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Vitamin D, the Vitamin D Receptor and Chronic Disease --

Brain Lesions, Vascular Calcification and Osteoporosis: Two Views of Vitamin D Supplementation and Parathyroid Hormone

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Overview This article discusses new Duke University research showing a highly significant correlation (p = 0.007) between higher vitamin D intake and MRI brain lesions (http://www.fasebj.org/cgi/content/meeting_abstract/21/6/A1072), as well as the potential for lesion reversal. These lesions have been associated with cognitive impairment, stroke, psychiatric disorders and mortality. This article also discusses the levels of vitamin D and calcium needed to avoid osteoporosis and vascular calcification in the light of new research on blockage of the vitamin D receptor due to bacterial products and elevated 25D.

Introduction

Recently, there have been increasing calls for higher levels of vitamin D intake, particularly for the prevention and treatment of various chronic conditions, including osteoporosis in older adults (1). Such calls for increasing vitamin D intake continue, despite a large meta analysis that recently failed to show that vitamin D when added to calcium supplementation had a significantly greater reduction in fractures than calcium alone (2, 3). And another large meta analysis looking at mortality over a 1-5 year period, also failed to show a statistically significant effect from vitamin D supplementation (3, 4). Despite these meta analyses, vitamin D supplementation is still being urged at higher and higher levels and some contend that there is still evidence in its favor (1, 5, 6).

There is another emerging view that centers on the vitamin D receptor (VDR). It is based on the work of Trevor Marshall, Ph.D., who argues that vitamin D receptor (VDR) competence is a crucial, but over looked factor in chronic disease (7, 8). His disease model is based on molecular modeling and clinical research that provides a model of chronic inflammatory disease (7, 8, 9). In this view, a properly functioning vitamin D receptor is seen as key to innate immune function (7, 10, 11).

This new work has revealed that the ability of the VDR to properly stimulate the innate immune system is impeded by high levels of vitamin D – (measured as the precursor form, the secosteroid 25D) - which binds and decreases the activity of the receptor. Thus higher levels of 25D decrease the ability of the active hormonal form of vitamin D, 1,25D, to activate the VDR. Bacterial products have been identified that also block the activity of the VDR (8). Sophisticated computer modeling has determined that olmesartan, an angiotensin receptor blocker, is able to displace substances that block the VDR and itself, activate the VDR (7, 8, 9). When combined with vitamin D reduction and low dose pulsed antibiotics, Marshall’s protocol is gradually able to eliminate cell wall deficient (CWD L-form) and biofilm bacteria at the heart of many unexplained inflammatory diseases. These treatment-resistant bacteria, acquired over a lifetime, are thought to stimulate inflammation in many diseases, ranging from sarcoidosis, "autoimmune" diseases and diseases of aging, such as diabetes, osteoporosis and cardiovascular disease.

As a result of the problems with VDR blockage just mentioned, this new view does not regard vitamin D supplementation and a higher 25D as generally beneficial for the treatment or prevention of chronic inflammatory diseases. These new findings call for a re examination of past research on vitamin D in the light of Marshall's work and other new research.

Association of Higher Vitamin D Intakes with Increased Volume of Brain Lesions
Although a few researchers have cautioned against a general recommendation for increased vitamin D and have stressed the need for more research (7, 13) these calls have not received much attention of late. A new study may help change this, especially when considered along with Marshall's work.

Researchers at Duke University (14) have found a correlation between higher intakes of vitamin D and increased brain lesions shown by MRI (white matter hyperintensities – WMH). Although calcium intake was also correlated with increased lesions, vitamin D was the only variable that retained its correlation with lesion volume in a multivariate analysis. This was true, despite the fact that vitamin D intake in the 232 patients never exceeded 1015 IU, and was seldom even above 800 IU (mean 341 IU). Calcium failed to show a correlation with lesion volume in the multivariate analysis, despite several patients consuming more than the recognized safe upper limit of 2500 mg (mean 1280 mg).

