < 0.01$).	Confirmative for neuropsychiatric symptoms. Not confirmative for motor symptoms
Huntington's Chorea (TD)						
Chel [81]	2013	Netherlands	28	cross-sectional	Functional Ambulation Classification (FAC) scores ($p = 0.023$)	Confirmative for motor symptoms
Dystonia						
Serefoglu Cabuk [93]	2020	Turkey	20	cross-sectional	Jankovic severity scale for essential blepharospasm ($r = -0.375$, $p = 0.043$)	Confirmative for motor symptoms

UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr stages; sign., significant.

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Appendix Table 3. Characteristics of vitamin D supplementation studies in patients with basal ganglia disorders.

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Diseases	Author	year	Country	Sub-jects (n) T/C	Study design	Period	Dose (application)	Clinical effect	Other effects
Parkinson's disease	Hiller [51]	2018	USA	27/24	RCT	16 w	10,000 IU/d (p.o.)	Balance improvement	no adverse events
	Habibi [52]	2018	Iran		RCT	12 w	1000 IU/d (p.o.)	no improvement	
	Suzuki [36]	2013	Japan	56/58	RCT	12 m	1200 IU/d (p.o.)	stabilizing effect	no adverse events
RLS	Wali [66]	2015	Saudi Arabia	def. pts (12)	open label	12 w	28,000 IU/w (p.o) or 200,000 IU/m (i.m.)	improvement	vitamin D serum level correction
	Wali [67]	2019	Saudi Arabia	all pts (22)	RCT	12 w	50,000 IU/w (p.o.)	no improvement	
	Tutuncu [115]	2020	Turkey	def. pts (19)	SCCS	8 w	50,000 IU /w (p.o.)	improvement	vitamin D serum level increase
Tics	Gemawat [116]	2017	India	all pts (34)	RCT	24 w	not specified	improvement	
	Li [73]	2019	China	36 def. pts /84 (5–14 ys)	open lable	12 w	300 IU/kg/d (<5000 IU/d) (p.o.)	improvement	vitamin D serum level increase
Dyskinesia L-dopa-induced	Habibi [52]	2018	Iran	all pts (120)	RCT	12 w	1000 IU/d (p.o.)	no improvement	

RCT, randomized controlled trial; SCCS, prospective self-controlled case study; n.s., not specified; p.o., per os; i.m., intra muscular; /d, daily; /w, weekly; /m, monthly.
def. pts.: Vitamin D deficient patients (<50 nmol/L).

benefit profile, we and others [113] believe that there is adequate scientific justification already to advise practitioners to monitor VitD levels and supplement as needed.

Abbreviations

AD, Alzheimer's disease; BG, basal ganglia; BGDs, basal ganglia diseases; H&Y; Hoehn and Yahr; HC, Huntinton's chorea; IRLSSG-RS; International Restless Legs Syndrome Study Group rating scale; MS, multiple sclerosis; PD, Parkinson's disease; RLS, Restless legs syndrome; TDs, Ticdisorders; UPDRS, Unified Parkinson's Disease Rating Scale; VDR, vitamin D receptor; VitD, Vitamin D; YGTSS, Yale Global Tic Severity Scale.

Author Contributions

CNH and BH designed the research study. CNH performed the research. CNH and BH analyzed the data. CNH and BH wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Appendix

See Appendix Tables 1,2,3.

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