A Best Practice Guideline For Screening and Treating Vitamin D Deficiency in a Primary Care Setting: Moving Beyond the Bones

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DEDICATION

I dedicate this work to my parents whose continual support is unfathomable. I would not be where I am today had it not been for the sacrifices made on their behalf as well as their never ending encouragement. Thank you from the bottom of my heart for always giving me the opportunity to follow my dreams.

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ABSTRACT

The importance of vitamin D to bone health is well known, yet new research has linked vitamin D to numerous chronic diseases severely affecting our society. Recent studies have suggested vitamin D plays a critical role in conditions such as diabetes, cancers, and cardiovascular diseases. These chronic conditions are among the main causes of morbidity and mortality in our society. In addition, a deficiency in vitamin D has become all too common with a majority of Americans deficient in this essential vitamin. Guidelines directing healthcare providers when to screen for vitamin D deficiency beyond bone health and also how to treat the disease do not currently exist. In addition, routine screening does not generally occur in the healthcare setting if the patient is not at risk for bone disease or fractures. Current guidelines are not sufficient to prevent the harmful effects related to a deficiency in vitamin D and adequate intake is essential to the health of all individuals. This paper provides an evidence-based guideline to educate providers on the numerous implications of vitamin D deficiency beyond bone health and explores whether sufficient levels of vitamin D reduce future health risks associated with numerous chronic diseases.

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CHAPTER 1

Background

Background and Significance of the Problem

Vitamin D deficiency is quickly becoming a major problem of epidemic proportions. It is estimated that nearly three out of every four Americans are vitamin D deficient (Ginde, Liu, & Camargo, 2009). In fact, over the last 10-15 years, the serum concentration of vitamin D in Americans has rapidly declined (Drown, 2009; Ginde, Liu et al.; Looker et al., 2008). Once thought to only be associated with rickets in children and osteomalacia in adults, vitamin D has been largely overlooked in the last several decades. Recent research, however, is shedding new light on the "sunshine vitamin" and is alerting providers to the importance of vitamin D and its links to numerous chronic disease states.

Vitamin D deficiency is becoming rampant throughout the United States. A study by Gordon DePeter, Feldman, Grace, and Emans (2004) found that among healthy adolescents, 42% were vitamin D deficient. Another study found that nearly 73% of mothers and 80% of infants were vitamin D deficient, despite adequate nutritional intake and prenatal care (J. M. Lee et al., 2007). A disease once thought eradicated, rickets is once again becoming prevalent throughout the country (Holick, 2006b; Weisberg, Scanlon, Li, & Cogswell, 2004). In addition, up to 50% of adults are estimated to have lower levels of vitamin D than what is required for optimal health

(Holick, 2006a, 2007). The cause of this recent vitamin D deficiency is unclear.

There are numerous reasons and causes underlying the prevalence of vitamin D deficiency in our society. Warnings and guidelines on preventing skin cancer suggest people avoid prolonged exposure to direct sunshine, wear protective clothing, or use sun block when they are outside (American Cancer Society, 2010). Sun exposure is the primary source of vitamin D intake, and is a principal function of skin (Cannell & Hollis, 2008). Avoiding the sun or using sunscreen will decrease the conversion of UVB to vitamin D in the skin (Matsuoka, Ide, Wortsman, MacLaughlin, & Holick, 1987). When used properly, a sunscreen with a sun protection factor (SPF) of 8 will block 95% of cutaneous production of pre-vitamin D and an SPF of 15 will prevent 99% production of pre-vitamin D (Holick, 2004). Also, an increase in air pollution, which has been apparent in recent decades, will also block the natural absorption of vitamin D from the sun (Pilz, Tomaschitz, Ritz, & Pieber, 2009). Other factors include a lack of vitamin D rich dietary sources or lack of supplementation. An inadequate intake of vitamin D over prolonged periods will lead to vitamin D deficiency.

Several populations are at greater risk for being vitamin D deficient. Those with increased pigmentation in their skin which blocks UVB radiation will need higher supplementation or increased UVB exposure to achieve adequate vitamin D stores (Fiscella & Franks, 2010; Reis, Michos, von Muhlen, & Miller, 2008). It has been suggested that perhaps the racial disparities seen in healthcare are partially related to the differences in vitamin D levels, as blacks are at a higher risk of being deficient in vitamin D than whites (Reis et al., 2008). Vitamin D deficiency is also extremely common in the elderly population due to a decline in the ability of the skin to absorb vitamin D and also

a decrease in the metabolism (Pilz, Dobnig et al., 2009; Wilkins, Sheline, Roe, Birge, & Morris, 2006). In addition, obese individuals have been shown to have a decline in their vitamin D levels because fat sequesters vitamin D (Drown, 2009; Jorde, Sneve, Figenschau, Svartberg, & Waterloo, 2008; McKinney, Breitkopf, & Berenson, 2008). In addition to specific populations at risk of being vitamin D deficient, certain medications can also cause a decline in vitamin D levels. Medications that have known side effects of decreasing vitamin D levels include anticonvulsants, glucocorticoids, and several medications used in the treatment of AIDS (Holick, 2007). Patients suffering from chronic kidney or liver disease or those with fat-malabsorption syndrome are also more at risk of being vitamin D deficient (Arteh, Narra, & Nair, 2009; Gal-Moscovici & Sprague, 2007; Holick, 2007).

Vitamin D has been called the vitamin of the century and is linked to most of the diseases afflicting our population (Cannell, Hollis, Zasloff, & Heaney, 2008). Recent research has linked vitamin D deficiency to a host of various diseases including heart disease, cancer, diabetes mellitus types 1 and 2, hypertension, obesity, mood disorders, chronic liver and kidney diseases, fibromyalgia, and bone disorders (Annweiler et al., 2010; Armstrong et al., 2007; Arteh et al., 2009; Berk et al., 2007; Botella-Carretero et al., 2007; Cheng et al., 2010; Cranney, Weiler, O'Donnell, & Puil, 2008; Gal-Moscovici & Sprague, 2007; Holick, 2004; Jorde et al., 2008; Judd & Tangpricha, 2009; Luong & Nguyen, 2010; Mertens & Muller, 2009; Murphy & Wagner, 2008; Suzuki et al., 2006; Ullah, Uwaifo, Nicholas, & Koch, 2010; Wilkins et al., 2006). More importantly though, vitamin D has been associated with a rise in all cause mortality, thus creating great public health implications for preventing such a deficiency (Autier & Gandini, 2007; Ginde,

Scragg, Schwartz, & Camargo, 2009; Melamed, Michos, Post, & Astor, 2008; Semba et al., 2009; Zittermann, Gummert, & Borgermann, 2009). With heart disease, cancer, and stroke accounting for more than half of all American deaths each year, and 70% of all deaths related to chronic diseases, the relationship between vitamin D deficiency and chronic disease deserves further investigation (Kung, Hoyert, Xu, & Murphy, 2008).

Pathophysiology.

Recent research on vitamin D has lead to new knowledge that it is not simply a vitamin, but a powerful and potent secosteroid hormone. Its primary function is regulating calcium through the endocrine system, but new evidence has found that vitamin D regulates over 200 genes through its newly known autocrine functions and thus regulating nearly 3% of the human genome (Cannell & Hollis, 2008; Zittermann & Gummert, 2010).

Solar UV-B radiation absorbed through the skin is the major source of vitamin D for humans. When solar radiation penetrates the skin, a substrate found in the dermis called 7-dehydrocholesterol is converted to pre-vitamin D_3, which subsequently converts to a more stable form called vitamin D_3 (Holick, 2007). Vitamin D refers to either vitamin D_3 or vitamin D_2. Vitamin D_3, or cholecalciferol, is one of the major forms of vitamin D in the body. Once converted to vitamin D_3, the vitamin D binding protein then transports it to the liver where hydroxylation occurs, converting the vitamin D_3 to 25(OH)D, an inactive form (Holick, 2005; Kulie, Groff, Redmer, Hounshell, & Schrager, 2009). It is then transported once again to the kidneys and undergoes further hydroxylation via the enzyme 1 α-hydroxlase where it is converted to its active form called 1,25(OH_2)D or calcitriol (Cannell, Hollis et al., 2008; Holick, 2005; Kulie et al.,

2009). This transformation from sun to a usable form of vitamin D occurs extremely rapidly and intoxication of vitamin D through sun exposure is not possible (Holick, 2006a). This is because pre-vitamin D and vitamin D_3 are converted to many other usable substances in the body other than just vitamin D (Holick, 2004). Obtaining vitamin D through sun exposure is very quick and powerful and in fact, a fair-skinned person can obtain as much as 20,000 IU of vitamin D_3 in as little as 30 minutes of sun exposure (Hollis, 2005).