These MRI lesions have been shown to be associated with Alzheimer's disease and mild cognitive impairment (15), stroke (16), conduct disorder/attention deficit disorder and depression (17), bipolar disorder (17, 18), several measures of brain atrophy (19). Greater progression of lesion volume is also associated with poor outcomes in late life depression (22). In a community-based study of older adults, higher lesion volume was associated with a two-fold increase in death in the 11 years following the MRI assessment (20). In another study conducted over a 3 year period, the lesions increased in most patients, however in a small percentage of patients the lesions regressed slightly, leaving room for hope that they are reversible (3, 21).

Few other variables seem to predict the extent of lesions, although in some cases, vascular disease risk factors are associated with lesion volume (15). One study found that the only factor that predicted the future increase in lesion volume was the current lesion volume (21).

It appears that the lesions are related both to calcium deposition in blood vessels and to the degeneration of tissue that occurs in Alzheimer's disease (15). Below, the calcium deposition issue will be addressed.

Vascular Calcification and Osteoporosis
There have been increasing calls to increase intake of calcium and vitamin D based primarily on research on osteoporosis and fracture risk (1, 5, 6). The research discussed above, however indicates that vitamin D supplementation may increase the risk of vascular calcification and diseases associated with brain lesion progression and other chronic diseases.

This seems to pose a dilemma for patients. This is likely to be a very common dilemma in aging patients, since it is widely recognized that vascular calcification is frequently associated with osteoporosis (12). The question raised by the brain lesion study (14) is whether patients who supplement with calcium and/or vitamin D are increasing their risk of vascular calcification leading to blockage of arteries, heart attack and stroke, and the other neurological impairments associated with the brain lesions shown by MRI?

By looking more deeply into past research and into some new studies, one solution to this dilemma regarding supplementation becomes apparent. As mentioned above, a recent meta analysis indicates that calcium alone is probably as effective as calcium and vitamin D for improving fracture rates and bone density (2, 3). Furthermore, a team of researchers in Germany (23) recently reported that calcium and vitamin D together are no better than calcium alone in correcting disturbed bone metabolism in congestive heart failure. They noted that another team's finding (24) supported their own observations (23) and concluded that "calcium supplementation with 500 mg/day may be more effective than increasing 25(OH)D levels by 60 nmol/l [24 ng/ml]".

Thus, empirically, part of the answer with regard to supplementation may be to use supplemental calcium, but not supplemental vitamin D. However, many researchers still contend that adding vitamin D leads to superior results (1, 5, 6). The foundation of their reasons for seeking to obtain higher vitamin D levels (e.g., above 10-15 ng/ml) is related to parathyroid hormone production and this requires an examination of the most recent studies looking at this issue. What is revealed is that the foundation for recommending high 25D levels based on parathyroid hormone has many serious flaws.

The view that low vitamin D automatically causes poorer health status due to elevated PTH in all or most patients and that consuming more vitamin D results in long term improved health does not appear to be justified by the most recent analyses, as will be discussed below.

What is the Optimum Level of Vitamin D? Vitamin D and Secondary Hyperparathyroidism (SHPT)

Vitamin D supplementation is commonly recommended for osteoporosis based on studies that focus on what is purported to be a strong direct causal relationship between low 25D levels and elevated parathyroid hormone (1).

The parathyroid gland produces parathyroid hormone (PTH) when serum calcium levels are low. PTH elevation then causes increased conversion of the precursor 25D to the active 1,25D hormonal form in the kidneys. The elevated 1,25D is thought to lead to increased activation of the VDR, which increases calcium reabsorption in the kidneys, intestinal calcium absorption and mobilization of calcium from bone. These changes are important to maintain calcium levels within the narrow range necessary for life. However, a prolonged high PTH also increases excretion of phosphorus and has been associated with negative outcomes in bone density and longevity (25). The conventional view, is that secondary hyperparathyroidism occurs primarily when calcium intake is low, or when serum phosphate levels are high (usually due to reduced kidney function) or when vitamin D status (measured as 25D) is too low.

The levels of serum 25D recommended for optimal PTH levels and calcium absorption vary from 16 ng/ml (27) to 30 ng/ml and above (1, 5, 26). These recommendations are usually made based on cross sectional studies in which the precursor form of vitamin D, 25D, has been measured and the level of PTH has been reported. Many studies have used a statistical correlational analysis to determine what blood level of 25D is necessary to avoid an elevated PTH.

