

The Dual Vitamin D Pathways: Considerations for Adequate Supplementation



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Recently, a substantial increase in the body of work emanating from a variety of clinical and scientific areas has identified an association between vitamin D insufficiency and poor clinical outcomes. These observations have promoted an increased interest among healthcare providers and researchers in the possible benefits of vitamin D supplementation. New investigations into the effects of vitamin D and its metabolites and analogs has generated some significant changes in the understanding of the use and metabolism of vitamin D and the extent of its roles in the endocrine system and other multiple localized systems involving specific tissues and organs (Rostand & Warnock, 2008). Vitamin D, when metabolized to its hormonal forms, exerts its actions through the vitamin D receptor (VDR), which is widely distributed throughout the body. By binding to the VDR, the vitamin D hormone initiates a series of events thought to affect cellular proliferation and differentiation, inflammation, the immune system, and the endocrine system, including calcium and phosphorus homeostasis, the renin-angiotensin system, insulin resistance, and lipid metabolism.

Supplementation with Vitamin D₃ Or Vitamin D₂

Vitamin D is naturally produced by ultraviolet irradiation of precursor sterols in both the skin (vitamin D₃ or

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Cronin, S.C. (2010). The dual vitamin D pathways: Considerations for adequate supplementation. *Nephrology Nursing Journal*, 37(1), 19-28, 36.

Vitamin D insufficiency and deficiency have been identified as having a correlation with poor clinical outcomes in patients with chronic kidney disease (CKD). The availability of vitamin D for metabolism into 25(OH)D and the ability to further metabolize to 1,25(OH)D are known to have a significant impact on the endocrine system and the modulation of iPTH, calcium, and phosphorus imbalances in patients with CKD. Until recently, the focus of care for these patients has been to support the endocrine need for 1,25(OH)D because the loss of kidney function eliminates the ability to synthesize calcitriol effectively. However, recent findings have identified an autocrine role for vitamin D and its metabolism at local sites as having a potentially profound impact on gene transcription and clinical outcomes in multiple body systems. The National Kidney Foundation Kidney Disease Outcomes Quality Improvement guidelines recommend the use of ergocalciferol in the treatment of vitamin D insufficiency in CKD Stages 3 and 4, and the use of active vitamin D hormone in the treatment of vitamin D deficiency in patients with CKD Stage 5 who also have secondary hyperparathyroidism. Data clearly identify that the insufficiency of 25(OH)D persists as patients progress through Stage 3 and Stage 4 CKD into Stage 5 CKD. This article discusses the treatment of both the deficiency and insufficiency by supplementing both the endocrine and autocrine pathways with appropriate vitamin D therapies.

Goal

To provide an overview of the treatment of vitamin D deficiency and insufficiency in patients with CKD with vitamin D supplementation via the endocrine and autocrine pathways.

Objectives

Upon completion of this continuing nursing education program, the learner will be able to:

1. Discuss the physiologic and molecular functions of vitamin D.
2. Describe the pathogenesis of secondary hyperparathyroidism.
3. Discuss non-kidney related outcomes that result from lack of adequate therapy.
4. Understand the rationale for dual therapies in Stage 5 chronic kidney disease.

cholecalciferol) and in plants (vitamin D₂ or ergocalciferol). These two forms of vitamin D have been considered interchangeable and equivalent until recently. Both forms are hydroxylated

at carbon 25 in the liver to form 25-hydroxyvitamin D₃ and 25-hydroxyvitamin D₂, respectively, which collectively are referred to as "25(OH)D." However, 25-hydroxyvi-

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Statement of Disclosure: *The author has disclosed that she is an employee of Cytochroma, Inc., a clinical stage specialty pharmaceutical company developing vitamin D products for commercialization.*

Acknowledgment: *The author would like to acknowledge Robert P. Heaney, MD, for his article "Vitamin D in Health and Disease," which served as a primary resource in the development of this article.*

This offering for 1.4 contact hours and 80 pharmacology minutes is being provided by the American Nephrology Nurses' Association (ANNA).

