

# Hypovitaminosis D: A Contributor to Psychiatric Disorders in Elderly?



Jennifer Ford, M.S.L.P., M.D.<sup>1</sup>, Ana Hategan, M.D.<sup>1,2</sup>, James A. Bourgeois, O.D., M.D.<sup>1,2</sup>, Daniel K. Tisi, R.D., M.Sc.<sup>2</sup>

<sup>1</sup>Department of Psychiatry and Behavioural Neurosciences, Michael G. DeGroot School of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, ON; <sup>2</sup>St. Joseph's Healthcare Hamilton, West 5th Campus, Hamilton, ON

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## ABSTRACT

### Background

Hypovitaminosis D is unrecognized and remarkably common in geriatric patients, with various clinical manifestations. The purpose of this study was to prospectively assess the vitamin D (VD) status in newly admitted psychogeriatric patients, and to study the correlation of VD status with indicators of calcium metabolism.

### Methods

A valid VD sample, as measured by serum 25-hydroxyvitamin D (25-OHD), was obtained from nine consecutive psychogeriatric inpatients (66% women), during a one-month period in 2011. The Research Ethics Boards at St. Joseph's Healthcare Hamilton approved this project.

### Results

All participants showed VD inadequacy (defined as 25-OHD  $\leq$  75 nmol/L) with a mean level of serum 25-OHD of 45.5  $\pm$  14.6 (range 28.5–73.4) nmol/L. None of the patients in the sample met criteria for VD deficiency (currently defined by expert consensus as 25-OHD  $<$  25 nmol/L). Mean serum VD levels were lower in females (38.8  $\pm$  9.8 nmol/L) than in males (59.0  $\pm$  14.3 nmol/L),  $p = .03$ . Magnesium and PTH were both higher in females ( $p = .03$  and  $.02$ , respectively). Univariate linear regression analysis showed that VD levels were strongly negatively associated with magnesium ( $p = .001$ ) and PTH ( $p = .02$ ).

### Conclusion

Since research links VD deficiency to psychiatric conditions, high rates of insufficiency in this population is very common and routine supplements are strongly suggested, regardless of patients' living environment.

**Key words:** vitamin D, vitamin D insufficiency, geriatric, acute inpatient, psychiatric disorders

## INTRODUCTION

In geriatric psychiatric disorders, vigilance for potentially reversible causes of morbidity and mortality is especially important. Traditionally the focus has been on metabolic indices such as TSH and B12. Recently, some authors have suggested the importance of screening for VD sufficiency, as well. Serum concentration of 25-OHD, or calcidiol, is the best indicator of VD status.<sup>(1)</sup> Estimating the exact prevalence of VD deficiency has been difficult due to lack of consensus regarding both optimal and frankly deficient VD levels among experts in the field. Expert consensus within the field suggests that a minimum VD level of 75 nmol/L is desirable as the lower end of the normal range.<sup>(2)</sup> A recent review by Schwalfenberg et al.<sup>(3)</sup> found that up to 97% of the general Canadian population showed inadequate VD levels (low end of adequate VD level was defined as about 80 nmol/L in most studies included in this review). This finding led them to declare the current state of VD status to be a public health crisis.<sup>(3)</sup> However, based on the 2007 to 2009 Canadian Health Measures Survey, Statistics Canada<sup>(4)</sup> indicated that only about 5% of males and 3% of females aged 6 to 79 were considered VD deficient (with a cutoff level defined as 25-OHD  $<$  27.5 nmol/L).

