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University of Nevada, Reno

**The Adequacy of Current Dietary  
Vitamin D Recommendations**

A thesis submitted in partial fulfillment  
Of the requirements for the degree of  
Bachelor of Science in Nutritional Science and the Honors Program

By

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Vitamin D Recommendations**

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## Abstract

There has been a recent resurgence of media attention and research on the topic of Vitamin D due to an increased prevalence of deficiency. Thus leading to the question, is the current *Daily Recommended Intake* (DRI) enough? This review will be examining evidence based research articles in the scientific literature (peer reviewed) regarding the adequacy of current recommendations for Vitamin D intake to maintain normal levels in the blood and the recommended intake to restore deficient levels of Vitamin D to normal range. Additional detailed background information on the mechanisms of the activation of Vitamin D, effects of Vitamin D deficiency, measurements of Vitamin D status in the blood, and the current recommendations for Vitamin D intake is also discussed. The literature review indicates that the current DRI (5ug/d or 200 IU) to maintain normal levels is not sufficient and does in fact needs to be increased to 800-1000 IU (20 ug-25 ug). Once Vitamin D deficient, there were conflicting recommendations in the scientific literature as to the dose needed and the length of treatment to restore blood levels back to normal. Further research is indicated regarding this topic.

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## INTRODUCTION:

Vitamin D can be referred to as calciferol and is called the sunshine vitamin, since the human body, in a sunny climate, can create this nutrient from sunlight on the skin using cholesterol from the body (DeLuca, 2004). Vitamin D belongs to the group of fat-soluble vitamins. The two important forms of Vitamin D are D2 also known as ergocalciferol - the plant source of vitamin D and Vitamin D3 referred to as cholecalciferol (Fieser and Fieser, 1959). Vitamin D3 is produced in the skin when exposed to sunlight. If an individual is exposed *adequately* to sunlight there is no further need for Vitamin D from food or in the form of supplements (DeLuca and Zierold, 1998). However, food sources alone may not provide adequate amounts of Vitamin D to prevent a deficiency and so a conscious consumption of Vitamin D rich foods and deliberate exposure of the skin to sunlight is required to prevent any possible deficiencies. The major food sources of Vitamin D include fortified milk, cheese, cottage cheese, egg yolk, cod liver oil, and fish including herring, mackerel and salmon (see Appendix A)( U.S. Department of Agriculture, Agricultural Research Service, 2009). Vitamin D has several important roles in the body.

Whether Vitamin D is obtained from sunlight or from food sources, a sufficient supply of Vitamin D is essential in maintaining strong and healthy bones and joints since Vitamin D is required for calcium absorption from food. It's been proven that people who have a sufficient and regular intake of Vitamin D are less likely to develop osteoporosis and joint pains (Parfitt, 1990). Vitamin D has also been found to be highly beneficial in slowing down and lessening the effects of arthritis and reducing backache. Research conducted towards the advantages of Vitamin D has shown that it can be helpful in preventing certain types of cancers (Davis, 2008).

The role of Vitamin D in the human body and obtaining adequate amounts is important as a deficiency of Vitamin D can have consequences. Vitamin D deficiency in adults often leads to osteomalacia, which results in muscular weakness in addition to weak bones, if the vitamin deficiency is chronic (Goldring, 1995). Other than osteomalacia, Vitamin D deficiency can result in osteoporosis, a