This relationship with PTH has led some to conclude that 15-20 ng/ml is adequate and led others to conclude 30-40 ng/ml of 25D is needed for optimal PTH levels and calcium absorption. The intake of vitamin D needed is said by some vitamin D proponents to be at least 800-1000 IU daily (6) and by others, 2,000 IU or more (26), although these values exceed the current suggested intake levels set by various government health agencies in Europe and North America. There is reason to question whether even the current 200-600 IU recommendations are appropriate, especially for some populations (7).

The following points regarding the causes of elevated parathyroid hormone in secondary hyperparathyroidism (SHPT) can be gleaned from a variety of recent studies. These points show that high levels of vitamin D ingestion are not necessary or desirable and that calcium supplementation is what deserves the greater focus.

1. PTH and vitamin D studies often do not take into account calcium intake and thus have been flawed.

A recent study points out one of the flaws in many of the studies on vitamin D and one of the reasons for their divergence with regard to the 25D levels they recommend (27). Most studies do not ensure adequate calcium intake before assessing the relationship between vitamin D and PTH. Aloia et al (27), in contrast, did ensure adequate calcium and concluded that 16 ng/ml was an adequate 25D level in the calcium replete patients they studied. They did a systematic review of studies that tried to determine the optimal 25D level based on PTH levels. They found that in the studies in which the calcium intake was adequate (exceeding 1000 mg daily), the estimated optimal 25D level to avoid SHPT was less than or equal to 20 ng/ml (50 nmol/L). It was the studies that reported lower calcium intake or did not consider it at all, that recommended the higher 25D levels.

2. PTH and patient outcome is usually normal when 25D is low as long as calcium intake is adequate.

When calcium intake is adequate, Aloia et al (27) found that only a small percentage of those with low 25D levels had elevated levels of PTH (see Figure 1). This was confirmed recently in a study that found that PTH levels were frequently normal in patients with even very low 25D (25). In these frail elderly patients with normal PTH and low 25D, the bone density and survival were comparable with those with higher vitamin D levels. By the same token, elevated PTH was associated with a poorer outcome, and this occurred whether or not vitamin D levels were considered normal or low.

3. Lowering PTH is neither necessary nor sufficient to improve bone status.

Besides the issue of calcium, there are other flaws in the work relating 25D to PTH. For instance, Schleithoff et al (23) reported that findings in congestive heart failure agreed with previous research showing that "a change in serum PTH levels is not necessary to result in a decrease in bone turnover markers in subjects with improved calcium supply." Thus lowering average PTH is not necessary to improve bone density.

Another study showed that lowering PTH is not sufficient to improve bone density. This was shown in the only study to date to directly compare supplemental calcium alone to vitamin D alone, which revealed that lowering PTH does not automatically improve BMD (25). They found that the addition of supplemental calcium alone or vitamin D alone were both effective in lowering PTH levels. Yet they found that the calcium supplementation had a significant benefit for bone density over the 4 years of the study, while the vitamin D did not.

4. Variation in 25D accounts for only a very small percentage of PTH variability.
Many studies make it clear that variation in 25D only accounts for a very small percentage of variation in PTH (e.g., 4%-10%), especially when there is adequate calcium intake (27). And other factors, such as low magnesium (29, 30), increasing age (31) or elevated serum phosphate and creatinine due to kidney disease are also implicated in contributing to elevated PTH (as discussed in reference 32). Saleh et al (32) found that most subjects with elevated PTH had normal values for calcium and vitamin D intake, as well as fractional calcium absorption. And they concluded that the cause of elevated PTH "is therefore probably a combination of factors." Another study looking at vitamin D intake, 25D levels and PTH in patients aged from 19 to 97 and found a strong relationship between PTH and kidney function as measured by creatinine levels particularly in older age groups (31). They found strong age-related differences in PTH that could not be explained on the basis of vitamin D intake alone.