Ergocalciferol, or vitamin D_2 , is the other major form of vitamin D in the body. Vitamin D_2 is plant derived and obtained through diet by eating sources like shitake mushrooms or egg yolks (Wolpowitz & Gilchrest, 2006). Vitamin D_3 sources obtained through the diet come from fatty fish such as salmon, sardines, mackerel, tuna, or cod (Cannell, Hollis et al., 2008). In addition, fortified milk, juices, cereals, or dairy products also contain small amounts of vitamin D_3 (Holick, 2007). Through gastrointestinal absorption, vitamin D can then enter the circulation and cause an increase in the serum levels of 25(OH)D. Some sources claim that there is a biologic difference between vitamin D_2 and vitamin D_3 and that vitamin D_3 raises serum values more, others do not agree and there is still further research to be done on this matter (Armas, Hollis, & Heaney, 2004; Rapuri, Gallagher, & Haynatzki, 2004).

Vitamin D's main function is to maintain calcium and phosphorus homeostasis. Declines in vitamin D levels cause a decrease in calcium absorption from the small intestine (Ullah et al., 2010). The active form of 1,25(OH_2)D functions to increase the absorption of calcium and phosphorus in the small intestine. This leads to increase production of parathyroid hormone, or PTH, into the bloodstream to increase calcium

reabsorption and bone demineralization (Janssens et al., 2009). In cases of low calcium and vitamin D, parathyroid hormone increases causing osteoclasts to dissolve bone matrix, therefore leading to osteomalacia and rickets (Holick, 2006a, 2006b, 2007). The vitamin D receptor, or VDR, has been found in nearly all cells and tissues in the body with much more far-reaching effects than simply calcium homeostasis.

Current guidelines.

Current recommendations of vitamin D intake from the Institute of Health have not been updated since 1997. Currently, adequate intake recommendations of vitamin D for those 0 months old to 50 years old are only 200 IU daily (Institute of Medicine, 1997). Those aged 51-70 should consume 400 IU per day and those older than 71 years of age should ensure 600 IU daily of vitamin D intake (Institute of Medicine, 1997). The recommendation for pregnant and lactating women is 200 IU of vitamin D daily (Institute of Medicine, 1997). The International Unit is the form used for supplementation amounts of vitamin D and 40 IU is equivalent to 1 microgram, making 1000 IU equivalent to 25 micrograms (Cannell & Hollis, 2008). As this paper shows, these recommendations are not reflecting current research and new recommendations are needed. In addition, they do not take into account a person's weight, race, or chronic disease state. It is grossly outdated to assume that a 250 pound 49 year old male should consume the same amount of vitamin D daily as an eight-pound newborn.

The half-life of vitamin D in the liver is only three weeks (Kulie et al., 2009). Frequent supplementation is required and stores from the summer will not last throughout the winter months when UVB exposure is reduced (Kulie et al.). Toxic levels of vitamin D are those serum 25(OH)D levels that meet or exceed 150 ng/ml (Cannell & Hollis,

2008) . These levels are rare and usually difficult to achieve without supplementation of 10,00 IU of vitamin D_3 daily over a long period of time (Cannell & Hollis, 2008). Signs of vitamin D toxicity include hypercalcemia and calcified organs, primarily the kidneys or kidney stones. However, the evidence that one can become vitamin D toxic is rare (Brannon, Yetley, Bailey, & Picciano, 2008).

Vitamin D level is measured using the serum 25-hydroxyvitamin D, or 25(OH)D, level. The other active form of vitamin D in the body is $1,25(OH_2)D$ which has a half-life of only 8 hours, therefore not showing an adequate representation of the true levels of serum vitamin D (Cannell & Hollis, 2008; Holick, 2004; Judd & Tangpricha, 2009). In addition, 25(OH)D levels in the serum are much higher than $1,25(OH_2)D$ and $1,25(OH_2)D$ levels could falsely be elevated in cases of severe vitamin D deficiency due to it being primarily regulated by PTH (Judd & Tangpricha). It is widely accepted that the proper test to measure adequate vitamin D levels is a serum 25(OH)D or 25-hyrdroxyvitamin D test. Serum 25(OH)D levels are reported in either ng/ml or nmol/L. These values are interchangeable by a factor of 2.496 (Ginde, Liu et al., 2009).

Purpose

With the recent interest in vitamin D deficiency, and its association with numerous chronic disease states, it is critical for practitioners to know when to screen for deficiencies and subsequently how to eradicate low levels. Current guidelines are not based on new research that is emerging and, currently, no evidence-based guide for practitioners in a primary care setting is available. The current recommended daily allowance guides are over a decade old and focus primarily on bone health and do not consider vitamin D related to any other diseases (Institute of Medicine, 1997). It is

critical that a guideline be developed to quickly transfer new evidence-based research into clinical practice to improve the health and well being of patients.

This project creates a best practice guideline for healthcare professionals on screening and treating vitamin D deficiency associated with chronic diseases in a primary care setting. Upon examining the research and clinical guidelines, no such guide currently exists for an easy to use protocol for practitioners. This paper will (a) educate healthcare providers when and how to screen for vitamin D deficiency, (b) educate providers on what vitamin D deficiency is and why it is important to patient's health, and (c) provide a guide on how to monitor and treat vitamin D deficiency. The purpose of this paper is to examine if increasing daily intake of vitamin D to a level of sufficiency for individuals with vitamin D deficiency will reduce their future health risks for chronic diseases including cardiovascular disease, cancer, type 2 diabetes, cognitive disorders, and mortality compared to those who do not consume adequate vitamin D.

PICO Definitions and Description

1. Vitamin D deficiency: Vitamin D deficiency is defined as a serum 25(OH)D level of less than or equal to 10 ng/ml (25 nmol/L) (Jones, Horst, Carter, & Makin, 2007) (National Institutes of Health, 2009). Vitamin D deficiency can also be defined as possessing a disease state that negatively impacts skeletal health (Wolpowitz & Gilchrest, 2006).

2. Vitamin D insufficiency: Vitamin D insufficiency is defined as a serum 25(OH)D level between the range of 10-20 ng/ml (25-50 nmol/L) (Holick, 2007; Jones et al., 2007). Insufficiency includes a vitamin D level that is negatively associated with adverse health outcomes (Wolpowitz & Gilchrest, 2006).

3. Vitamin D sufficiency: Sufficiency levels of serum 25(OH)D are those levels greater than 30 ng/ml (75 nmol/L) (Melamed et al., 2008; Norman, 2008). Sufficient levels of vitamin D will provide optimal health and benefits as well as prevention of the diseases associated with low levels of vitamin D in the body.

4. Primary care setting: A primary care setting is a healthcare facility that manages both acute and chronic conditions of the family including Family Practice and Internal Medicine clinics.

5. Chronic conditions: A chronic condition is that of long duration, lasting at least three or more months, and slow progression. Chronic disease states comprise the leading causes of death in the United States (Kung et al., 2008).

Summary

Vitamin D deficiency is a huge problem of epidemic proportions. With links to numerous chronic disease states and majority of persons deficient, a call to action is required. Current guidelines are not up to date with new research. Also, an evidence-based guide is not available to educate providers on the new and emerging uses of vitamin D as well as how to screen for a deficiency and treat it. This paper will aim to provide such a guideline.

CHAPTER 2

Analysis of the Literature

Overview of Literature Analysis

A thorough search of the literature was conducted to synthesize a best practice guideline for practitioners of when to screen for a deficiency in vitamin D and subsequently how to treat if one is found. Numerous electronic databases were searched including MEDLINE/Pubmed (from 1998-2010), CINAHL Plus with full text (from 2000-2010), The Cochrane Library, The Joanna Briggs Institute, ISI Web of Science, MEDLINE (Ovid), and National Guideline Clearinghouse. In addition, Gamecock Power Search was used which is a multi-database search engine available via the Thomas Cooper Library online at the University of South Carolina. Other searches included Google Scholar and the Vitamin D Council website at www.vitamindcouncil.org. In addition, reference lists from relevant articles and reviews were analyzed for further articles and information. Keywords searched included vitamin D, vitamin D deficiency, 25(OH)D, coupled with terms chronic, mortality, cancer, diabetes, depression, anxiety, cognition, memory, cardiovascular, supplementation, and treatment.

When searching the databases, several rules were used in selecting relevant articles. All meta-analysis, systematic reviews, randomized and quasi-randomized studies, cross-sectional, case-control, and cohort studies were examined. Clinical articles and guidelines were also considered. In addition, unless it was a seminal work, only articles in the last five years were considered. Only articles in English were considered

due to a lack of fluency in other languages. The population of concern was limited to chronic conditions that would commonly be managed in a primary care setting such as a family practice or internal medicine clinic, and not restricted by sex or race. Adults only were considered as these chronic conditions primarily affect those over the age of 18. Bone health was not considered in this study as the purpose of this guideline is to investigate new aspects of vitamin D deficiency that are commonly unknown to healthcare providers. Only conditions relating to vitamin D deficiency were considered.