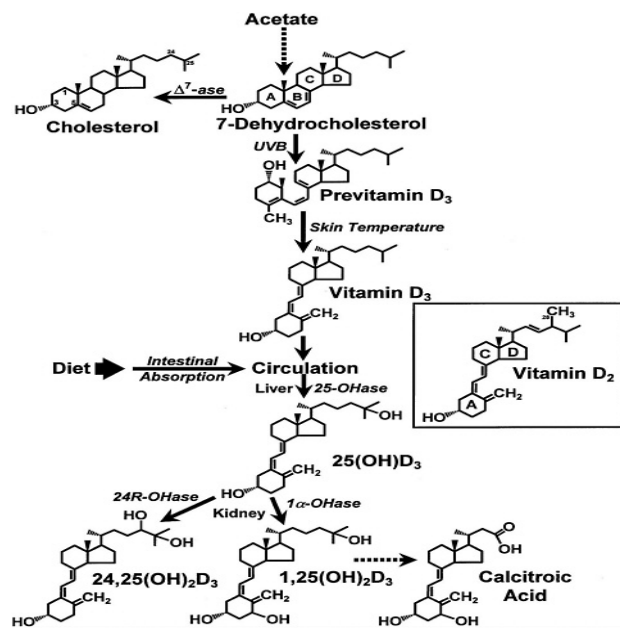
serious bone degeneration disease that effects as many as “1 in 3 women over 50 will suffer a fracture due to osteoporosis; this increases to 1 in 2 over 60, and 1 in 5 men over 50 will suffer a fracture due to osteoporosis; this increases to 1 in 3 over 60” (Osteoporosis Australia, 2004). Vitamin D deficiency has also been associated with other diseases such as cancer, memory loss, depression, high blood pressure and a few autoimmune diseases (Natural Standard Research Collaboration, 2008; Gloth, Alam, and Hollis B, 1999; Llewellyn, Langa and Lang, 2009; Tavera-Mendoza and White, 2007; Holick, 2004). There are numerous at risk populations for Vitamin D deficiency and they include the elderly, obese individuals, exclusively breastfed infants, and those who have limited sun exposure (Holick, 2002; Wortsman, Chen, Lu and Holick, 2000; Wagner and Greer, 2008; Webb, Kline and Holick 1988).

There has been a recent resurgence of Vitamin D research due to the increased prevalence of deficiency over the past ten years (Ray et al., 2009). Recommendations for adequate intake of Vitamin D are 200 IU (5 ug) per day for adults aged 19-50 years old (NIH Supplements, 2009). However this recommended intake amount has been the focus of much scrutiny and debate (Wolpowitz and Gilchrest, 2006). With many well-known and respected Vitamin D experts suggesting that higher intake levels are required to maintain normal levels in the blood. For example, Holick et al. recommends between 800-1000 IU and the Linus Pauling Institute recommend that at least 2000 IU is needed to maintain normal levels of Vitamin D<sub>3</sub> in the blood. This review will be examining evidence based research articles in the scientific literature regarding the adequacy of current recommendations for Vitamin D intake to maintain normal levels in the blood and the recommended intake to restore deficient levels of Vitamin D to normal range. As well as, giving detailed background information on the mechanisms of the activation of Vitamin D, effects of Vitamin D deficiency, measurements of Vitamin D status in the blood and the current recommendations for Vitamin D intake.

## ROLES AND MECHANISMS OF VITAMIN D:

Vitamin D (calciferol), makes up a collection of fat soluble seco-sterols that are rarely found in foods naturally. It is photosynthesized in the skin of vertebrates by the action of solar ultraviolet B radiation (Holick, 1994) when it is exposed to UVB rays with a wavelength of 290-315 nanometers from the sun (National Institute of Health, 2009). Vitamin D<sub>2</sub> is made from yeast and ergosterol, which is a sterol found in plants. Vitamin D<sub>3</sub> starts out as the metabolite 7-dehydrocholesterol, which is considered to be a precursor of cholesterol, and is produced in the skin when it is exposed to sunlight (Figure 1).

**Figure 1:** The photochemical, thermal, and metabolic pathways for vitamin D<sub>3</sub> (Holick, 1996).



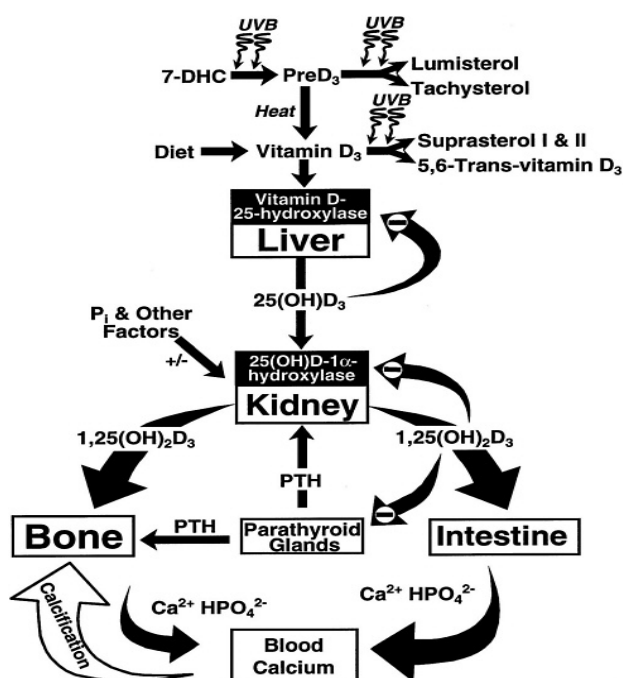
The most important biologically activating steps involved with the metabolism of Vitamin D<sub>2</sub> are nearly the same as the steps in the metabolism of Vitamin D<sub>3</sub>. The writing of Vitamin D that does not contain a subscript can be either the ergocalciferol (D<sub>2</sub>) or the cholecalciferol (D<sub>3</sub>) form of the vitamin. The written form lacking a subscript also represents the biologically inert form that requires two hydroxylations in the kidney and the liver to form the physiologically active metabolite, 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D) (DeLuca, 1988) (see Appendix B).