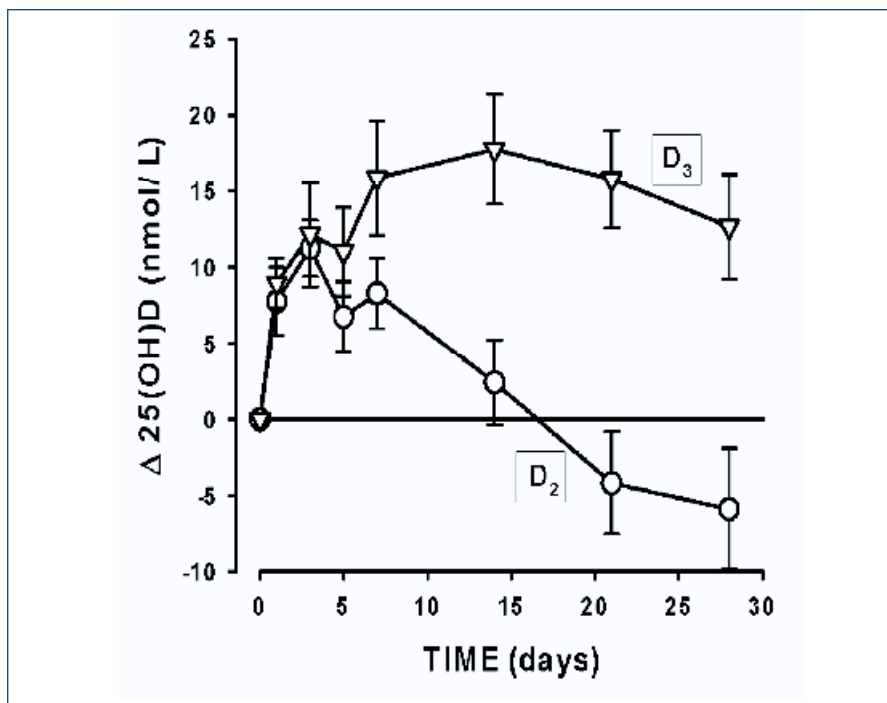
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This CNE article meets the Nephrology Nursing Certification Commission's (NNCC's) continuing nursing education requirements for certification and recertification.

Figure 1
D₂ Degrades Faster Than D₃



Source: Armas et al., 2004. Reprinted with permission.

tamin D₂ is more prone to metabolic degradation via 24-hydroxylation (see Figure 1) (Armas, Hollis, & Heaney, 2004). While active vitamin D₂ or one of its analogs is recommended for treating the endocrine deficiency in patients with Stage 5 chronic kidney disease (CKD), the literature clearly points to the current challenges of achieving National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Improvement (KDOQI) target ranges. Though it is possible to treat vitamin D insufficiency or deficiency with either form, vitamin D₃ appears to have an advantage over vitamin D₂ as a 25(OH)D repletion therapy (Heaney, Barger-Lux, Dowell, Chen, & Holick, 1997).

The Prevalence and Treatment of Sub-Optimal Vitamin D Status

A number of studies have reported vitamin D status in the general population by age group as well as in

subgroups of the population with various diseases (Chatfield, Brand, Ebling, & Russell, 2007; Gilbert, Arum, & Smith, 2009; Melamed, Michos, Post, & Astor, 2009; Orwall et al., 2009; Yetley, 2008). Many study subjects screened as “healthy” have been found to have sub-optimal serum total 25(OH)D levels less than 80 nmol/L (less than 32 ng/mL), and many had overt vitamin D insufficiency with levels of 50 to 65 nmol/L (20 to 26 ng/mL) (Heaney, 2008). These studies raise the concern that vitamin D insufficiency and the resulting vitamin D hormone deficiency may be the most widespread vitamin deficiency in developed nations. A recent study concluded that vitamin D deficiency is a major public health problem in many parts of the world requiring urgent attention (Prentice, Goldberg, & Schoenmakers, 2008).