Analysis

The articles collected were examined and rated using the SIGN 50 guideline of levels of evidence (Scottish Intercollegiate Guidelines Network, 2008) (Table 1). The rating system uses a scale of 1++ to 4 with 1++ being the highest level of evidence such as a very high quality meta-analysis or randomized control trial with very low bias, and 4 representing an expert opinion (Appendix A). A majority of the studies received either a 2+ or 2- rating because they had a mild to moderate casual relationship indicated and also because of the study design implemented. Studies that received a 3 rating showed evidence of bias and did not state a relationship in the results. The studies that received a rating of 1 were systematic reviews, randomized control trials, or meta-analysis. The following sections provide a synthesis of the articles related to specific issues.

Mortality.

The literature does show an association between vitamin D deficiency and in increase in mortality (Table 2.1). A meta-analysis of eighteen randomized controlled trials shows that an intake of even a small dose of vitamin D is strongly linked to a decline in mortality risk from chronic conditions such as cardiovascular diseases, cancer,

and diabetes mellitus (Autier & Gandini, 2007). Another prospective population-based study examining the relationship between older adults aged 50-75 and vitamin D levels found that there is a strong association between low levels of vitamin D and all-cause mortality (Pilz, Dobnig et al., 2009).

Table 2.1. *Literature analysis: Mortality*

Author	Journal	Study design	Sample	Findings	Level of evidence
Autier & Gandini, 2007	Archives of Internal Medicine	Meta-analysis	18 independent RCTs	Intake of vitamin D is associated with decrease mortality rates from chronic conditions	1++
Dobnig, Pilz, Scharnagl, Renner, Seelhorst, Wellnitz, . . . Maerz, 2008	Archives of Internal Medicine	Cohort study	3258 male and female patients scheduled for coronary angiography	Low levels of vitamin D are associated with cardiovascular and all-cause mortality	2-
Fiscella & Franks, 2010	Annals of Family Medicine	Cohort study	15,363 US adults aged 18 years and older	Low serum vitamin D levels associated with increased cardiovascular mortality	2+
Ginde, Scragg, Schwartz, & Camargo, 2009	Journal of the American Geriatrics Society	Cohort study	3,480 US adults aged 65 and older	There is an inverse relationship with vitamin D and all-cause mortality and CVD	2+

Author	Journal	Study design	Sample	Findings	Level of evidence
Melamed, Michos, Post, & Astor, 2008	Archives of Internal Medicine	Cohort study	13,331 US adults aged 20 or older	Low levels of vitamin D are independently associated with all-cause mortality	2-
Pilz, Dobnig, Nijpels, Heine, Stehouwer, Snijder, . . . Dekker, 2009	Clinical Endocrinology	Cohort study	648 white participants from Hoorn, Netherlands	Low vitamin D levels are associated with all-cause mortality and strongly associated with cardiovascular mortality	2+
Semba, Houston, Ferrucci, Cappola, Sun, Guralnik, & Fried, 2009	Nutrition Research	Cohort study	714 community-dwelling women aged 70-79 years old	Those who were vitamin D deficient were at an increased risk of death	2+

Levels of serum 25(OH)D less than 17.8 ng/ml were found to be independently associated with mortality in the general population according to a prospective cohort study by Melamed and colleagues (Melamed et al., 2008). This research study examined over 13,000 adults aged 20 and older from the Third National Health and Nutrition Examination Survey and found low vitamin D levels linked to a higher BMI, tobacco use, increasing age, and nonwhite ethnicity (Melamed et al., 2008). In similar studies, low levels of vitamin D were also linked to an increased risk of cardiovascular and all-cause mortality (Dobnig et al., 2008; Fiscella & Franks, 2010; Ginde, Scragg et al., 2009). An additional prospective population-based study examined elderly community-dwelling

women and found that those women who were considered vitamin D deficient were at fact at an increased risk of mortality (Semba et al., 2009). Such a strong association between vitamin D and mortality may be attributed to the anti-inflammatory and immune responses associated with vitamin D (Blaney, Albert, & Proal, 2009).

Cardiovascular system.

In addition to decreasing premature mortality, vitamin D has also been shown in recent research to have an effect on cardiovascular disease (CVD) (Table 2.2). The vitamin D receptor (VDR) has been found in numerous cells throughout the body including cardiomyocytes, endothelium, and vascular smooth muscle (Mertens & Muller, 2009). It is believed that vitamin D has direct effects on renin to lower blood pressure, decrease parathryroid hormone levels, and improve glycemic control (Judd & Tangpricha, 2009). Low levels of vitamin D activate the renin-angiotensin-aldosterone system and increase the risk of hypertension and left ventricular hypertrophy (Judd, Nanes, Ziegler, Wilson, & Tangpricha, 2008; J. H. Lee, O'Keefe, Bell, Hensrud, & Holick, 2008). One systematic review of 17 prospective studies and randomized controlled trials found that supplementation with 1000 IU of vitamin D daily is likely to reduce the risk of developing CVD (L. Wang, Manson, Song, & Sesso, 2010). In a prospective study of over 1700 participants of the Framingham Offspring Study found a linkage between vitamin D deficiency and cardiovascular disease (T. J. Wang et al., 2008). Those with levels of serum 25(OH)D of less than or equal to 15ng/ml were more likely after five years to experience a cardiovascular event than those who had adequate stores of vitamin D (T. J. Wang et al., 2008). In contrast, a randomized trial of postmenopausal women supplemented with 500mg of calcium or 400 IU of vitamin D

did not show any association with coronary or cerebrovascular risk (Hsia et al., 2007). This study, however, used a very low dose of vitamin D supplementation and much higher doses close to 1000 IU per day are recommended to ensure cardiovascular protection (L. Wang et al., 2010).

Maintaining sufficient levels of vitamin D are also highly associated with a lower risk of myocardial infarction (Giovannucci, Liu, Hollis, & Rimm, 2008). In a prospective study, men with serum vitamin D levels less than 15 ng/ml were at a much higher risk for having a myocardial infarction than those with levels greater than or equal to 30ng/ml (Giovannucci et al., 2008). Another study of adolescents in the United States found low serum levels of vitamin D to not only be strongly associated with hypertension, but also with hyperglycemia and obesity (Reis, von Muhlen, Miller, Michos, & Appel, 2009). In addition, low serum vitamin D levels have been shown to predict stroke, myocardial dysfunction, and sudden cardiac deaths (Kim, Sabour, Sagar, Adams, & Whellan, 2008; Pilz, Dobnig et al., 2008; Pilz, Marz et al., 2008). A randomized control trial did not show any significant improvement in quality of life or cardiovascular function in patients with heart failure when treated with two doses of 100,000 IU of vitamin D, suggesting perhaps that supplementation is more beneficial in the early stages of cardiovascular disease or as prevention (Witham, Crighton, Gillespie, Struthers, & McMurdo, 2010). Another study found that vitamin D deficiency is associated with peripheral arterial disease and perhaps is a likely contributor to the racial disparities seen between whites and blacks related to cardiovascular disease (Reis et al., 2008).

Ensuring that patients have levels of vitamin D greater than 30 ng/ml will decrease cardiovascular disease risk (Zittermann & Gummert, 2010). The literature also

suggests that those with adequate vitamin D stores will better be able to control their blood pressure within an acceptable range and possibly prevent hypertension (Bouillon, 2009; Ullah et al., 2010). A systematic review showed no significant positive effect of vitamin D supplementation on patients with hypertension; however, a significant finding of reduction in diastolic blood pressure was seen (Witham, Nadir, & Struthers, 2009). Further research on supplementation and treatment with vitamin D is needed in this area, but the research is highly suggestive that vitamin D will decrease patient's risk of cardiovascular disease.