In general, people meet their Vitamin D needs through the diet, including fortified foods and exposure to the sun. The Vitamin D acquired from sun exposure is biologically inert and therefore must undergo two hydroxylations within the human body to reach the active form. When the UVB wavelengths penetrate the uncovered skin, it converts cutaneous 7-dehydrocholesterol to previtamin D<sub>3</sub>, which will eventually become vitamin D<sub>3</sub>. The first hydroxylation in the activation of Vitamin D happens in the liver and converts Vitamin D to 25-hydroxyvitamin D [25(OH)D] or calcidiol. The second hydroxylation occurs in the kidneys and forms the active version of Vitamin D (1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] called calcitriol or Vitamin D<sub>3</sub>).

Vitamin D's primary physiologic function within the body is to sustain blood levels of calcium and phosphorus within healthy levels by increasing the effectiveness of the small intestine's ability to absorb these nutrients from the foods in a person's diet (DeLuca, 1988; Reichel, Koeffler and Norman, 1989) (**Figure 2**). 1,25(OH)<sub>2</sub>D improves the efficiency of intestinal calcium absorption along the whole of the small intestine. Though it primarily increases absorption in the duodenum and jejunum. Additionally, 1,25(OH)<sub>2</sub>D<sub>3</sub> amplifies the absorption of dietary phosphorus throughout the entire small intestine (Chen, Castillo, Korycka-Dahl and DeLuca, 1974). Though to reiterate, 1,25(OH)<sub>2</sub>D's primary sites of action are the jejunum and ileum. When calcium consumption in the diet is not adequate to maintain the body's calcium requirement, Vitamin D and parathyroid hormone (PTH), activate and organize the monocytic stem cells located in the bone marrow, resulting in mature osteoclasts which are cells that break down bone and release calcium into the blood (Holick, 1995; Merke, Ritz and Schettler, 1986).

Once the osteoclasts have matured they are stimulated primarily by cytokines to increase the release of calcium stores from the bone and into the blood (**Figure 3**). All of this indicates that Vitamin D sustains the blood calcium and phosphorus levels in higher than required concentrations by storing calcium in the bone as calcium hydroxyapatite.

**Figure 2:** Photosynthesis of Vitamin D3 and the metabolism of Vitamin D3 to 25(OH)D3 and 1,25(OH)2D3 (Holick, 1996).



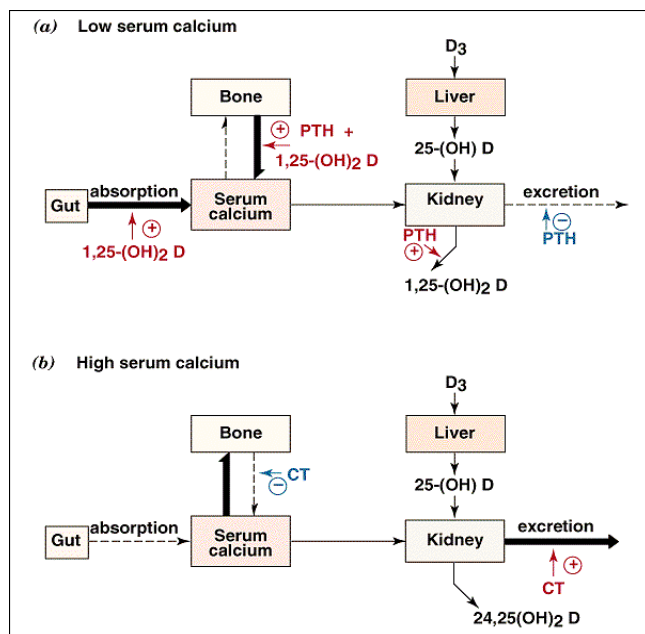
Vitamin D regulates calcium and phosphorus levels by effecting the intestines, bone, and kidney. The effects of Vitamin D on the kidney include causing the kidneys to reabsorb calcium and returning it to the blood (Northwestern University, 2007). In the intestines, Vitamin D acts as a co-factor for absorption of calcium. This occurs because Vitamin D causes an increase in the number of calcium binding proteins involved in calcium absorption through the apical membrane of the cells in the small intestine. The mechanism involved includes calcitriol binding to nuclear receptors, which leads to the production of messenger RNA (mRNA) for intestinal calcium-binding protein (Northwestern University,