The National Osteoporosis Foundation (2008) recommends that adults under the age of 50 need 400 to 800

IU/day of vitamin D, and adults aged 50 and older need 800 to 1,000 IU/day. The escalating requirement of vitamin D with age reflects the declining endogenous synthesis and possible increased catabolism of vitamin D as one ages (MacLaughlin & Holick, 1985). Quantitative studies evaluating daily vitamin D requirements have suggested that the optimal blood level of 25(OH)D is greater than 80 nmol/L (greater than 32 ng/mL) and that the daily metabolic utilization is about 4,000 IU (Heaney, Davis, Chen, Holick, & Barger-Lux, 2003). Dietary sources contribute to only about 5% to 10% of this total daily requirement because the vitamin D content of foods is normally low (Heaney, 2008). The remainder must come from cutaneous production or previously accumulated stores in adipose tissue. Without adequate dietary intake and exposure to sunshine, sub-optimal serum levels of 25(OH)D can readily occur (Heaney, 2008).

More research needs to be completed for medical professionals to have a complete understanding of cutaneous vitamin D production and tissue catabolism and their contributions to total vitamin D status. For now, the emphasis needs to be on improving supplementation and monitoring vitamin D levels in an effort to achieve and maintain adequate serum 25(OH)D concentrations. Quantitative work completed in healthy individuals has resulted in this simple calculation: every 100 IU of daily oral vitamin D intake results in an elevation of serum 25(OH)D of approximately 1 ng/mL (Heaney et al., 2003). For the patient with a baseline serum 25(OH)D level of 15 ng/mL, the amount of supplemental vitamin D required would be at least 1,500 IU/day to bring the serum 25(OH)D level up to at least 30 ng/mL (Heaney, 2008). Individual responses to standard dosages often vary considerably, and certain subgroups of the population, such as patients with CKD, may require substantially higher doses than healthy individuals (Heaney, 2008).

Endocrine and Autocrine Vitamin D Pathways

Vitamin D functions in the body through both endocrine and autocrine pathways. The major source of vitamin D is ultraviolet B sunlight, which converts in the skin to pre-vitamin D₃. Vitamin D₃ from skin becomes bound to vitamin D binding protein. Vitamin D₂ and vitamin D₃ from the diet are bound to vitamin D binding protein and lipoproteins (Holick, 2008). Both forms are then hydroxylated in the liver. The better known endocrine pathway achieves calcium homeostasis by regulating the blood levels of vitamin D hormone, primarily calcitriol (Heaney, 2008). The primary effect of vitamin D in the endocrine system is to facilitate absorption of calcium in the intestine and mobilizing calcium from the skeleton (Holick, 2008).

The autocrine pathway facilitates tissue-specific gene expression by regulating vitamin D hormone production at the cellular level. Because the autocrine pathway contains cells and tissues that utilize the synthesized calcitriol as a signaling mechanism, the autocrine pathway is able to connect extracellular stimuli to genomic response. The many tissues of the autocrine pathway contain the specific proteins and molecules with the necessary encoded DNA in the nucleus of the cell. When the cells of these tissues are exposed to the stimuli or signal, a reaction is initiated, which requires a response from the DNA. This genomic response provides the appropriate proteins or catalyst for the transcription of the information encoded in the DNA (Heaney, 2008).

Current dietary intake recommendations for vitamin D are based only on the requirements of the endocrine pathway. In this pathway, vitamin D supplied to the body by either cutaneous or oral routes is metabolized to 25(OH)D in the liver and subsequently to hormone 1,25(OH)₂D in the kidneys. The more prominent hormone, calcitriol (1,25(OH)₂D₃), circulates in the blood to the small intestine and kidneys, where it stimulates the absorption and reabsorption, respec-

tively, of calcium, yielding an increase in serum calcium (Clements et al., 1992). While most guidelines focus on the endocrine pathway requirements, the current dietary intake recommendations ignore the requirements of the autocrine pathway. In this second pathway, a variety of tissues, particularly of the immune apparatus, synthesize vitamin D hormone from circulating 25(OH)D. Unlike the endocrine pathway, the autocrine pathway is highly dependent on sufficient blood levels of 25(OH)D to provide adequate substrate for local tissue hormone production.