Table 2.2. *Literature analysis: Cardiovascular system*

Author	Journal	Study design	Sample	Findings	Level of evidence
Giovannucci, Liu, Hollis, & Rimm, 2008	Archives of Internal Medicine	Case-control study	18,225 men aged 40 to 75 years old, free from cardiovascular disease at start of study	Low levels of vitamin D are associated with increased risk of myocardial infarctions	2-
Hsia, Heiss, Ren, Allison, Dolan, Greenland, . . . Trevisan, 2007	Circulation	Random-ized control trial	36,282 postmenopausal women aged 50-79 received calcium carbonate 500 mg with vitamin D 200 IU bid or placebo over 7 years	Supplementation with vitamin D and calcium daily did not show any effect of coronary or cerebrovas-cular risk. There is no adverse effect to taking these supplements	1-

Author	Journal	Study design	Sample	Findings	Level of evidence
Kim, Sabour, Sagar, Adams, & Whellan, 2008	The American Journal of Cardiology	Cohort study	8,351 adults over 20 years old from NHANES 2001 and 2004 data	Low vitamin D is associated with coronary heart disease and heart failure	2+
Pilz, Dobnig, Fischer, Wellnitz, Seelhorst, Boehm, & Marz, 2008	Stroke	Cohort study	3,316 white patients presenting for coronary angiography in Germany	Low levels of vitamin D were predictive of fatal strokes	2-
Pilz, Marz, Wellnitz, Seelhorst, Fahrleitner-Pammer, Dimai, . . . Dobnig, 2008	Journal of Clinical Endocrin-ology and Metabolism	Cohort study	3,316 white patients presenting for coronary angiography in Germany	Vitamin D deficiency is associated with myocardial dysfunction, heart failure, and sudden cardiac deaths	2+
Reis, Michos, von Muhlen, & Miller, 2008	The American Journal of Clinical Nutrition	Cross-sectional cohort study	2987 white and 866 black persons 40 years old or older	Racial differences in vitamin D status contribute to an increase risk in PAD in blacks compared to whites	2-
Reis, von Muhlen, Miller, Michos, Appel, 2009	Pediatrics	Cross-sectional cohort study	3577 non-pregnant adolescents without diabetes diagnosis	Vitamin D deficiency is strongly associated with hypertension, elevated blood sugar, metabolic syndrome, and obesity	2++

Author	Journal	Study design	Sample	Findings	Level of evidence
Ullah, Uwaifo, Nicholas, & Koch, 2010	International Journal of Endocrin-ology	Narrative Review	33 epidemiologic al, prospective, and clinical studies	There is an association between vitamin D deficiency and hypertension	3
Wang, Manson, Song, & Sesso, 2010	Annals of Internal Medicine	Meta-analysis	17 prospective studies and RCTs	Supplementati on with moderate to high levels of vitamin D reduces CVD risk; calcium supplements have minimal effect on CVD risk	1+
Wang, Pencina, Booth, Jacques, Ingelsson, Lanier, . . . Vasan, 2008	Circulation	Cohort study	1739 white participants without cardiovascular disease or kidney disease	There is an association between vitamin D deficiency and cardiovascular disease	2+
Witham, Crighton, Gillespie, Struthers, & McMurdo, 2010	Circulation. Heart Failure	Random-ized control trial	Double-Blind placebo trial of persons 70 years and older with chronic heart failure and vitamin D_2 deficient. Either supplemented with 100,000 IU Vitamin D one and then 10 weeks later, or placebo	Supplementati on with vitamin D proved no effect on physical function or quality of life on those suffering from chronic heart failure	1+

Author	Journal	Study design	Sample	Findings	Level of evidence
Witham, Nadir, & Struthers, 2009	Journal of Hypertension	Meta-analysis	11 RCTs	Weak evidence to support a lowered blood pressure with vitamin D supplemen-tation	1-
Zitterman & Gummert, 2010	Journal of Photochemistry and Photobiology	Narrative review	20 Experimental, RCTs, and case-control and cohort studies	Improvement of vitamin D levels is recommended to prevent cardiovascular disease	3

Cancer.

Recent studies have linked a low serum concentration of vitamin D to various cancers (Table 2.3). Ecological studies in the past noted an increase in the incidence of cancers, particularly those of the digestive tract, in areas of less sunny, more northern latitudes (Garland & Garland, 1980). The hypothesis and subsequent research lead to the discovery that perhaps vitamin D has a protective effect against the development of cancer. The vitamin D receptor, or VDR, is expressed in virtually all tissues in the body including colon epithelium, prostate, and breast (Garland et al., 2006). Its role has been shown in cell differentiation, inhibition, proliferation, and even apoptosis, making its link to cancer plausible (Luong & Nguyen, 2010). In a review by Garland and colleagues, it is suggestive that vitamin D has a protective effect against cancers and that consumption and intake of vitamin D can decrease cancer-related mortalities (Garland et al., 2006).

Numerous studies have been conducted that link a deficiency in vitamin D with colorectal cancer. Several prospective studies examined the association between

25(OH)D levels and colorectal cancer occurrence and found that lower levels of vitamin D are associated with increased incidence of cancer and cancer mortality (Freedman, Looker, Chang, & Graubard, 2007; Giovannucci, Liu, Rimm et al., 2006; Giovannucci, Liu, & Willett, 2006). One prospective study found that those who were already diagnosed with colorectal cancer had a much better chance at survival if they had adequate serum vitamin D levels (Ng et al., 2009). A large meta-analysis conducted by Wei and colleagues found a direct inverse relationship between both vitamin D intake and serum vitamin D levels with colorectal adenoma incidence (Wei, Garland, Gorham, Mohr, & Giovannucci, 2008). The researchers conclude that vitamin D is necessary in the prevention of colorectal cancer. Two studies suggest that daily vitamin D intake should be between 1000 IU and 2000 IU daily to reduce the risk of developing digestive-cancer, which is much higher than the current recommendation of just 200 IU daily (Giovannucci, Liu, Rimm et al., 2006; Gorham et al., 2007).

In a cohort study of the U.S. population, researchers found that those who consumed high levels of vitamin D were at a decreased risk of developing pancreatic cancer, which is a leading cause of all cancer deaths in the United States (Skinner et al., 2006). Persons who consumed a minimum of 600 IU of vitamin D daily decreased their risk of contracting the deadly cancer by more than 40% (Skinner, et al., 2006). A longitudinal population-based study did not find an association between vitamin D deficiency and ovarian cancer (Toriola et al., 2010). However, the researchers did suggest that low levels of serum vitamin D put patients at risk of developing ovarian cancer (Toriola et al.). In a pooled analysis conducted on vitamin D and breast cancer risk, having a 25(OH)D level of at least 50 ng/ml concentration would decrease the risk

of developing breast cancer by as much as 50% (Garland et al., 2007). In order to maintain and achieve this level of serum vitamin D, approximately 2000 IU of vitamin D_3 should be consumed daily and 10-15 minutes of UVB exposure daily (Garland et al., 2007). Again, much of the research presented recommends much higher vitamin D intake than the current recommendations. A powerful four-year double blind randomized control trial of almost 1200 subjects concluded that improving vitamin D levels in the body will drastically decrease all-cancer risk in postmenopausal women (Lappe, Travers-Gustafson, Davies, Recker, & Heaney, 2007).

Table 2.3. *Literature analysis: Cancer*

Author	Journal	Study design	Sample	Findings	Level of evidence
Freedman, Looker, Chang, & Graubard, 2007	Journal of the National Cancer Institute	Cohort study	16,818 participants aged 17 and older	No evidence of an association between serum vitamin D levels and total cancer mortality. There is an inverse relationship between vitamin D levels and colorectal cancer mortality	2-
Garland, Garland, Gorham, Lipkin, Newmark, Mohr, & Holick, 2006	American Journal of Public Health	Narrative review	63 epidemiological studies	Improving vitamin D status could reduce risk of cancer and mortality with few side effects and low cost	1-
Garland, Gorham, Mohr, Grant, Giovannucci, Lipkin, . .	The Journal of Steroid Biochemistry and Molecular	Meta-analysis	2 case control studies	Maintaining serum vitamin D levels greater than 52 ng/ml reduces the risk of breast cancer	2-

Author	Journal	Study design	Sample	Findings	Level of evidence
. Garland, 2007	Biology			by 50%. In order to maintain this serum vitamin D level, an intake of at least 2000 IU/d is necessary	
Giovannucci, Liu, Rimm, Hollis, Fuchs, Stampfer, & Willett, 2006	Journal of the National Cancer Institute	Cohort study	1,095 men aged 40-75 years old	Low levels of vitamin D are associated with digestive-system cancers and likely associated with increase incidence of all-cause cancer in men. Daily supplementation should be 1500IU/day	2++
Giovannucci, Liu, & Willett, 2006	Cancer Epidemiology, Biomarkers & Prevention	Cohort study	43,468 white men and 481 black men aged 40-75	Blacks have a higher incidence of cancer and mortality due to their higher risk for vitamin D deficiency	2-
Lappe, Travers-Gustafson, Davies, Recker, & Heaney, 2007	The American Journal of Clinical Nutrition	Randomized control trial	1179 community-dwelling women aged 55 or greater, postmenopausal over 4 years supplemented with 1100 IU/d vitamin D plus calcium, calcium alone, or placebo	All cancer risk was decreased with increased vitamin D status in postmenopausal women. Vitamin D serum levels are strong predictors of cancer risk	1+

Author	Journal	Study design	Sample	Findings	Level of evidence
Ng, Wolpin, Meyerhardt, Wu, Chan, Hollis, . . . Fuchs, 2009	British Journal of Cancer	Cohort study	1017 participants in Nurses' Health Study and Health Professionals Follow-up study diagnosed with colorectal cancer	Higher serum vitamin D levels after colorectal cancer diagnosis are associated with increased survival rates	2-
Skinner, Michaud, Giovannucci, Willett, Colditz, & Fuchs, 2006	Cancer Epidemi-ology, Biomarker & Prevention	Cohort study	75,427 women from NHS study and 46,771 men from HPFS study	A higher intake of vitamin D is associated with decreased risk of developing pancreatic cancer	2+
Toriola, Surcel, Agborsangaya, Grankvist, Tuohimaa, Toniolo, . . . Lehtinen, 2010	European Journal of Cancer	Case-control study	Females diagnosed with ovarian cancer from Finnish Maternity Cohort study plus matching controls	Increased risk of ovarian cancer is associated with low levels of vitamin D, but no significant association	2-
Wei, Garland, Gorham, Mohr, & Giovannucci, 2008	Cancer Epidemi-ology, Biomarker & Prevention	Meta-analysis	17 epidemiological studies	Serum vitamin D and vitamin D intake are associated with colorectal adenoma incidence and recurrence. Vitamin D is necessary for prevention	1++

Cognition and mood.