These results were obviously based on much lower VD cutoff levels to define VD deficiency, which were set in 1997 by the Institute of Medicine (IOM).<sup>(5)</sup> Consequently, the IOM was recently requested by the Canadian and U.S. governments to conduct a review of data pertaining to calcium and VD requirements; new dietary intake guidelines were identified in 2010, which tripled the VD daily dietary allowance to 600 international units (IU) for ages 1–70, and 800 IU thereafter.<sup>(5)</sup> According to the IOM, a serum concentration of 50 nmol/L was sufficient for 97% of the population, including bone health as the main endpoint.<sup>(5)</sup> Using these levels, a recent study found

that about a quarter of Canadians had a VD level less than 50 nmol/L.<sup>(6)</sup> But the 2010 IOM recommendations were widely criticized, as the focus was on giving randomized clinical trials the most weight and excluding cohort and other studies about the role of VD in lowering the risk of several chronic diseases that did not meet its stringent criteria of evidence. In contrast to the IOM report, in the large population-based National Health and Nutrition Examination Surveys (NHANES) analysis, bone density increased with higher 25-OHD levels far beyond 50 nmol/L in younger and older adults, suggesting that the IOM threshold recommendation is suboptimal, even for bone health.<sup>(7)</sup> As well, in the 2010 position paper on VD by the International Osteoporosis Foundation, a threshold of 75 nmol/L for optimal fall and fracture reduction and a daily VD dose of 800 to 1,000 IU for individuals aged 60 and older was recommended.<sup>(8)</sup> At a minimum, the IOM doubled the safe upper limit to 4,000 IU of daily VD in support of a greater safety margin.<sup>(5)</sup> Therefore, will this “normal” low end range of VD level truly hold? The “Vitamin D and Omega-3 Trial,” or VITAL, which is currently underway, aims to sort out the inconclusive and conflicting evidence from earlier research.

## METHODS

This prospective consecutive case series study performed in an Ontario university hospital was an audit of hospitalized psychogeriatric patients, admitted consecutively during a one-month period, starting September 20, 2011. Patients were assessed for VD status, as measured by fasting serum 25-OHD, total intact parathyroid hormone (PTH), total calcium, phosphorus, and magnesium. The confirmed cases of VD inadequacy were reviewed in detail to determine estimates of the prevalence and clinical profiles. Potentially confounding factors (e.g., age, sex, number of chronic conditions, and number of medications) and explanatory factors (e.g., season of data acquisition, household type) were taken into consideration. All statistical analyses were conducted using the SAS version 9.2 (SAS Institute Inc., Cary, NC).

## RESULTS

Table 1 summarizes the demographic, diagnostic features, and laboratory findings of the enrolled subjects. All patients were living in Ontario during the previous three months; eight were Caucasian and one was of Asian descent. They were either admitted through the emergency department or directly from the community. All the patients had vitamin B12 levels performed upon admission. Medical history included cardiac disease in 77% ( $n = 7$ ); osteoporosis in 66% ( $n = 6$ ); pain syndromes, such as chronic discogenic back pain, osteoarthritis, and/or fibromyalgia, in 55% ( $n = 5$ ); history of falls in 44% ( $n = 4$ ); hypovitaminosis B12 in 22% ( $n = 2$ ); and diabetes mellitus in 8% ( $n = 1$ ). Dementia with co-morbid

depression and psychosis were the Axis I disorders in 5 of 9 (55%) of patients.

The participants ( $n = 9$ ) showed a mean level of serum 25-OHD of  $45.5 \pm 14.6$  (range, 28.5–73.4) nmol/L (see Table 2). VD insufficiency ( $25\text{-OHD} \leq 75$  nmol/L) affected 100% of the participants at this time in the year. No statistical difference of VD levels was found in participants from private households (mean  $42.7 \pm 6.3$ ) versus institutions (mean  $47.8 \pm 7.7$ ), or in number of medications. As none of the subjects had been assigned a diagnosis of hypovitaminosis D prior to admission, the mean age at diagnosis was  $77.4 \pm 7.6$  years. Serum 25-OHD levels were lower in females ( $n = 6$ ;  $38.8 \pm 9.8$  nmol/L) compared with males ( $n = 3$ ;  $59.0 \pm 14.3$  nmol/L),  $p = .03$ ; however, this significance was eliminated once controlled for magnesium and PTH. Magnesium and PTH were both higher in females compared with males ( $0.93 \pm 0.02$  vs.  $0.83 \pm 0.03$ ;  $p = .03$ ; and  $10.27 \pm 1.6$  vs.  $3.73 \pm 0.37$ ;  $p = .02$ , respectively). There was an inverse correlation using Pearson's coefficients between VD and calcium, as well as between VD and PTH. Univariate linear regression analysis revealed that VD was negatively associated with magnesium ( $p = .001$ ), and PTH ( $p = .02$ ), with each model accounting for 78% and 52% of VD variability, respectively.