The Dual Vitamin D Pathways

The metabolic pathways for vitamin D are shown in Figure 2. Whether from skin exposure to sun or dietary intake, vitamin D is converted to 25 hydroxyvitamin D (25(OH)D) in the liver. In the endocrine pathway, the 25(OH)D is converted to calcitriol (1,25(OH)₂D) in the kidney by CYP 27b1, the enzyme responsible for hydroxylation. The endocrine pathway has long been the accepted process by which the body metabolizes vitamin D. However, vitamin D receptors (VDRs) have been identified in most tissues in the body. Many of these tissues contain the enzyme CYP 27b1 and are capable of converting 25(OH)D to 1,25(OH)₂D (Bikle, 2009). This extrarenal metabolism appears to remain local and not systemically measurable (Heaney, 2008).

While the endocrine and autocrine pathways (see Figure 2) are well recognized, it remains unclear how each pathway accounts for overall vitamin D utilization. Is the endocrine pathway the primary route for the activation of vitamin D and therefore allowed preferential use of the available vitamin D stores? Is the autocrine pathway a more passive mechanism that is active only when blood levels of 25(OH)D are adequate? The answers to these questions are not yet available. What is known is that when vitamin D status is ade-

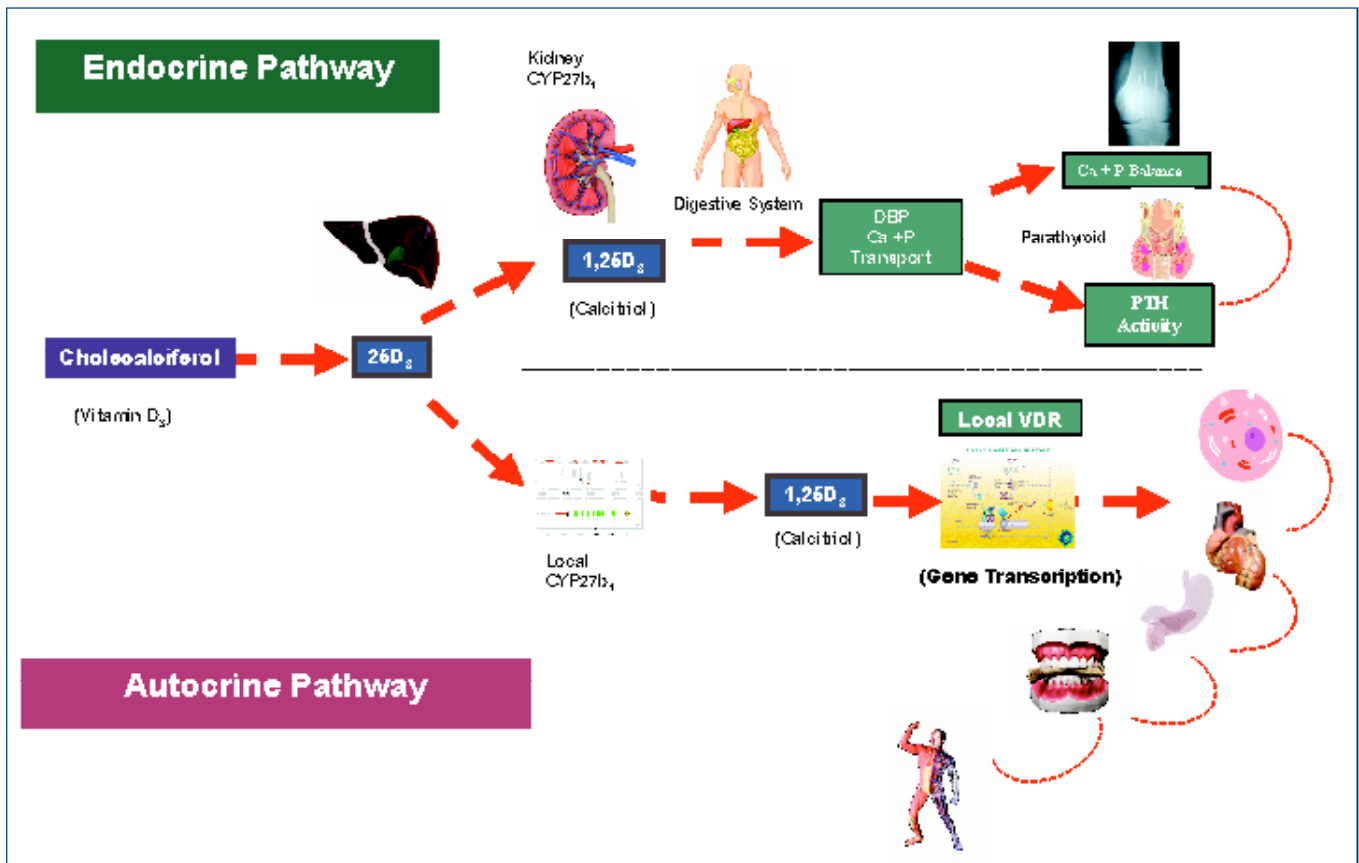
quate, the autocrine pathway uses the majority of the available vitamin D. Further, the autocrine pathway produces local concentrations of vitamin D hormone that are often higher than serum concentrations and are required for tissue responses (Heaney, 2008).