Recently, new research has shown a possible link between vitamin D levels and cognition and mood (Table 2.4). In a study of nearly 18,000 adults in England, researchers found that low levels of vitamin D are suggestive of increased cognitive impairment (Llewellyn, Langa, & Lang, 2009). In a large observational cohort study, 752 female subjects aged 75 and older were examined to test the hypothesis that vitamin D deficiency is associated with a decrease in cognitive function (Annweiler et al., 2010). The researchers found that after adjusting for confounders, there was a significant association between low serum 25(OH)D and cognitive impairment (Annweiler et al., 2010). Another cross-sectional study of 80 adults at the Alzheimer's Disease Research Center at Washington University found that vitamin D deficiency was also associated with low cognitive performance but also with depression (Wilkins et al., 2006). Vitamin D has been linked to many other mood disorders including major depressive disorder, seasonal affective disorder, and premenstrual syndrome (Murphy & Wagner, 2008). The exact mechanism of why vitamin D negatively affects cognition and mood is not fully understood, but it is thought that the vitamin D receptors somehow affect glucocorticoid signaling, influencing the cortisol levels in the brain (Murphy & Wagner). Supplementation with vitamin D showed to be more beneficial than phototherapy for enhancing affects in those suffering from seasonal affective disorder (Wilkins et al.).

Table 2.4. *Literature analysis: Cognition and mood*

Author	Journal	Study design	Sample	Findings	Level of evidence
Annweiler, Schott, Allali, Bridenbaugh, Kressig, Allain, . . . Beauchet, 2010	Neurology	Cross-sectional cohort study	752 women aged 75 or older	Vitamin D deficiency is significantly associated with cognitive impairment	2++
Llewellyn, Langa, & Lang, 2009	Journal of Geriatric Psychiatry and Neurology	Cohort study	1766 adults aged 65 and older from population-based study	Low levels of vitamin D are associated with cognitive impairment	2-
Murphy & Wagner, 2008	Journal of Midwifery and Women's Health	Integrative Review	6 quantitative research studies	There is evidence to support an association between mood disorders and low levels of vitamin D	2-
Wilkins, Sheline, Roe, Birge, & Morris, 2006	The American Journal of Geriatric Psychiatry	Cross-sectional cohort study	40 participants with Alzheimer Disease and 40 controls	Vitamin D deficiency is associated with low mood and cognitive impairment	2-

Type 2 diabetes.

Vitamin D is also shown to have a pivotal role in diabetes (Table 2.5). Research has shown a link to vitamin D and pancreatic beta-cell function and insulin sensitivity (Chiu, Chu, Go, & Saad, 2004; Pittas, Lau, Hu, & Dawson-Hughes, 2007). Studies on animals have shown that with low vitamin D levels, beta cells have decreased insulin

sensitivity and production, but are restored to normal functioning when vitamin D levels are restored (Chiu et al.; Pittas et al., 2006). Evidence also indicates that persons with diabetes have lower serum levels of vitamin D than persons without diabetes (Penckofer, Kouba, Wallis, & Emanuele, 2008). In a comprehensive review of the literature by Mathieu and colleagues, vitamin D deficiency was shown to be harmful on beta cell functioning, therefore predisposing individuals to develop type 2 diabetes (Mathieu, Gysemans, Giulietti, & Bouillon, 2005). Many studies have shown an inverse relationship between vitamin D levels and type 2 diabetes (Cigolini et al., 2006; Forouhi, Luan, Cooper, Boucher, & Wareham, 2008; Liu et al., 2009; Pittas, Harris, Stark, & Dawson-Hughes, 2007). In addition, African Americans are known to be at an increased risk for both type 2 diabetes mellitus and vitamin D deficiency. In a study by Youssef and colleagues, supplementation with vitamin D not only showed significant improvement in glycemic control for a previously uncontrolled African American diabetic, but also that minorities with diabetes should be closely monitored for vitamin D deficiency (Youssef, El Abbassi, Jones, Woodby, & Peiris, 2010).

Knowing that there is an association between vitamin D deficiency and type 2 diabetes, research on whether supplementation with vitamin D is beneficial to the disease process of diabetes is warranted. A double-blind randomized control trial found that supplementation with 400 IU of vitamin D_3 did not have any preventive effect on developing diabetes (de Boer et al., 2008). However, the dosage used was lower than current research recommendations and the study was limited by not being able to control for confounding variables such as diet and genetics (de Boer et al.). Another study by Borissova and colleagues (2003) found that supplementation with 1332 IU to diabetics

resulted in a 70% improvement in glycemic control (Borissova, Tankova, Kirilov, Dakovska, & Kovacheva, 2003). In a large meta-analysis of over 55 studies, researchers found that vitamin D, when combined with adequate levels of calcium intake, showed significant benefits in improving glucose metabolism (Pittas, Lau et al., 2007). An observational study of nearly 600 type 2 diabetics in Japan found that there was a direct association between low levels of vitamin D and microvascular complications that were often accompanied with diabetes complications (Suzuki et al., 2006).

Table 2.5. *Literature analysis: Type 2 diabetes*

Author	Journal	Study design	Sample	Findings	Level of evidence
Chiu, Chu, Go, & Saad, 2004	The American Journal of Clinical Nutrition	Cross-sectional cohort study	126 healthy glucose tolerant subjects	Low levels of vitamin D are associated with a higher risk of insulin resistance and metabolic syndrome	3
Cigolini, Iagulli, Miconi, Galiotto, Lombardi, & Targher, 2006	Diabetes Care	Cross-sectional cohort study	459 type 2 diabetic outpatients and 459 non-diabetic controls	Low levels of serum vitamin D levels are associated with high CVD risk factors in type 2 diabetics	2-
deBoer, Tinker, Connelly,Curb, Howard, Kestenbaum, . . . Weiss, 2008	Diabetes Care	Randomized control trial	33, 951 postmenopausal women without diabetes enrolled in the Women's health initiative calcium/vitamin D trial	Calcium plus vitamin D_3 did not prevent the development of type 2 diabetes	1+

Author	Journal	Study design	Sample	Findings	Level of evidence
Forouhi, Luan, Cooper, Boucher, & Wareham, 2008	Diabetes	Cohort study	524 nondiabetic men and women 40-69 years old	Baseline serum 25 (OH) D is inversely associated with a ten-year risk of hyperglycemia	2+
Liu, Meigs, Pittas, McKeown, Economos, Booth, & Jacques, 2009	The Journal of Nutrition	Cross-sectional cohort study	2, 803 nondiabetic members of the 7th examination cycle (1998-2001) of the Framingham study group	Vitamin D is inversely related to fasting measures of insulin resistance, thus indicating a link between vitamin D and type 2 diabetes	2+
Mathieu, Gysemans, Giulietti, & Bouillon, 2005	Diabetologia	Narrative review	13 observational and case-control studies	Vitamin D deficiency is detrimental to beta-cell function, leads to glucose intolerance and predisposes to type 2 diabetes	2-
Penckofer, Kouba, Wallis, & Emanuele, 2008	The Diabetes Educator	Narrative review	33 epidemiological studies including RCTs, meta-analysis, systematic reviews, case-control, and cohort studies	Adequate intake of vitamin D prevents and delays the onset of diabetes and reduces complications associated with diabetes	1+

Author	Journal	Study design	Sample	Findings	Level of evidence
Pittas, Dawson-Hughes, Li, Dam, Willett, Manson, & Hu, 2006	Diabetes Care	Cohort study	83,779 women from Nurses' Health Study with no history of diabetes, CVD, or cancer	4,843 cases of diabetes were documented, and found no association between total vitamin D intake and type 2 diabetes, however it was shown to reduce the risk of developing diabetes	3
Pittas, Harris, Starck, & Dawson-Hughes, 2007	Diabetes Care	Randomized control trial	314 Caucasian Adults	Those with impaired fasting glucose at baseline had a lower rise in fasting plasma glucose when using calcium and vitamin D compared with placebo	2++
Pittas, Lau, Hu, & Dawson-Hughes, 2007	The Journal of Clinical Endocrinology and Metabolism	Meta-analysis	55 studies reviewed including RCTs, cross-sectional, case-control, and prospective studies	Vitamin D and calcium insufficiency negatively influence glycemic control. When combined, they show beneficial effects of improving glucose metabolism	1++

Author	Journal	Study design	Sample	Findings	Level of evidence
Suzuki, Kotake, Ono, Kato, Oda, Hayakawa, . . . Itoh, 2006	Endocrine Journal	Case-control cohort study	581 adult type 2 diabetes patients and comparable controls	Microvascular complications and insulin treatment is associated with vitamin D deficiency. Also, vitamin D deficiency is related to osteoporotic fractures in type 2 diabetics using insulin	2-

Other conditions.