5. Giving vitamin D to patients with low 25D and high PTH does not always normalize PTH.
Studies have noted that giving vitamin D to patients with low levels of 25D often does not bring the PTH down to normal levels (34, 35). For example, one patient in a study where several patients with myopathy associated with low 25D levels were studied, the 25D was raised through supplementation of vitamin D to 55 ng/ml and the PTH still was abnormally high (34). This supports the view that PTH may often be due to inflammation or some other cause, as discussed above, rather than being caused by low 25D.

6. The effect of 25D on calcium absorption is not as strong as some researchers contend.
The conventional view of vitamin D arose from research on Rickets in the middle of the last century. And this research indicates that a very low 25D level may occur under conditions of sun avoidance leading to bone abnormalities in children. Infants and children are most susceptible to this disease due to their high mineral requirements during phases of rapid growth. The response has been to supplement with vitamin D and calcium to help correct this condition.

Use of vitamin D is aimed at increasing the percentage of calcium absorbed via a VDR-dependent mechanism. Many countries have even added vitamin D to milk or other products. But in many cases, there is also inadequate calcium and/or phosphorus intake and often the contribution of the mineral deficiency is not assessed (36, 37). Most cases of Rickets occur in developing countries where malnutrition is widespread and the role of inadequate vitamin D relative to other nutritional factors (38) and acute or chronic infection (see discussion in reference 3), is unknown. In Nigeria, a careful study of children with Rickets revealed calcium deficiency to be the likely cause (39) but in other countries there may be more than one cause (38).

Despite a possible role for a small amount of exogenous vitamin D in selected cases, such as darker skinned infants living at high latitudes, recent proposals to greatly increase vitamin D supplementation for all infants and children (e.g., 26) seem ill-advised. The proposal is based on much of the same research that is discussed here and does not take into account VDR blockage at higher levels of 25D and the role of bacteria discussed above. Proponents argue that breast milk is too low in vitamin D, but it would seem that if high vitamin D in milk were crucial to health, humans would have evolved to supply it through a higher level in breast milk.

The position taken here is that sometimes a higher vitamin D e.g. (10 –15 ng/ml as compared to lower levels) may increase active calcium absorption in healthy patients with an unblocked VDR, but that it does so to a lesser extent than previously thought. Furthermore, consuming the recommended level of calcium is generally a safer and more effective solution to obtaining more calcium.

When it comes to adults, recent research (23, 24) indicates that calcium absorption is not increased as much by higher 25D as some have asserted (1, 41). A recent analysis showed that a change in 25D from 12 ng/ml to 40 ng/ml only increased the percentage of calcium absorption by around 9% (23, 24). Examining Figure 1 (24), it is quite doubtful that the relationship would have been significant if only the upper half of the 25D range had been examined (e.g., above 20 ng/ml). As it is, the relationship only explained about 12% of the variability in the percentage of calcium absorption (CV=0.12). Despite the relationship between calcium and absorption rate and 25D found in this study, no relation between 25D and measures of bone or calcium metabolism were found (24), which agreed with the findings of other research teams (23, 25).

7. Correlation does not imply causation – both 25D and PTH levels may be a direct or indirect result of inflammatory disease.

Despite all of the above flaws with the association of low vitamin D and elevated PTH, there is still some degree of association. However, correlation of two variables does not imply causation, since they may both be results of the same underlying disease process. It may be that just as some patients have excess thyroid production in chronic inflammatory disease, others may have excessive PTH production. Both may arise from chronic inflammation caused by bacteria or other factors that may be related to inflammation, such as low magnesium or reduced kidney function, as mentioned above. In the case of PTH, blockage of the Vitamin D receptor may also be involved in abnormal PTH when 25D reaches higher levels (7, 8).

The assumption that low 25D is the cause of high PTH may be viewed as analogous to the assumption that low 25D is a causal factor in a variety of diseases (e.g., cancer, autoimmune diseases) when instead they may both result from the disease process (see discussion of evidence and references, see 3).

As Michos et al noted (33), it may turn out that just as with folic acid and a number of other nutrients studied recently, a deficiency of vitamin D being associated with a disease, does not necessarily mean that patients will benefit from supplementation with it.