Locally synthesized vitamin D hormone is the link that connects extracellular stimuli to genomic responses in the cells and tissues involved in the autocrine pathway. It is clear that most tissues throughout the body possess the necessary signaling apparatus to respond to vitamin D hormone via opening access to chromatin bound DNA, thus allowing transcription of the specific genes that encode proteins needed for tissue-specific responses. Without adequate intracellular 25(OH)D substrate levels, the cell is unable to produce the sufficient hormone to respond appropriately to the pathologic and physiologic signals. Thus, serum 25(OH)D is critical for the transcription of genes that regulate cell differentiation, proliferation, and apoptosis, and vitamin D sufficiency becomes a critical factor for optimal functioning of various systems that require vitamin D as part of their signaling apparatus (Heaney, 2008; Prentice et al., 2008).

Vitamin D Therapy for Patients With CKD

Customary management of patients with Stage 5 CKD has focused on the endocrine pathway and involves chronic treatment with calcitriol or one of the vitamin D hormone analogs because synthesis of calcitriol diminishes with the loss of kidney function. Serum concentrations of calcitriol during routine treatment are usually sufficient to control secondary hyperparathyroidism (SHPT) but are often inadequate to support the needs of the autocrine pathway. This may be due to calcitriol's short half-life, leading to periods between dosing where calcitriol is unavailable. Further, use of calcitriol as a vitamin D hormone replacement therapy can cause increased catabolism and clear-

Figure 2
The Dual Mechanisms of Vitamin D



ance of 25(OH)D, thereby reducing the circulating levels of 25(OH)D that would otherwise support the autocrine pathway (Clements et al., 1992). Vitamin D insufficiency or deficiency is corrected by raising serum 25(OH)D levels and not by raising serum calcitriol levels. Thus, optimal control of both SHPT and vitamin D insufficiency requires administration of both vitamin D hormone replacement therapy (calcitriol) and vitamin D repletion therapy (ergocalciferol) (Heaney, 2008).

Patients at Stage 5 CKD who are dialysis-dependent tend to be very sick with multiple complex co-morbidities. Their kidney disease and associated complications often prevent them from spending time outdoors and can cause them to have darkened skin pigmentation, which reduces cutaneous production of vita-

min D during infrequent exposure to sunlight. Their 25(OH)D stores are less than optimal and often deficient (Heaney, 2008). Data from the United States Renal Data System (USRDS) (2008) and the Dialysis Outcomes and Practice Patterns Study (DOPPS) (Tentori et al., 2009) document that these patients have high mortality rates and are at increased risk for other chronic debilitating diseases. The extent to which vitamin D insufficiency increases these risks is yet to be determined.

The literature supports the recommendations of the NKF KDOQI Clinical Practice Guidelines for Bone Metabolism and Chronic Kidney Disease (Guidelines 7, 8a, and 8b) (NKF, 2003), supporting the increased use of vitamin D in the patient with CKD Stage 5 (Palmer,

Craig, & Strippoli, 2009). As Wolf (2008) writes in a recent editorial:

Vitamin D is more than just a therapeutic tool for lowering elevated levels of parathyroid hormone in patients on dialysis... Deficiencies in the vitamin D axis cause osteomalacia, rickets, and myopathy, and are associated with a variety of extra skeletal problems, including cardiovascular disease, infection, malignancy, and death... observational studies of dialysis cohorts were the first to report a survival benefit of therapy versus no therapy (p. 1442).