There are numerous other chronic conditions that have recently been linked to vitamin D deficiency (Table 2.6). One study found that 92% of patients suffering from chronic liver disease were vitamin D deficient and those with cirrhosis where likely to be severely deficient with level less than 7 ng/ml (Arteh et al., 2009). Patients suffering from chronic kidney disease are often afflicted with vitamin D deficiency secondary to the changes in calcitriol and PTH caused by the decline in renal function (Gal-Moscovici & Sprague, 2007). Two Cochrane reviews examined chronic kidney disease and vitamin D and did not find that supplementation with vitamin D decreased morbidity or mortality in these patients, but it did decrease PTH levels, positively impacting those patients undergoing dialysis treatment (Palmer et al., 2009a, 2009b). Further research into this area is needed. Conditions with possible links to vitamin D deficiency requiring future research include chronic obstructive pulmonary disease (COPD), anemia, Parkinson and Alzheimer disease, systemic lupus erythematosus, multiple sclerosis, allergic rhinitis, and

influenza (Cannell et al., 2006; Cannell, Zasloff, Garland, Scragg, & Giovannucci, 2008; Evatt et al., 2008; Janssens et al., 2009; Myhr, 2009; Ruiz-Irastorza, Egurbide, Olivares, Martinez-Berriotxoa, & Aguirre, 2008; Sim et al., 2010; Wjst & Hypponen, 2007).

Table 2.6. *Literature analysis: Other conditions*

Author	Journal	Study design	Sample	Findings	Level of evidence
Arteh, Narra, & Nair, 2009	Digestive Diseases and Sciences	Cross-sectional cohort study	118 patients with chronic liver disease	Patients with chronic liver disease suffer from severe vitamin D deficiency (<7 ng/mL) and adequate levels of 25(OH)D should be considered in management of CLD	2-
Cannel, Vieth, Umhau, Holick, Grant, Madronich, . . . Giovannucci, 2006	Epidemi-ology and Infection	Narrative review	10 epidemiological studies reviewed	Vitamin D may be associated with viral respiratory illnesses	3
Cannell, Zasloff, Garland, Scragg, Giovannucci, 2008	Virology Journal	Narrative review	9 prospective, epidemiological, clinical studies and RCTs	Vitamin D may be the seasonal cause of influenza	3

Author	Journal	Study design	Sample	Findings	Level of evidence
Evatt, DeLong, Khazai, Rosen, Triche, & Tangpricha, 2008	Archives of Neurology	Cohort study	300 patients from the Clinical Research in Neurology database, 100 with Parkinsons, 100 with Alzheimers, and 100 controls	Prevalence of vitamin D insufficiency (<30 ng/ml) was significantly higher in patients with Parkinson Disease than in the healthy control group. Also, patients with Parkinson Disease have lower vitamin D levels compared to patients with Alzheimer Disease	2+
Gal-Moscovici & Sprague, 2007	Journal of Bone and Mineral Research	Narrative review	20 prospective, clinical, and epidemiological studies	Vitamin D deficiency occurs very early in the development of chronic kidney disease. RCTs are needed in this area	3
Janssens, Lehouck, Carremans, Bouillon, Mathieu, & Decramer, 2009	American Journal of Respiratory and Critical Care Medicine	Narrative review	27 epidemiological studies	Vitamin D supplementation should be considered to all patients with COPD and RCTs are needed in this area	3

Author	Journal	Study design	Sample	Findings	Level of evidence
Myhr, 2009	Journal of the Neurological Sciences	Narrative review	23 prospective, clinical, and epidemiological studies	Vitamin D influences susceptibility to Multiple Sclerosis and also affects disease activity	3
Palmer, McGregor, Craig, Elder, Macaskill, & Strippoli, 2009a	Cochrane Database of Systematic Reviews	Systematic review	60 RCTs	There is no sufficient evidence to suggest that supplementation with vitamin D to persons with chronic kidney disease requiring dialysis alters risk of death, bone pain, or parathyroidectomy	1++
Palmer, McGregor, Craig, Elder, Macaskill, & Strippoli, 2009b	Cochrane Database of Systematic Reviews	Systematic review	16 RCTs	There is not sufficient evidence to suggest that supplementation of vitamin D to persons with chronic kidney disease but not requiring dialysis alters mortality risk or need for dialysis	1++
Ruiz-Irastorza, Egurbide, Olivares, Martinez-Berriotxoa,	Rheumatology (Oxford)	Cross-sectional cohort study	92 patients attending a Lupus clinic, all diagnosed with SLE	75% patients tested were vitamin D deficient, associated with avoidance of	2+

Author	Journal	Study design	Sample	Findings	Level of evidence
& Aguirre, 2008				sun. No relation between severity of SLE and vitamin D levels. Lower levels of vitamin D was associated with increased fatigue	
Sim, Lac, Liu, Meguerditchian, Kumar, Kujubu, & Rasgon, 2010	Annals of Hematology	Cross-sectional cohort study	554 subjects aged 17 and older enrolled with Kaiser Permanente Southern California	Subjects who were vitamin D deficient had a lower mean hemoglobin level compared with those who had normal vitamin D levels	2-
Wjst & Hypponen, 2007	Allergy	Cohort Study	18,223 participants non-Hispanic white or African American with known age and vitamin D level	Those with higher levels of vitamin D were more likely to suffer from allergic rhinitis	2-

Summary

The literature is not clear on the exact amount of daily vitamin D supplementation necessary to achieve adequate health. However, it is clear that the current RDA guidelines need to be amended (Hathcock, Shao, Vieth, & Heaney, 2007; Holick, 2007; Vieth et al., 2007). The guidelines were written in 1997, with sources cited that are over

15-20 years out of date (Institute of Medicine, 1997). The need for higher supplementation and guidance for practitioners is required to prevent the harmful effects associated with vitamin D deficiency (Table 2.7). What is known is that patients need to be properly supplemented with vitamin D or intake adequate UVB radiation and consume vitamin D sources in their diet to achieve and maintain serum 25(OH)D levels of at least 30ng/ml year round, some studies recommending even higher levels of 40-70 ng/ml (Cannell & Hollis, 2008). There is no single dose of vitamin D that is acceptable for all patients as factors such as age, body fat, skin color, season, latitude, chronic conditions, and UVB exposure should all be taken into consideration (Cannell, Hollis et al., 2008). A safe amount for all individuals is at least 800 - 1000 IU daily, taking into account the previously mentioned factors (Bischoff-Ferrari et al., 2009; Hathcock et al., 2007; Holick, 2007). Monitoring of serum 25(OH)D levels is necessary, especially for those suffering from chronic conditions.

