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A Short Review and Hypothesis: Does Vitamin D's Protective Role Against Ischemic Stroke a Consequence of Its Negative Connection to Parathyroid Hormone (PTH) Levels?

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ABSTRACT

A short hypothesis that connects the dots regarding the Vitamin D – PTH hormone cycle and its impact on Ischemic Stroke. This review will bring evidence of a negative correlation between Vitamin D and Parathyroid Hormone levels and suggest that this correlation is the reason for the hazardous relationship between lacking vitamin D levels and the formation of aneurysm and stroke. This connection between Vitamin D and Ischemic Stroke should be thoroughly examined for a possible therapeutic effect of vitamin D supplementation while the Vitamin D-PTH hormone negative correlation should be further studied for its possible involvement in stroke but also in other bodily hazards stemming from insufficient Vitamin D levels.

Keywords

Ischemic Stroke, Vitamin D, Parayhtroid Hormone, PTH, Calcium.

Background

Vitamin D correlates negatively with Parathyroid Hormone which leads to Calcium transfer from the bones to the blood stream. The first time I've learned of the negative correlation between Vitamin D and Parathyroid Hormone (PTH) was on this study called "A global study of Vitamin D status and parathyroid function in postmenopausal women with osteoporosis: Baseline data from the multiple outcomes of raloxifene evaluation" by Lips et al. [1], they observed (in their own words) that "Serum PTH correlated negatively with serum 25OHD ($r = -0.25$; $P < 0.001$). This significant negative correlation was observed in all regions. When serum 25OHD was less than 25, 25-50, or more than 50 nmol/L, respectively, mean serum PTH levels were 4.8, 4.1, and 3.5 pmol/L, respectively (by ANOVA, $P < 0.001$)" [1].

Since then I've found ample proof for this negative correlation, just to bring a few examples, this study by Martins et al. [2], that found "It was also shown that there was a negative correlation between 25(OH)D and PTH levels" or this study by Chen et al. [3], that found (according to their highlights) that "25(OH)D and iPTH were inversely correlated across sex and different stages of age in outpatients with normal kidney function/ The correlation of 25(OH)D and iPTH was independent of age, sex, creatinine, calcium and phosphate/ The inverse correlation of 25(OH)D and iPTH was observed over the entire spectrum of 25(OH)D concentrations"[3]. Other studies, in their turn, showed similar results: "serum PTH was lowest in the group with a serum 25-hydroxyvitamin D level of more than 18 ng/mL but highest in the group with a serum 25-hydroxyvitamin D level of less than 10 ng/mL" say Steingrimsdottir and co [4]. Mosiehr and co. assessed studies that checked Vitamin D supplementation and its impact on Parathyroid Hormone levels [5]. Their Results: "Thirty-three vitamin D supplementation RCT were included. Vitamin D supplementation significantly raised circulating 25-hydroxyvitamin D (25(OH)D) with significant heterogeneity among studies with a pooled mean difference (PMD) of 15.5 ng/ml (test for heterogeneity: $P<0{\cdot}001$ and $I2=97{\cdot}3$ %). Vitamin D supplementation significantly reduced PTH level with PMD of $-8{\cdot}0$ pg/ml, with significant heterogeneity ((test for heterogeneity: $P<0{\cdot}001$) and the I2 value was $97{\cdot}3$ %) [5].

What is Paraythroid Hormone? The common medical knowledge is as such [6]: "Parathyroid hormone (PTH) is a hormone your parathyroid glands release to control calcium levels in your blood. It also controls phosphorus and vitamin D levels. If your body has too much or too little parathyroid hormone, it can cause

symptoms related to abnormal blood calcium levels" [6]. What the hormone actually does is raise calcium blood levels by releasing calcium from the bones to the blood stream, this calcium transfer is considered to be beneficial somewhat but it seems the vitamin D deficiency correlating with the Hormone production makes it a symptom of low vitamin D levels, The lower the levels of sunlight exposure, the more intense this process of bone deterioration into the blood stream. One disease characterized by deterioration in bone density is Osteoporosis where Vitamin D is part of the current treatment, allegedly to help the absorbent of Calcium to the bones whereas it's more likely that the vitamin D supplementation reverses the process of PTH secretion, leading to elevated bone density and even more importantly, to clearance of Calcium from the bloodstream.