In the same journal, Shoben, Rudser, deBoer, Young, and Kestenbaum (2008) extend this observation to patients at Stages 3 and 4 CKD reporting a survival benefit using active vitamin D vs. no vitamin D therapy.

The Endocrine Role of Vitamin D In CKD Co-Morbidities

Secondary Hyperparathyroidism

SHPT is a disorder characterized by elevated parathyroid hormone (PTH) levels and the progressive development of bone disease. It has been well established that SHPT begins early in the course of CKD and progresses as the glomerular filtration rate (GFR) declines (Al-Badr & Martin, 2008). The pathogenic factors that contribute to the progression of SHPT are multiple but principally involve phosphate retention and abnormalities of vitamin D metabolism. As CKD progresses and kidney function declines, there is a decrease in the levels of $1,25(\text{OH})_2\text{D}$. This results in a reduction in the intestinal absorption of calcium, which persists despite the increasing levels of PTH. Elevated PTH attempts to maintain adequate serum levels of calcium by triggering increased vitamin D hormone production in the kidneys and osteoclastic activity in the bone. However, prolonged increased levels of secretion of PTH lead to hyperplasia of the parathyroid glands. Chronically elevated PTH continues to draw calcium from the bone leading to osteodystrophy, skeletal weakness, and metastatic calcifications (Martinez, Saracho, Montenegro, & Llach, 1997; McCarley, 2006).

Osteoporosis

The pathogenesis of osteoporosis can often involve vitamin D insufficiency. Without adequate vitamin D, the endocrine function is simply unable to provide adequate calcium from the diet to meet the body's needs. Likewise, the body cannot absorb sufficient calcium, regardless of the vitamin D level, if the calcium intake is low (Estelle & Riggs, 2005). Moreover, widespread prevalence of inadequate dietary calcium and vitamin D intake, and reduced exposure to sunlight, markedly increase the risk of osteoporosis.

Many clinical trials have investigated the effects of vitamin D and cal-

cium supplementation on fracture prevention (Bischoff-Ferrari et al., 2009; Bonjour, Guéguen, Palacios, Shearer, & Weaver, 2009; Cooper & Burfield, 2003). These trials have demonstrated the prevention of age-related bone loss and in many instances, reduction in fracture risk. Where fracture risk was reduced, serum $25(\text{OH})\text{D}$ levels exceeded 75 to 80 nmol/L (30 to 32 ng/mL) (Bischoff-Ferrari, 2007). Vitamin D supplementation has been shown to reduce the risk of falling within only a few weeks of initiating treatment, in some cases, by as much as 50% (Bischoff-Ferrari, Conzelmann, Dick, Theiler, & Stähelin, 2003; Bischoff et al., 2003).

The Autocrine Role of Vitamin D In CKD Co-Morbidities

A number of chronic disorders have been found to be associated with vitamin D insufficiency either from epidemiologic studies or from randomized controlled trials. These disorders include autoimmune diseases, cancer, cardiovascular disease, chronic pain, depression, type 1 and type 2 diabetes mellitus, hypertension, infection, multiple sclerosis, osteoarthritis, periodontal disease, seasonal affective disorder (SAD), schizophrenia, and tuberculosis (Holick & Chen, 2008; Sanz Moreno et al., 2008). Evidence linking vitamin D insufficiency to some of these disorders is described below.

Cancer

A significant body of epidemiologic evidence has accumulated strongly, indicating an inverse association between serum $25(\text{OH})\text{D}$ levels and subsequent incident risk for prostate, colon, breast, lung, and marrow/lymphoma cancers (Holick & Chen, 2008). There is substantive supportive evidence from animal studies showing that vitamin D insufficiency predisposes to the development of certain types of cancers (Mehta et al., 1997). This latter evidence was derived from experimental models lacking the VDR gene or

induced vitamin D deficiency. Data from a recent 4-year study of postmenopausal women demonstrated a reduction of all cancer risks ranging from 60% to 75% in response to vitamin D supplementation (Lappe, Travers-Gustafson, Davies, Recker, & Heaney, 2007).