Table 2. 7. *Literature analysis: Supplementation*

Author	Journal	Study Design	Sample	Findings	Level of Evidence
Bischoff-Ferrari, Shao, Dawson-Hughes, Hathcock, Giovannucci, & Willet, 2009	Osteoporosis International	Meta-analysis	8 double-blind RCTs for falls (n=2426); 12 double-blind RCTs for non-vertebral fractures (n=42,279)	Vitamin D levels should be at least 30 ng/mL to prevent fractures, falls, mortality, colorectal cancer, and maintain cardiovascular health. No hypercalcemic risk was associated with these levels. Intake levels of 100,000 IU/d were associated	1+

Author	Journal	Study Design	Sample	Findings	Level of Evidence
				with hypercalcemia. Doses of 1,800 to 4,000 IU/d is acceptable.	
Hathcock, Shao, Vieth, & Heaney, 2007	The American Journal of Clinical Nutrition	Systematic review	30 human-based clinical trials examining dosage and toxicity	Through a risk assessment, the current tolerable upper limit of vitamin D (2000 IU/d) should be increased based on randomized controlled trials to 10,000 IU/d of vitamin D_3	1++
Holick, 2007	The New England Journal of Medicine	Systematic review	38 RCTs, prospective studies, and clinical studies	Vitamin D deficiency is common and is linked to bone health, cancer, and other chronic diseases. Supplementation with at least 800 IU daily of vitamin D_3 is necessary to ensure vitamin D sufficiency	1+
Vieth, Bischoff-Ferrari, Boucher, Dawson-Hughes, Garland, Heaney, . . . Zitterman, 2006	The American Journal of Clinical Nutrition	Narrative review	7 prospective, clinical, and epidemiological studies	The current guidelines of the tolerable upper limit of vitamin D intake (2000 IU/d) per the Institute of Medicine should be revised and increased based on current research	3

CHAPTER 3

Guideline for Screening and Treating Vitamin D Deficiency

Vitamin D deficiency has become a hot topic among the medical community in recent years. Vitamin D, once thought to only be associated with bone health, has been linked to a host of chronic conditions including cardiovascular disease, diabetes, cancer, disorders of mood and cognition, and even to all-cause mortality rates (Annweiler et al., 2010; Autier & Gandini, 2007; Lappe et al., 2007; Penckofer et al., 2008; Pilz, Marz, et al., 2008; Reis et al., 2009. Current guidelines of necessary daily intake of vitamin D are grossly outdated with new research providing evidence that adults should take in more daily vitamin D than currently recommended and that maintaining sufficient vitamin D levels can have vast beneficial effects on health. This guideline is a comprehensive systematic review of current evidence. The recommendations that comprise the guideline are graded using the SIGN 50 grades of recommendation (Scottish Intercollegiate Guidelines Network, 2008). (Appendix B). The grade indicates the strength of the evidence for each particular recommendation.

Evidence Linked to Recommendations

1. Healthcare providers should perform a baseline screen of all adult patients for vitamin D deficiency (Grade D) and supplement accordingly to maintain levels of a minimum of 30 ng/ml (Grade A). Vitamin D is not only essential to bone health, but recently has been linked to numerous chronic disease states. By screening patients and

adequately supplementing with necessary vitamin D, prevention of these adverse health outcomes may be possible. Current intake recommendations of 400 IU daily for adults is not adequate to maintain a sufficient vitamin D status (Institute of Medicine, 1997). Supplementation of at least 800 to 1000 IU daily of vitamin D is necessary to maintain vitamin D sufficiency (Bischoff-Ferrari et al., 2009; Holick, 2007). Tolerable safe upper limits of vitamin D intake were found to be near 100,000 IU daily without adverse effects, an amount exceedingly higher than any person should need to consume to reach an adequate serum level (Hathcock et al., 2007; Vieth et al., 2007). Vitamin D toxicity is extremely rare, with serum levels greater than 150 ng/ml and side effects including hypercalcemia, pancreatitis, nausea, and vomiting (Cannell & Hollis, 2008; Cannell, Hollis et al., 2008; Holick, 2007). Contraindications to vitamin D supplementation include allergy to vitamin D, metastatic bone disease, granulomatous diseases, or sarcoidosis. (Bordelon et al., 2009)

Repletion of vitamin D is achieved primarily through supplementation. The most commonly available forms are ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Current treatment of vitamin D deficiency for healthy adults is 50,000 IU of vitamin D weekly for six to eight weeks (Bordelon, Ghetu, & Langan, 2009). Serum 25(OH)D levels should again be monitored three months after therapy to adjust vitamin D dosages accordingly with the goal of a minimum level of 30 ng/ml. Maintenance doses of 800 to 2000 IU daily may then be prescribed. Patients who are obese or have malabsorptive states or chronic liver or kidney disease may require much higher supplementation to

achieve adequate serum 25(OH)D levels (Arteh et al., 2009; Gal-Moscovici & Sprague, 2007; Holick, 2007).

In addition, more emphasis should be placed on populations at high risk for vitamin D deficiency. The elderly, obese, and those suffering from chronic kidney and liver disease, or those with diseases affecting absorption such as cystic fibrosis or Crohn's disease should all be monitored more closely for vitamin D deficiency (Arteh et al., 2009; Gal-Moscovici & Sprague, 2007; Holick, 2004; Holick, 2007). In addition, those with increased skin pigmentation, such as African Americans, are also at an increased risk of deficiency due to the decline in absorption of vitamin D from UVB, blocked by increased melanin in the skin (Fiscella & Franks, 2010; Reis et al., 2008). This is particularly important considering the racial disparities that exist between blacks and whites. African Americans are at a greater increased risk of cardiovascular disease, type 2 diabetes, asthma, breast cancer, and colorectal cancer (Agency for Healthcare Research and Quality, 2000; Bodnar & Simhan, 2010; Reis et al., 2008; Youssef et al., 2010). With the proven associations between vitamin D deficiency and these chronic diseases, adequate screening and supplementation of these minority populations is critical to aid in eliminating these healthcare disparities.

Not only is general screening beneficial for the health and lives of the patients, but it also is cost effective. Serum 25(OH)D tests are relatively inexpensive, averaging from no fee to $250, but vary depending on insurance coverage and test availability (Vitamin D Council, 2008). Supplementation is also reasonably affordable, with over the counter preparations costing much less than average medications for diabetes or heart disease and obtaining vitamin D through sun exposure is free (Vitamin D Council, 2008).

In addition, the cost of chronic diseases in the country are staggering. Nearly 75% of all healthcare costs are incurred due to chronic diseases, including heart disease, cancer, and diabetes (Centers for Disease Control and Prevention [CDC], 2009). Supplementation with vitamin D, or obtaining adequate sun intake, can greatly decrease the risk of development of these chronic diseases, and ultimately reduce the cost of healthcare spending.

2. Vitamin D deficiency is associated with an increased risk of all-cause and cardiovascular mortality (Grade A); therefore, healthcare providers should perform a serum 25(OH)D screen to assess patient's vitamin D status (Grade D). The evidence shows a strong significant correlation between vitamin D deficiency and mortality (Autier & Gandini, 2007; Fiscella & Franks, 2010; Ginde, Scragg et al., 2009; Pilz, Dobnig et al., 2009). Low levels of serum vitamin D are linked to increased risk of death. It is important for healthcare providers to ensure that patients maintain a sufficient level of vitamin D of at least 30 ng/ml in order to decrease mortality risk and prolong the lives of their patients.

3. There is an association between vitamin D deficiency and cardiovascular disease (Grade A) and supplementation with vitamin D reduces cardiovascular disease risk (Grade B). Evaluation of the literature did demonstrate an association between low levels of vitamin D and cardiovascular disease, particularly hypertension, stroke, and heart failure (Pilz, Marz et al., 2008; Reis et al., 2009; L. Wang et al., 2010; T. J. Wang et al., 2008; Witham et al., 2009). In addition, by adding regular supplementation of vitamin D daily to the diet, the evidence showed it could possibly reduce a patient's risk of developing cardiovascular disease with no adverse effects (Hsia et al., 2007; L. Wang

et al., 2010; Witham et al., 2009). Heart disease is the leading cause of death in the United States and reducing risk factors of developing such a deadly disease is imperative (Centers for Disease Control and Prevention, 2009).

4. Increased intake of vitamin D is associated with a decreased risk of developing certain types of cancer (Grade A). Numerous studies showed that by increasing the daily intake of vitamin D, the risk to developing cancers including breast, digestive system, colorectal, and pancreatic was drastically decreased (Garland et al., 2007; Giovannucci, Liu, Rimm et al., 2006; Gorham et al., 2007; Lappe et al., 2007; Skinner et al., 2006; Wei et al., 2008). Supplementation was much greater than the current daily recommendation, including amounts between1000 to 2000 IU daily to reduce the risk of developing these types of cancer. In addition, one large randomized control trial found that all cancer risk for postmenopausal women was decreased when supplemented with 1100 IU daily of vitamin D_3 (Lappe et al., 2007). It is safe to infer from these data that healthcare providers should ensure that all patients increase their daily vitamin D intake, primarily through supplementation, to help prevent the development of cancer.

5. Low levels of vitamin D are associated with a decline in cognitive function (Grade C); therefore, healthcare providers should screen the elderly population for vitamin D deficiency (Grade D). While the body of knowledge on this guideline is not vast, there is still substantial evidence to suggest that a serum vitamin D deficiency could contribute to cognitive decline (Annweiler et al., 2009; Llewellyn et al., 2009; Murphy & Wagner, 2008; Wilkins et al., 2006). Healthcare providers should screen for vitamin D deficiency, particularly in the elderly population where cognitive decline is an issue, and supplement accordingly to maintain sufficient levels of serum vitamin D.