## DISCUSSION

This prospective cohort of consecutively admitted psychogeriatric inpatients during a one-month period, considered to mark the transition to the autumn season, revealed inadequate serum 25-OHD found in all participants. Seasonal effects on VD levels, with lower concentrations in autumn and winter than in spring and summer, have been reported.<sup>(9,10)</sup>

Our findings are not surprising as VD deficiency is globally widespread, particularly within nations at a significantly northern latitude, such as Canada. This is due to the ultraviolet B (UVB) rays being stronger near the equator and weaker at higher latitudes, therefore interfering with the production of VD from the sun.<sup>(11)</sup> The most important VD deficiency contributing factor is considered to be insufficient UVB rays exposure. This is needed to cutaneously convert 7-dehydrocholesterol into cholecalciferol (the preliminary form of 25-OHD). However, serum 25-OHD measurements are influenced not only by ecological factors (e.g., latitude, season, local weather), but also by individual factors (e.g., race, skin pigmentation, age), and lifestyle factors (e.g., sunshine exposure, dietary, clothing coverage). Although all our subjects were fair-skinned, darker skin was found to be a risk factor for VD deficiency in regions above and below  $36^\circ$  in the Northern and Southern hemisphere, respectively.<sup>(6)</sup> Unprotected sun exposure is not recommended as a way to obtain VD due to increased risk of skin cancer. Notably, with correctly applied sunscreen, the production of VD is reduced by more than 90%.<sup>(11)</sup>

Additionally, previous research indicated that institutionalized older adults are at increased risk of VD deficiency.<sup>(12)</sup>

TABLE 1.

Demographics, laboratory, and clinical features of nine geriatric cases of hypovitaminosis D on an acute inpatient psychiatry unit

Case#	Age	Sex	Household	Axis I Diagnoses	Axis III Diagnoses	Laboratory		
						25-OHD	PTH	Ca/Mg/PO4/B12
1	88	F	Home	DAT Psychosis NOS	CAD, HTN, OP, chronic pain, constipation	38	12.1	2.37/0.97/0.88/744
2	64	F	Institution	Somatoform Disorder NOS	FM, gait disturbance, falls, chronic pain	36.3	16.5	2.36/1.0/0.8/605
3	69	M	Home	Dementia due to GMC Psychosis NOS	CAD, Parkinson disease, OP, falls	58.9	4.2	2.27/0.86/260
4	75	M	Institution	Mixed Dementia	CAD, HTN, DM, OP, chronic pain, falls, constipation	73.4	3.0	2.27/0.77/1.02/203
5	74	F	Institution	Dementia due to GMC MDD	CAD, HTN, OP, falls, constipation	49.3	6.1	2.23/0.85/1.01/303
6	81	M	Institution	DAT MDD	CAD, constipation	44.7	4.0	2.32/0.87/0.95/377
7	83	F	Home	DAT	HTN, OA, OP, hypovitaminosis B12 <sup>a</sup>	29.1	8.6	2.49/0.8/1.3/648
8	81	F	Home	Mixed Dementia Psychosis NOS	HTN, OA, OP	51.5	6.8	2.49/0.8/1.3/355
9	82	F	Home	DAT	Hypovitaminosis B12 <sup>a</sup>	28.5	11.5	2.23/0.96/1.35/741

<sup>a</sup> Diagnosed and corrected preadmission

CAD = coronary artery disease; DAT =dementia of the Alzheimer’s type; DM = diabetes mellitus; FM=fibromyalgia; GMC = general medical condition; HTN = hypertension; Institution = retirement home, nursing home, hospital; MDD = major depressive disorder; OA=osteoarthritis; OP = osteoporosis; PTH = parathyroid hormone.