Chronic Pain

Several studies have shown that vitamin D insufficiency may exacerbate chronic pain, and it is well established that vitamin D deficiency can sometimes cause pain and muscle weakness. In a study at the Mayo Comprehensive Pain Rehabilitation Center in Rochester, Minnesota, researchers studied 267 adults who were receiving outpatient treatment for chronic pain (Gloth & Greenough, 2004). The researchers recorded patients' serum vitamin D levels, morphine dosages, and duration of use, as well as physical and general health functioning, and found that 26% of those tested had a vitamin D insufficiency. The average morphine doses recorded for these patients with vitamin D insufficiency was nearly twice that of the rest of the group. Those with vitamin D insufficiency also had a more prolonged use of morphine (average of 71.1 months versus 43.8 months), exhibited lower levels of physical functioning, and had a poorer view of their overall health (Gloth & Greenough, 2004).

Diabetes Mellitus

Type 1 and type 2 diabetes mellitus have been associated with vitamin D deficiency (Scragg, 2008). In the National Health and Nutrition Examination Survey (NHANES), individuals without a documented history or diagnosis of diabetes mellitus were more likely to have high serum glucose levels both fasting and following a glucose challenge when they had vitamin D insufficiency (Scragg, Sowers, & Bell, 2004).

In one study in Finland (where intrinsic production of vitamin D is low due to low natural light levels), vitamin D administered in doses of 2,000 IU/day given during the first

year of a child's life has been connected with an 80% reduction in the risk of acquiring type 1 diabetes mellitus later in life (Hyppönen, Läärä, Reunanen, Järvelin, & Virtanen, 2001). Some researchers have suggested that vitamin D deficiency may be an important pathogenic factor in type 1 diabetes mellitus independent of geographical latitude and available sun exposure (Zipitis & Akobeng, 2008).

In a recent animal study, combining a vitamin D analog with an angiotensin II type I receptor blocker (ARB) was shown to further reduce kidney injury seen in diabetic nephropathy (Zhou et al., 2008). Kidney injury was moderately reduced when a vitamin D analog or an ARB was given alone. When both agents were given together, albuminuria was fully prevented, the glomerular filtration barrier structure was restored, and glomerular sclerosis was significantly reduced. Li (2008) writes:

This is the first demonstration that vitamin D analogs can be used to block the compensatory renin increase in a combination therapy with renin-angiotensin system inhibitors... The promising therapeutic effects of the combination seen in diabetic mice provide insight into the pharmacological intervention of diabetic nephropathy (p. 466).

Hypertension and Cardiovascular Disease

An individual's vitamin D status has been shown to be strongly associated with the propensity of developing hypertension and cardiovascular disease (Forman et al., 2007). Thus, the role of vitamin D in maintaining normal blood pressure and heart health has been a topic of significant investigation. Research has shown that both the blood vessels and the heart express VDR, suggesting that vitamin D provides some function in regulating these tissues (Rostand & Drueke, 1999; Sanz-Moreno et al., 2008). Interestingly, controlled studies of subjects with established hypertension have shown a protective effect

of high calcium intake (Lind, Wengle, Wide, & Ljunghall, 1989).

Studies in which vitamin D has been administered to older adults with hypertension have shown that both the systolic blood pressure and diastolic blood pressure decrease (Lind, Wengle, Wide, Sörensen, & Ljunghall, 1988; Szabó, Merkely, & Takács, 2009). When vitamin D and calcium are given together, even greater decreases in both systolic and diastolic blood pressure have been observed. These data suggest that vitamin D and calcium work together to cause a reduction in blood pressure and that high levels of dietary calcium enhance the blood pressure-reducing action of vitamin D (Lind et al., 1989). Furthermore, the risk of hypertension has been shown to be inversely related to previously measured serum 25(OH)D. In a 4-year prospective study by Forman et al. (2007), the reported relative risk for incident hypertension was 3.18 for those with 25(OH)D levels less than 15 ng/mL (less than 37 nmol/L) relative to those with levels greater than 30 ng/mL (greater than 75 nmol/L). The Framingham Offspring Study with a 5.4-year follow up reported that individuals with serum 25(OH)D levels less than 15 ng/mL (less than 37 nmol/L) were 53% more likely to experience a cardiovascular event than those with higher levels, and those with serum 25(OH)D levels below 10 ng/mL (less than 25 nmol/L) were 80% more likely (Forman et al., 2007; Wang et al., 2008). Giovannucci, Liu, Hollis, and Rimm (2008) analyzed data from the Health Professional Follow-Up Study and reported a nearly 2.5-fold increase in the risk of a myocardial infarction for individuals with 25(OH)D levels below 15 ng/mL (less than 37 nmol/L) compared to those above 30 ng/mL (greater than 75 nmol/L).