This study by D.Phil et al. [7] tried a treatment with Sodium Fluoride, Vitamin D and Calcium in Osteoporotics and concluded that "In order to restore bone mass in osteoporotic subjects without producing roentgenographic or microscopic evidence of fluorosis, a therapeutic regimen of 50 mg of sodium fluoride and at least 900 mg of calcium per day and 50,000 units of vitamin D twice weekly is recommended." [7].

The first result of searching for "Vitamin D Osteoporosis" in google, to show today's current knowledge leads to this result from the Royal Osteoporosis Society [8]: "Vitamin D helps your body absorb and use calcium, which gives your bones their strength and hardness. There are three ways you can get vitamin D: Low vitamin D levels could increase your risk of osteoporosis and broken bones. And a severe shortage of vitamin D causes rickets and osteomalacia, which is soft, weak bones" [8]. However, this article I'm writing is not on Osteoporosis but on Ischemic Stroke and its connection to Vitamin D deficiency, perhaps through this mechanism of PTH elevation being a consequence of such deficiency. The Calcium transferred from the bones to the blood or the reversal of this process is, according to this logic, what leads to Vitamin D's role in Stroke.

Vitamin D and Ischemic Stroke, Going Through the Literature

According to Min Su Kim et al. [9] "192 patients were finally included and divided into three groups: Vit D sufficient (n = 28), insufficient (n = 49), and deficient (n = 115). Multivariate analysis showed that the Vit D deficient group presented with a higher risk of initially severe stroke (p = 0.025) and poor functional outcomes on the BBS (p = 0.048), MFT (p = 0.017), K-MMSE (p = 0.001), K-MBI (p = 0.003), and mRS (p = 0.032) compared to the Vit D sufficient group. Vit D deficiency", they say "may be associated with severe initial stroke and poor short-term post-stroke functional outcomes" [9].

Fahmy et al. observed 48 stroke patients in comparison to healthy controls and checked for their vitamin D levels. Their results: "Stroke patients had significantly lower serum vitamin D levels compared to healthy subjects. Vitamin D deficiency and insufficiency were significantly prevalent among patients compared to healthy controls. Significant negative correlation was detected between serum vitamin D and NIHSS scores on admission and after 72 h. Significant negative correlation was also detected between serum vitamin D and mRS scores on discharge and after 3 months. An increased risk of stroke of 2.88 times was found in patients with insufficient vitamin D in comparison to sufficient subgroup, and this likelihood increases to be 13.78 times in the deficient compared to sufficient subgroups" [10].

Majumdar and co. found results along the same lines: "The relationship between vitamin D deficiency and stroke was cross-sectionally evaluated in the high-risk Asian Indian population. Age- and gender-matched, 239 ischemic stroke patients and 241 control subjects were recruited. Vitamin D status was estimated by measuring serum 25-hydroxyvitamin D (25(OH)D) levels. After multivariate adjustment for a range of potential covariates in a logistic regression model, an inverse association was found between serum 25(OH)D concentration and risk of ischemic stroke: subjects with severely low 25(OH)D levels (<9.33 ng ml−1) were found to be at 3.13-fold (95% confidence interval (CI), (1.22–8.07)) increased risk of ischemic stroke as compared with those with high levels"[11].

Alfieri et al. aimed to examine if vitamin d deficiency is associated with ischemic stroke and their results are as follows: "Patients had lower levels of 25(OH)D, higher frequency of VDD (43.45% vs. 5.08%, OR: 16.64, 95% CI: 5.66–42.92, $p<0.001$), and higher inflammatory markers than controls ($p<0.05$). Patients with VDD showed increased high sensitivity C-reactive protein (hsCRP) levels than those with VDS status ($p=0.043$); those with poor outcome presented with lower 25(OH)D levels than those with good outcome ($p=0.008$); moreover, 25(OH)D levels were negatively correlated with mRS after three-months follow-up ($r=-0.239$, $p=0.005$)" [12].