2007). An increase in calcium-binding protein leads to an increase in the rate of intestinal uptake of calcium. Because intestinal membrane permeability to calcium is improved by Vitamin D, a parallel increase of phosphorous absorption will occur in order to maintain electrical neutrality and homeostasis within the body.

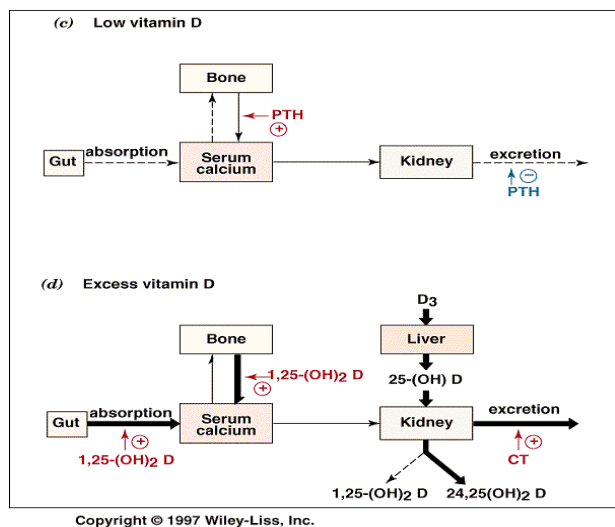
In bone, the metabolite calcitriol stimulates osteoclastic activity, which then leads to an increase in bone re-absorption in order to release calcium and phosphorus into the blood. Bone re-absorption must occur prior to formation and is a requisite first step in the remodeling process. In the kidney, calcitriol causes an increase in the re-absorption of calcium and phosphorus from the blood (Northwestern University, 2007). The activation of Vitamin D is directly caused by a reduction in serum phosphorus levels. These changes in blood calcium levels affect Vitamin D via parathyroid hormone (PTH) prompting of renal hydroxylation. Activation of the vitamin is slowed or even stopped by an increase in serum phosphorus concentrations or increased serum concentrations of calcitonin. The regulatory effects of blood phosphate levels on Vitamin D metabolism makes phosphorus balance a significant factor in blood calcium homeostasis, which is generally mediated by Vitamin D. (Northwestern University, 2007).

The process by which Vitamin D maintains calcium homeostasis is through the up or down regulatory actions of both parathyroid hormone and calcitonin **Figure 3 & 4**. The only real regulatory organ for this process is the parathyroid gland. The parathyroid glands are located behind the thyroid in the neck region, and produce parathyroid hormone in response to low calcium levels in the blood. The parafollicular cells of the thyroid are what produce calcitonin in response to high calcium levels, but calcitonin's role is much smaller than that of Parathyroid Hormone (PTH) (Mayo Clinic, 2009).

**Figure 3:** Regulatory actions of changes in serum calcium status (Gropper, Smith J and Groff, 2005).



**Figure 4:** Regulatory actions of changes in Vitamin D status (Gropper, Smith and Groff, 2005).



Vitamin D is primarily produced endogenously when ultraviolet light from the sun penetrates the skin and triggers the synthesis of Vitamin D. It is thought that as little as ten minutes a day in the sun is enough to prevent a vitamin deficiency (National Institute of Health, 2009). Vitamin D is vital for enhancing calcium absorption in the small intestines and maintaining ample calcium and phosphate serum concentrations to permit ordinary bone mineralization and to stop hypocalcemic tetany. Vitamin D is also needed to maintain normal bone growth and remodeling by osteoblasts (cells that remove calcium from the blood and deposit it in the bone) and osteoclasts (cells that break down bone and release calcium into the blood). Without proper levels of Vitamin D, either from obtaining it from sunlight or from the diet, a deficiency can occur (National Institute of Health, 2009).