8. When increasing 25D to high levels does appear beneficial it may be due to short term immunosuppression leading to long term harm.

Another explanation for the reduction in average PTH with higher 25D levels (above 15-20 ng/ml) is in accord with Marshall's molecular modeling showing 25D blocks the VDR at higher levels. Higher levels of 25D could suppress inflammation by blocking the VDR (7), which has important effects on innate immunity (11). This effect would be particularly strong and occur at lower 25D levels in older people or patients with various chronic conditions, because bacterial products could also be contributing to VDR blockage (8).

A study by Schleithoff et al (42) showed that higher doses of vitamin D can, in fact, reduce TNF alpha, a pro inflammatory cytokine, in congestive heart failure patients. TNF alpha is an important cytokine involved in the immune response to pathogens. The immune suppressing effects of TNF blockage is supported by the increased danger of infection observed in patients taking drugs that reduce TNF alpha.

A reduction in TNF alpha is also known to be able to increase bone density as shown by a study of a drug that reduces available TNF alpha (42). This reduction of inflammation may account for the beneficial effect of high 25D levels on falls (44) bone density and fractures found in the short term in some studies (6). This anti-inflammatory effect may be responsible for a sometimes apparent improved calcium absorption (41, 47) and reduced PTH (23, 42) when 25D reaches high levels.

Although a reduced TNF alpha level indicating reduced inflammation may at first seem desirable, this is not necessarily the case. It could be harmful if one is also suppressing an immune response that is needed to fight chronic bacterial infection, which is now emerging as the underlying cause of many diseases (7, 8, 53, 54).

From the perspective of the new view of vitamin D and chronic disease, the ability of high 25D levels to bring average PTH down is more likely to be stemming from this immunosuppressive effect than any additional increase in active calcium absorption or utilization.

Summing up PTH and vitamin D studies

Thus, the above points indicate that a high 25D level is neither necessary nor sufficient to reduce levels of parathyroid hormone in SHPT. It may be true that when there are very low vitamin D levels, a competent VDR and an inadequate calcium supply, an increase in vitamin D (e.g., from 5 to 15 ng/ml) may lower PTH by increasing the fraction of calcium absorbed. But in chronic inflammatory diseases, new evidence indicates that there is not usually a fully competent VDR (3, 7, 55). And restoring calcium intake to adequate levels would be preferable, particularly in light of the newest research discussed here. The danger of blocking the VDR (7) and contributing to brain lesions (14) requires an urgent reassessment of recommendations regarding vitamin D.

This article has identified the many flaws in the research asserting the need for high 25D levels based on PTH levels. Much of what remains of the association between low 25D and high parathyroid hormone is likely to result from simple correlation without direct causation, particularly when 25D levels reach 25 ng/ml and higher. In other words, the observed values of the two variables arise from the same underlying inflammatory disease process rather than low 25D causing high parathyroid hormone. And in cases where levels of vitamin D above 25-30 ng/ml seem to benefit calcium absorption, this is typically more likely to be due to an immunosuppressive effect of the high 25D, particularly in older patients and the chronically ill.

Although the points listed above are contrary to the older view of vitamin D, they are nevertheless able to explain the data on PTH and vitamin D. In contrast, the conventional view of vitamin D can not explain why vitamin D is associated with increased brain lesions even when intake is below 1000 IU (14). Nor can the conventional view explain how patients on Marshall's protocol, who suffer from a variety of chronic diseases, demonstrate increased VDR activation, enhanced bacterial killing, and substantial improvement of symptoms as their 25D levels fall below 15 ng/ml (7, 55, 56).

What is the Cause of Vascular Calcification?
So, to return to the issue of vascular calcification discussed previously in connection with the brain lesion study, the question is what is the mechanism for vascular calcification and how might it be reversed? Current research has not been able to determine what causes vascular calcification except in rather extreme cases of end stage kidney disease and a few other situations when the calcium and/or phosphate concentrations in the blood reach very high levels (45).