An analysis of findings from the Framingham Heart Study by Wang et al. (2008) suggests that vitamin D insufficiency nearly doubles the risk of myocardial infarction, stroke, and heart disease. Patients with low

25(OH)D levels (less than 10 ng/mL or 25 nmol/L) and hypertension were at substantially greater risk of cardiovascular events compared with patients with higher 25(OH)D levels.

While it is clear vitamin D plays some role in the regulation of blood pressure and individuals with vitamin D insufficiency are more likely to develop cardiovascular problems, the exact nature of these complex relationships must still be fully elucidated.

Immune System/Response to Infection

There are numerous studies suggesting that vitamin D may have a role in blocking certain types of infectious diseases (Liu et al., 2006; Wagner, Taylor, & Hollis, 2008). Children stricken with rickets suffer a high mortality rate largely due to respiratory infections. Calcitriol produced by the autocrine pathway has been recognized for nearly 20 years as having a role in boosting immune response (Cantorna & Mahon, 2004). Clinically, vitamin D co-therapy has been found to contribute substantially to improved response to antitubercular therapy in randomized controlled studies with subjects having advanced pulmonary tuberculosis (Nursyam, Amin, & Rumende, 2006). A secondary response of reduced risk of influenza in post-menopausal Black women who received vitamin D was also noted (Cannell et al., 2006).

These data raise the following question: "Does vitamin D reduce the risk of infection?" It is interesting to note that although the influenza virus exists year-round, influenza is most common during the winter months, and there is a higher seasonal mortality in older adults during this time. Vitamin D blood levels are generally thought to be at their highest in the summer and reach their lowest levels during the flu and cold season, particularly in the northern hemisphere. Could elevated 25(OH)D levels provide protection against infection (Cannell et al., 2006)? Phagocytic function of human macrophages is enhanced in individuals who receive supplemental vitamin D, suggesting

that adequate immunologic response to infection is hampered when 25 (OH)D levels are less than optimal (Martineau et al., 2007).

Summary and Final Thoughts

Vitamin D metabolism through the endocrine pathway exerts a significant effect on bone metabolism and the associated calcium and phosphorus balance. Vitamin D metabolism through the autocrine pathway exerts a profound effect on many other body systems. There are many potential benefits that arise from supporting both the endocrine and autocrine pathways through appropriate supplementation with vitamin D. Perhaps the most compelling evidence for these potential benefits is that there are roughly 800 human genes for which there is a vitamin D receptor. These genes impact multiple and varied human body systems, and most have little involvement with the endocrine function of vitamin D. Rather, they relate to the expression of proteins that control cell proliferation, differentiation, and apoptosis (Carlberg, 2003). Because these autocrine functions are so critical to the body, it is not surprising that inadequate vitamin D status has an adverse effect on a myriad of cellular function and health. To date, the major obstacle to the clinical use of vitamin D is its calcemic activity. There is a need for further research to identify a generation of novel vitamin D compounds with limited calcemic effects and the ability to modulate immune responses. Their discovery might lead to drugs designed for therapeutic use in a variety of immune diseases (May, Asadullah, & Zugel, 2004).

A number of diseases have been associated with poor vitamin D status. Until the current widespread prevalence of inadequate vitamin D levels has been corrected, it will be difficult to determine conclusively which disease entities are truly affected by limited vitamin D availability. While it is fairly certain that many of these diseases have epidemiological associa-

tions with latitude, data from properly designed prospective studies will be necessary to design appropriate and effective intervention by vitamin D supplementation (Heaney, 2008).

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