#### CAUSES AND EFFECTS OF VITAMIN D DEFICIENCY:

Deficiency of Vitamin D can be caused a variety of different reasons; such as inadequate intake from the diet, in addition to inadequate sun (UVB) exposure. A deficiency can also be caused by disorders that limit the vitamin's absorption from the gastrointestinal tract, that weaken the conversion of Vitamin D into its active metabolites. These would include conditions such as liver or kidney diseases or body characteristics such as skin color and the amount of body fat an individual has (WebMD, 2010; Biser-Rohrbah and Hadley-Miller, 2001). Rarely deficiency can result from a number of hereditary disorders. Deficiency results in impaired bone mineralization and leads to bone softening diseases such as rickets, osteomalacia and osteoporosis (Holick, 2004; Nelms, Sucher and Long, 2007).

In recent research, it has become clear that Vitamin D is useful in the protection from developing osteoporosis--decreased bone mineral and organic matrix which weakens bones, making them more susceptible to fracture and pain (Nelms, Sucher and Long, 2007). Rickets is the inadequate maturation and mineralization of bone in children characterized by lethargy, weakness, growth stunting, enlargement of ends of long bones and ribs, abnormally shaped thorax, bowing of legs. Osteomalacia is organic matrix of bones inadequately mineralized in adults and is characterized by the following symptoms: muscular weakness, bone pain, deformities of ribs, pelvis, and legs (Nelms, Sucher and Long, 2007). Vitamin D deficiency can have serious effects and can cause a number of disease states. There are multiple ways that can be used to measure Vitamin D status and identify a deficiency.

#### MEASUREMENT OF VITAMIN D STATUS:

Even though cholecalciferol and 1,25(OH)<sub>2</sub>D concentrations can be determined in the blood, the most accurate approximations of Vitamin D status are given by the determination of 25(OH)D levels. This is because 25(OH)D has a relatively long serum half-life of nearly 3 weeks, as well as the 25-



hydroxylation step in the liver is unregulated by the body, thus indicating how much substrate is available (Wootton, 2005). On the other hand, cholecalciferol has a brief half-life of about 24 hrs. Meaning that blood levels are dependent upon the individual's recent exposure to the sun and their Vitamin D intake. The currently used assay is problematic to use because of the lipophilic nature of the Vitamin D metabolites (Wootton, 2005).

Given that production of 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D), the active form of Vitamin D<sub>3</sub>, is tightly regulated by the body and the serum half life of this metabolite is 4–6 h (Zerwekh J.E., 2004). Its circulating levels provide very limited information about an individual's Vitamin D status and intake. Even though commercial radioimmunoassays and ELISAs are now available to measure 1,25(OH)<sub>2</sub>D levels in the individual's serum, it is mainly used while studying renal disease and continues to be the measurement of 1,25(OH)<sub>2</sub>D is principally of interest only in renal disease and continues to only be done in specialist laboratories (Zerwekh J.E., 2004).

Vast quantities of HPLC procedures for Vitamin D determination have been developed (Wootton, 2005). One example is chromatographic separation, this method is acceptable as a reference method for determining Vitamin D status of an individual because it is capable of resolving both D<sub>2</sub> and D<sub>3</sub> forms as well as the following Vitamin D metabolites: 25(OH)D, 1,25(OH)<sub>2</sub>D and 24,25(OH)<sub>2</sub>D (Wootton, 2005). Early versions of the Vitamin D assays made use of normal phase separation (Eisman, Shepard and DeLuca, 1977; Gilbertson and Stryd, 1977) and those early methods were then followed by reverse phase separation (Aksnes, 1992). The most common methods performed in laboratories employ “liquid-liquid or liquid-solid pre-sample cleanup with UV detection after column separation” (Wootton, 2005). “A carbon-18 reverse phase column with isocratic or gradient elution using acetonitrile/water is now the standard procedure and diode array detection following hexane extraction gives results of sufficient clinical sensitivity” (Wootton, 2005). Therefore, the determination of 25(OH)D levels by HPLC which use UV detection are considered the “gold standard” procedure (Wootton, 2005). That is not to say that it is not accepted and well known that the HPLC with UV method is inappropriate for routine laboratory

use. A more recently developed method uses chemiluminescent assays that contain both DBP27 and antibody-based binding (Wootton, 2005). The following are the major assays used to determine Vitamin D status using 25OHD:

### **Diasorin RIA**

“The Hollis assay was released commercially with FDA approval and has become widely used. Acetonitrile extraction is followed by competitive radioimmunoassay using 125I-labelled 25OHD and antibody to 25OHD. A second antibody is used as precipitating agent”(Wootton, 2005). Although Hollis found that the primary antibody recognizes 25OHD2 and 25OHD3 equally, 4 other authors have published data indicating that the assay under-recognizes 25OHD2 (Wootton, 2005).