However, one thing is agreed upon by all with regard to vascular calcification and that is "calcium begets calcium" (45). That is, once an area starts to calcify, calcification tends to increase in that area. This phenomenon is similar to what has been found in the brain lesions, where the increases in lesion volume over time occur mainly due to the large lesions increasing in size (21). A bacterial cause would fit this situation, since bacteria would tend to proliferate in an area once they are well established there.

Recent research has implicated bacteria as potentially being involved in atherosclerosis and vascular calcification (46, 48, 49). *Chlamydia pneumoniae* has been associate with heart disease, however there has been some inconsistency in results reported using PCR (49). More recent research has indicated that other methods can be more useful in that they can quantify the levels of bacteria, whereas PCR only detects presence or absence (46). Higuchi et al (46) used three different methods for quantifying bacteria. They found that atherosclerotic lesions had significantly higher levels of the intracellular cell bacteria, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. The areas of the highest calcification showed the highest levels of bacteria by all methods, suggesting a possible causal role for bacteria. Another team found similar results using a single method that allowed quantification of *Chlamydia pneumoniae* (48).

The data showing that bacteria were often present at quite low levels even in controls suggests that the ability of the innate immune system to keep these bacteria in check plays a major role in what level of calcification will result (46). Thus, the issue is not simply whether these two species of bacteria are present in a person's arteries that results in the calcification, but the adequacy of immune function. Therefore these findings fit well with Marshall's evidence that an immune defect, namely blockage of the VDR by substances produced by particular species of bacteria and higher levels of 25D, is involved in the process that leads to atherosclerosis and calcification.

Although a detailed mechanistic explanation for vascular calcification is not yet established, the new view of chronic disease and vitamin D points to possible new directions for research on the causes and mechanisms of calcification. For instance, the dysregulation of vitamin D metabolites and other minerals due to chronic infection and the possible production of substances by bacteria that injure tissue and promote calcification seem promising areas of inquiry. The effect of intracellular infection of macrophages and cells lining the blood vessel may be involved. Osteopontin, a glycoprotein that can be actively synthesized by macrophages has been linked to calcification in coronary artery disease (50) and aortic stenosis (51). Infected macrophages are thought to be key factors in the inflammatory process in chronic diseases caused by intracellular bacteria (3, 7, 53, 55).

Conclusions Regarding Osteoporosis, Vascular Calcification and Chronic Disease and the New View of Vitamin D

Thus, the above analyses concur in their conclusions. An adequate intake of calcium (1000-1500 mg) is important for bone density (2) and longevity (4). However, as discussed above there is increasing evidence from a variety of independent lines of clinical research as well as molecular modeling, that vitamin D supplementation is often counter productive, particularly in people with various chronic conditions and older adults. Higher levels of vitamin D intake appear to be harmful with regard to calcification and brain lesion formation (14). And vitamin D supplementation is not generally the best way to increase bone density (3, 7, 23, 25), but may actually hinder healing in chronic illness and in the aging (7, 8, 55). The elimination of bacteria through maximizing immune function through restoring vitamin D receptor competence (7) along with an effective antibiotic protocol (53, 54, 55, 56) would appear to be a promising area of future research.

Further Reading:

For discussion of data on vitamin D and disease associations, latitude and the issue of what is a natural amount of sun exposure: see Waterhouse JC, Marshall TG, Fenter B, Mangin M, Blaney G, "Vitamin D Metabolism in Chronic Disease"
In *Vitamin D: New Research,* Nova Science Publishers, NY, 2006.
http://winmlm.neostrada.pl/vitamindbook/vitamindnewresearch.pdf

For discussion of Vitamin D and cancer, see the transcript of the 2006 Los Angeles conference presentation on Vitamin D:
http://autoimmunityresearch.org/transcripts/waterhouse_lax2006.pdf
and www.bacteriality.com/category/vitamin-d/

For more on Marshall's model of many chronic diseases and protocol study site, see:
http://Autoimmunityresearch.org

For a list of papers and presentations by Professor Trevor Marshall, with links, see
http://marshallprotocol.com/forum2/2274.html

For those interested in food and supplement options that can lower their intake of vitamin D, see
http://members.aol.com/SynergyHN/lowerD

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