6. Vitamin D deficiency is associated with type 2 diabetes (Grade A) and patients with type 2 diabetes should be monitored for vitamin D deficiency to improve glucose metabolism (Grade D). The research presented showed a significant association between low levels of serum vitamin D and type 2 diabetes, particularly the process of glucose metabolism in the body (Forouhi et al., 2008; Liu et al., 2009; Mathieu et al., 2005; Pittas, Harris et al., 2007; Pittas, Lau et al., 2007). The evidence suggested that vitamin D contributes to glucose control and diabetic patients should maintain adequate serum vitamin D levels to prevent hyperglycemia. In addition, low levels of vitamin D seem to negatively effect beta cell function and can predispose an individual to developing type 2 diabetes. Healthcare providers should monitor serum 25(OH)D levels in type 2 diabetic patients, or those at risk of developing type 2 diabetes, to help improve glycemic control and better manage the disease process.

Summary

The recommendations provided should serve as a guideline to healthcare providers. Vitamin D deficiency as it relates to bone health has long been studied and applied in clinical practice. This guideline serves to provide new screening and treatment recommendations beyond bone health as it relates to vitamin D deficiency.

CHAPTER 4

Conclusion and Recommendations

General Recommendations

Primary care practitioners should be aware of the potential harmful effects of vitamin D deficiency and should take an aggressive approach to educate their patients on the importance of proper vitamin D intake, and also to screen all patients to establish their vitamin D levels. Those high-risk individuals already suffering from chronic diseases such as type 2 diabetes, cancer, or cardiovascular disease should be monitored more closely. Daily supplementation is often necessary to achieve adequate levels and patients should be encouraged to comply with the prescribed regime, but education is necessary to enforce the compliance.

Implication for Practice

The best practice guideline presented suggests that healthcare providers should implement vitamin D screening into their basic protocol for patient care. All patients should be screened for vitamin D deficiency at least once to establish a baseline of care. Perhaps the best method is to add a serum 25(OH)D with the annual blood work during physical exam of each patient. Those who are at a greater risk for being vitamin D deficient such as those of darker skin tone, the obese, those who are home-bound and, therefore, lacking in sun exposure, or those with chronic liver or kidney disease

should perhaps be screened more often than annually. In addition, those who are at risk for developing, or already possess cardiovascular disease, decreased cognition, type 2 diabetes, or breast or digestive system cancers should also be screened more frequently to ensure adequate vitamin D sufficiency. The evidence is clear that vitamin D is not important solely for bone health any longer, but has much further implications for health. In addition new evidence is linking vitamin D deficiency to conditions not previously mentioned including chronic pain, multiple sclerosis, and psorasis (Ferguson & Chang, 2009; Kulie et al., 2009; Straube, Derry, Moore, & McQuay, 2010).

Implication for Research

Further research on the topic of vitamin D deficiency as it relates to chronic disease states is warranted. The need for high-quality randomized control trials examining the exact relationship of vitamin D and its causal effects with mortality, cancers, diabetes, mood, cognition, and other chronic conditions discussed is necessary. Trials investigating various supplementation amounts and the long-term effects such supplementation has on an individual's health are also necessary. However, these randomized control trials necessary to prove this exact relationship pose an ethical dilemma. With the known effects of vitamin D on health including those further explored in this paper, it would be unethical to withhold adequate amounts of vitamin D. In addition, since vitamin D is attainable through sun exposure, trials would need to be properly designed to control for this factor such as season, latitude, and sun exposure times. Further high-quality long-term cohort studies investigating the effects of vitamin D deficiency on chronic diseases such as heart disease and cancer are warranted. The evidence presented does show strong associations between vitamin D deficiency and

various chronic diseases. Future research on the exact nature of racial disparities relating to vitamin D deficiency is also warranted. In addition, examining the effects of vitamin D levels as it relates to dementia and even other psychiatric disorders is warranted based on the findings showing a relationship between vitamin D deficiency and mood.

Implication for Education of Healthcare Professionals

Vitamin D deficiency usually goes undiagnosed or overlooked in primary care practice. Once thought to only be related to bone health, many providers do not consider testing vitamin D levels if a patient is not at risk for fractures or osteomalacia (Cannell & Hollis, 2008). In addition, providers often screen for calcium during routine blood work and assume vitamin D sufficiency if calcium levels are normal, which is a false assumption (Holick, 2004). Erroneous tests of vitamin D might also be ordered. The proper screening for a vitamin D level is a serum 25(OH)D, the major form of vitamin D in the blood, that produces the most accurate assessment of a patient's vitamin D status (Cannell & Hollis, 2008; Holick, 2004; Judd & Tangpricha, 2009). The cost of screening for vitamin D ranges from no fee to 250 dollars depending on the type of insurance (Vitamin D Council, 2008). In addition, current vitamin D intake recommendations are too low to achieve an adequate vitamin D level and providers need to be aware of proper supplementation guidelines.

Providers should educate patients on foods rich in vitamin D, proper sun exposure techniques, or prescribe adequate supplementation to achieve a level of at least 30ng/ml serum 25(OH)D as recommended in this guideline (Table 4.1). Evidence recommends that proper sun exposure includes five to thirty minutes twice weekly of arms and legs during mid-day to allow the body to produce sufficient levels of vitamin D_3 (Holick,

2007; Kulie et al., 2009). Yet researchers warn of the harmful effects of even short amounts of UVB exposure as cumulative UV rays contribute to skin cancer. The Skin Cancer Foundation recommends instead that daily multivitamins and vitamin D fortified foods are a safer alternative to achieving adequate vitamin D and supplementation should be 1000 IU daily (The Skin Cancer Foundation, 2010).

Table 4.1. *Food sources containing vitamin D*

Source	Vitamin D Content
Fortified Milk	100 IU per 8 ounces
Fortified orange juice	100 IU per 8 ounces
Fortified yogurt	100 IU per 8 ounces
Fortified butter	56 IU per 3.5 ounces
Fortified margarine	429 IU per 3.5 ounces
Fortified breakfast cereals	100 IU per serving
Shitake mushrooms	100 IU per 3.5 ounces
Oily fish: salmon, mackerel, sardines	400 IU per 3.5 ounces
Egg yolks	20 IU per yolk

Source: (Holick, 2006a, 2006b)

Over the counter forms of vitamin D_3 include 400, 800, 1000, and 2000 IU amounts. The cost of daily supplementation of vitamin D using an over the counter preparation averages 2-4 dollars a month (Vitamin D Council, 2008). The only available prescription form is vitamin D_2, also known as ergocalciferol, and includes 50,000 IU in capsule form or 8000 IU/mL in liquid form (Holick, 2007). This analogue is thought to be less potent at raising serum vitamin D levels than its more active form of vitamin D_3

and increased supplementation amounts might be necessary (Armas et al., 2004; Cannell & Hollis, 2008; Rapuri et al., 2004). Toxicity to vitamin D is uncommon and adverse effects with supplementation including kidney stones and hypercalcuria are difficult to produce without extreme supplement amounts exceeding 10,000 IU daily (Brannon et al., 2008; Cannell, Hollis et al., 2008). The only absolute contradiction to supplementation with vitamin D is allergy to vitamin D or vitamin D toxicity (Cannell, Hollis et al., 2008).

Summary

Vitamin D has emerged as a supplement that has far surpassed its once believed sole function of adequate bone health. While vitamin D is still critical for bone health, the steroid's use moves far beyond the bones affecting chronic conditions such as cancer, type 2 diabetes, cognitive functions, mood, the cardiovascular system, and even mortality rates. It is crucial for healthcare providers to not only be aware of the various functions of vitamin D, but to actively be screening and treating patients who are vitamin D deficient. The research of vitamin D and its effects has only begun and in the future additional mechanisms of vitamin D will likely be discovered.

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APPENDIX A--SIGN 50 LEVELS OF EVIDENCE

Rating	Definition
1++	High quality meta-analysis, systematic review of RCTs, or RCTs with a very low risk of bias.
1+	Well-conducted meta-analysis, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analysis, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with very low risk of confounding or bias and high probability of a casual relationship
2+	Well-conducted case control or cohort study with low risk of confounding or bias and moderate probability of a casual relationship
2-	Case control or cohort study with high risk of confounding or bias and significant risk that the relationship is not casual
3	Non-analytical studies
4	Expert opinion

Source: Scottish Intercollegiate Guidelines Network, 2008

APPENDIX B--SIGN 50 GRADES OF RECOMMENDATION

Grade	Definition
A	At least one meta-analysis, systematic review, or RCT rated 1++ and directly related to target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated 2++, directly applicable to target population, and demonstrating overall consistency or results; or extrapolated evidence from studies rated 1++ to 1+
C	A body of evidence including studies rated as 2+, directly applicable to target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated 2++
D	Evidence rated 3 or 4; or extrapolated evidence from studies rated 2+

Source: Scottish Intercollegiate Guidelines Network, 2008