Zhao-Nan et al. checked for vitamin d deficiency impact on poor clinical outcome after stroke. Their findings: The cut point of 25(OH) D level for vitamin D deficiency was 20 ng/ml. In the present study, 266 nondiabetic subjects with stroke were included; 149 out of the 266 patients were defined as vitamin D deficiency (56%). The poor outcome distribution across the 25(OH) D quartiles ranged between 64% (first quartile) and 13% (fourth quartile). In those 149 patients with vitamin D deficiency, 75 patients were defined as poor functional outcomes, giving a prevalence rate of 50% (95% confidence interval (CI): 42–58%). In multivariate analysis models, for vitamin D deficiency, the adjusted risk of poor functional outcomes and mortality increased by 220% (odds ratio (OR): 3.2; 95% CI: 1.7–4.2, P<0.001) and 290% (OR: 3.9; 95% CI: 2.1–5.8, P<0.001), respectively"[13].

Russel et al. in Bangladesh found results along the same lines. Here's from their abstract: "Objective: This study aimed to investigate the relationship of vitamin D status among acute ischemic stroke patients for assessing initial severity and short-term outcome. Methods: Fifty-one acute ischemic stroke patients and 51 matched healthy control subjects participated in the study. Subjects were divided according to vitamin D level into deficient,

insufficient, and sufficient groups. National Institute of Health Stroke Scale (NIHSS) on admission and after 72h and modified Rankin Scale (mRS) on discharge and after 3months were performed for all patients. Results: Acute ischaemic stroke patients (9.8%) had significantly lower serum vitamin D levels compared to healthy subjects (5.8%). In patients, serum vitamin D level ranged from 5 to 41ng/ml with a mean of 19.4 ± 9.98ng/ml. In controls, serum vitamin D levels ranged from 6 to 48ng/ml with a mean of 30.3±10.48 ng/ml. Vitamin D deficiency and insufficiency were significantly prevalent among stroke patients (66.7%) compared to healthy controls (51.9%). Significant correlation was detected between serum vitamin D and NIHSS scores on admission and after 72hrs (p=0.007). Significant correlation was also detected between serum vitamin D and mRS scores on discharge and after 3months (p=0.004). The patients with 'not sufficient' vitamin D (i.e. deficient and insufficient) were 11.2 time more likely to report severe stroke (p=0.006)" [14].

Selim et al. Examined "138 acute stroke patients and 138 age- and sex-matched controls from subjects attending outpatient clinic for other reasons". Their results: "Stroke patients had significant lower levels of vitamin D compared with the control group. Vitamin D deficiency remained significantly associated with the NIHSS stroke severity score and the mRS 3-month stroke outcome after controlling for other significant factors such as age, dyslipidemia, and infarction size using multivariable logistic regression analysis"[15].

Not Enough Data on Vitamin D Supplementation Trials in Human Subjects

Unlike the amount of studying on Vitamin D levels in stroke patients, the supplementation of vitamin d to stroke patients has yet to be thoroughly researched. In one study [16], they dvided the stroke patients to two groups, an intervention group and nonintervention group. The mean Vitamin D levels were much lower at onset than at admission and checkup, below 20 ng/ml at onset for both groups. However, the intervention received just one dosage of vitamin d ("received a single dose of 6 lac IU of Cholecalciferol Intramascular (IM) injection) [16]) and didn't show much separation from the nonintervention group at admission (32.50±11.61 for the intervention group and 35.82±8.56 for the nonintervention group) and follow up (around 38 for both groups) [16] so even though the study found better results in the intervention group it's hard to assess them to vitamin D levels. We did see the Vitamin D levels when the stroke happened were remarkably lower than in admission and follow up both for the intervention and nonintervention groups.

Conclusion

Vitamin D's impact on PTH levels could be the reason its deficiency correlates with stroke

I started this review explaining the negative correlation between Vitamin D and Parathyroid Hormones levels, Hyperparathyroidism stemming from low vitamin D levels could be responsible to an elevation in blood calcium levels that in turn could lead to the accumulation of an aneurysm and Ischemic Stroke. In fact, Ischemic stroke might be just one of the negative consequences of this correlation like for example Osteoporosis which is currently treated with Vitamin D. There has been very few studies who examined Vitamin D therapy to Ischemic Stroke patients, most of them shown positive results but their designs were lacking. A thorough examination of Ischemic Stroke treatment by continuous Vitamin D supplementation is therefore urgently needed.

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