However, 55% of our inadequate VD geriatric sample were living at home during the previous three months; therefore, elderly are at increased risk of VD deficiency, regardless of the household type. The aging process also decreases the production of VD precursors in the skin and conversion of VD to its active hormone form, 1,25-dihydroxyvitamin D, or calcitriol. Therefore, these factors may render subsets of populations in Canada to be particularly at high risk for deficiency.

It is known that low serum 25-OHD induces PTH production, maintaining serum calcium and phosphate homeostasis at the expense of increased bone resorption, increasing calcium reabsorption by the kidney, and increasing renal production of calcitriol, which increases intestinal absorption of calcium. Although controversial and likely significantly underestimating the variability of the PTH assay,<sup>(13)</sup> Chapuy et al.<sup>(14)</sup> suggest that 25-OHD levels above 78 nmol/L are required to avoid increases of PTH. In the present study, elevated PTH occurred with increasing frequency as the serum 25-OHD fell with a threshold level of about 40 nmol/L. Interestingly, lower VD levels were associated with elevated PTH and higher magnesium levels (see Figure 1). Individually, each univariate regression model (magnesium and PTH) accounted for 78% and 52% of the variability of VD levels in the study population. Magnesium is important for proper metabolism of VD and a decreased production of calcitriol was shown to occur with lower magnesium levels.<sup>(15)</sup> Although the negative association

TABLE 2.

Characteristics of study population and by location prior to admission

Variables	Overall	Institution	Home	Pr>F
Age (y)	77.4±2.5	75.2±3.2	80.2±4.03	NS
25-OHD	45.5±4.9	47.8±7.7	42.7±6.3	NS <sup>a</sup>
Total Calcium	2.31±0.03	2.32±0.05	2.31±0.02	NS
Parathyroid Hormone	8.09±1.5	8.78±2.36	7.22±1.9	NS
Magnesium	0.90±0.02	0.89±0.04	0.91±0.03	NS
Phosphate	1.05±0.07	1.10±0.10	0.98±0.07	NS
Number of Medications	8.33±0.97	7.60±1.72	9.25±0.48	NS
Gender (% Male)	33.3	20	50	NS

<sup>a</sup> Controlled for magnesium and parathyroid hormone.

of magnesium with VD levels is an incidental finding, this relation has not been reported previously, and further attention is necessary to elucidate any correlation.

Although optimal VD status has created an ongoing debate, recent studies associate VD deficiency with increased morbidity, including infectious diseases<sup>(16,17,18)</sup> (e.g., common cold, seasonal influenza A, and tuberculosis),

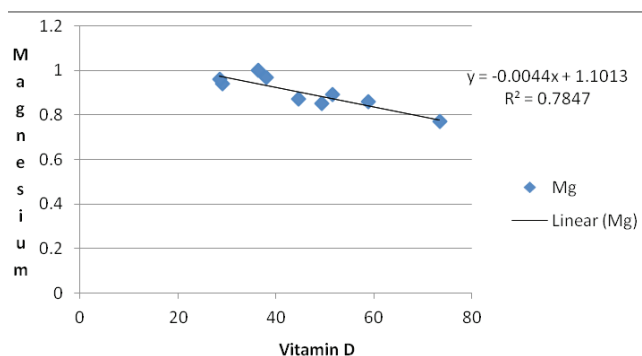


FIGURE 1. Regression analysis between vitamin D and magnesium

multiple sclerosis,<sup>(19)</sup> cardiovascular disease,<sup>(20)</sup> colon and breast cancer,<sup>(21,22)</sup> and diabetes.<sup>(23)</sup> Numerous studies indicate that VD, often at higher concentrations and intakes than those recommended by the IOM, may be beneficial for the prevention of these medical conditions. For example, recent studies found that while a circulating 25-OHD levels of > 80 nmol/L is associated with normal mineral metabolism, the optimal suggested level for breast cancer prevention should be  $\geq 100$  nmol/L.<sup>(22,24)</sup> Furthermore, a combined analysis of multiple studies found that taking modest levels of VD supplements was associated with a statistically significant 7% reduction in mortality from any cause.<sup>(25)</sup>

Most organs and tissues in the body have VD receptors including skeletal muscles.<sup>(26)</sup> While the causal link between VD deficiency, bone disease, and subsequent falls by associated decreased muscle strength is overwhelming,<sup>(7)</sup> low VD was also found to be an independent risk factor for falls among the elderly.<sup>(27)</sup> Notably, a fall history in our cohort was reported in 44%. Additionally, VD insufficiency is an established risk factor for osteoporosis;<sup>(28)</sup> this medical history was present in two-thirds of our participants. Interestingly, VD deficiency was also shown to play an increased role in major psychiatric disorders. An association between VD deficiency and seasonal depression,<sup>(29)</sup> geriatric depression,<sup>(30)</sup> anxiety disorders,<sup>(31)</sup> schizophrenia,<sup>(32)</sup> and alcoholism,<sup>(32)</sup> was reported. In individuals with secondary hyperparathyroidism, low serum 25-OHD was associated with higher depression scores<sup>(33)</sup> and, in those with fibromyalgia, there was an association with both depression and anxiety.<sup>(32)</sup> A protective effect of circulating 25-OHD on neurocognitive function was also reported.<sup>(34)</sup> Remarkably, considerable psychiatric improvement coincided with VD treatment in some of the patients whose deficiency was treated.<sup>(35)</sup> The benefits of VD beyond bone and muscle are currently based on epidemiological reports, but the VITAL study intends to answer these questions.

Despite the high rate of VD deficiency found in this sample, none of the patients were on VD supplement at admission, including multivitamins, and calcium/cholecalciferol tablets. There are several possible explanations for this. Higher demand for testing VD in recent years has led to governmental agencies trying to restrict the number of VD

tests ordered by physicians.<sup>(36)</sup> Therefore, routine testing of VD status has been discouraged because of cost and the safety of routine supplements. Simple oral supplementation with VD (in the absence of clinical malabsorption) is sufficient. However, polypharmacy is a common problem encountered in the elderly, and clinicians may be reluctant to empirically start VD treatment. As there is no consensus on optimal VD levels, clinicians may have to rely on considering factors that may influence the VD status such as age, latitude, skin pigmentation, and adequate sun exposure. Thus, little evidence guides clinicians on when to screen for VD deficiency, and if deficiency is found, an appropriate starting VD dosage.

The authors certainly acknowledge that there are clear limitations to any interpretations deriving from such small sample size, with dementia being the most prevalent diagnosis (88.8%), and consisting of only psychiatric inpatients, as well as not being able to account for dietary intakes prior to commencement of the study. Therefore, bias in the reporting of the data cannot be excluded.

## CONCLUSION

Despite previous reports of higher rates of low VD in those institutionalized, VD insufficiency is so widespread that the authors advocate routine supplementation of VD is warranted in elderly patients with late-onset psychiatric disorders, regardless of their living arrangements. The high rate of co-morbidity suggests that monitoring VD levels may have additional value in improving the general health in this population. Future larger studies are required to determine if 25-OHD can be used as a biomarker in the clinical determination and management of psychiatric disorders.

## CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

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**Correspondence to:** Ana Hategan, M.D., Department of Psychiatry and Behavioural Neurosciences, Division of Geriatric Psychiatry, Michael G. DeGroote School of Medicine, Faculty of Health Sciences, McMaster University, St. Joseph's Healthcare Hamilton, West 5th Campus, 100 West 5th Street, Hamilton ON L8N 3K7, Canada  
**E-mail:** ahategan@stjosham.on.ca