### **IDS Gamma-B**

“The sample obtained after acetonitrile extraction is incubated with antibody to 25OHD in competition with 125I-labelled 25OHD. A second antibody coupled to cellulose is used for separation of bound radioactivity. The manufacturers state that there is 75% cross reactivity of the antibody with 25OHD2 compared to 100% for the 25OHD3 form. Interestingly, data from the DEQAS indicate that the EIA version of this IDS assay performed better than the RIA, despite using the same antibody” (Wootton, 2005).

### **Nichols Advantage**

“This assay first separates 25OHD from DBP using a denaturing agent. Competition is then established in the same sample container between the newly separated sample of 25OHD and 25OHD on magnetic particles for human DBP. Separation utilizes the magnetic particles and detection is by chemiluminescence using acridinium-ester.

Despite the Nichols Advantage manufacturers earlier claims for 100% reactivity with 25OHD2, it has become apparent that the assay is unable to measure samples containing substantial amounts of 25OHD2 reliably. More recently, there has been data from the UK quality assurance program that has shown that

the assay displays a positive bias (~31%) with 25OHD3 and a negative one with 25OHD2. This under-recovery of 25OHD2 in some patient samples is now acknowledged in the information supplied with the kit” (Wootton, 2005).

### **Diasorin Liaison**

“This chemiluminescent assay has recently become available. In this process serum is incubated with antivitamin-D coated micro particles and an isoluminol derivative-conjugated 25OHD before measurement of the chemiluminescent signal. The antibody is said to be same one as that used in the DiaSorin RIA33 and the results correlate well with the radioimmunoassay” (Wootton, 2005). Although, this assay was found to recognize 25OHD2 more than 25OHD3, an anomaly that remains to be explained and should be considered before using in an experiment (Wootton, 2005).

### **Comparability of Assays**

Consistency of results between the different methods described above and among the different laboratories remains a considerable problem. Several possible reasons for this could be variability of temperature of antigen-antibody or protein-binding protein interactions or differences in the assays ability to recognize and differentiate between the Vitamin D2 and Vitamin D3 forms (Wootton, 2005).

Additionally, the Diasorin RIA demonstrated a strong correlation with HPLC in those who were very familiar with the procedure but compared badly in a laboratory that did not have technicians experienced with this particular method. Thus stressing the need for good quality assurance and standardization of methods and procedures. The Nichols Advantage demonstrated a weak comparison with HPLC and tended to give results that were an overestimate of basal 25OHD levels while at the same time underestimating the amount of 25(OH)D3 produced by the skin (Wootton, 200).

An alternative method used to establish Vitamin D status uses two pathologic indicators, radiologic evidence of rickets (Demay, 1995) and biochemical abnormalities linked with metabolic bone disease. The abnormalities could include raised concentrations of PTH concentrations in the blood as

well as raised levels of alkaline phosphatase (Demay, 1995) and these oddities have been linked with blood 25(OH)D levels. A 25(OH)D serum levels lower than 27.5 nmol/liter (11 ng/ml) is thought to be consistent with Vitamin D deficiency in young children (Specker, Ho, Oestreich, Yin, Shui, Chen and Tsang, 1992) and because of this fact can be used as the primary indicator for determining the Vitamin D status of an individual (Institute of Medicine, 1997).

The primary effect of Vitamin D on individual's health is to help maintain healthy bones and skeletal system. So, by reviewing previous research on accurately determining an individual's Vitamin D status, one of the most valuable indicators has been a person's skeletal health (Institute of Medicine, 1997). For people under the age of 18 bone health and prevention of the disease rickets in combination with the blood concentrations of PTH and 25(OH)D are good indicators of that person's Vitamin D status. As for adults, the mineral composition of the bone (BMC), bone mineral density (BMD), risk of bone fracture risk, and blood levels of PTH and 25(OH)D have been determined to be the most reliable indicators of a person's Vitamin D status (Institute of Medicine, 1997).

There has been very little research done dealing with the required concentration of 25(OH)D in the blood that is required for maintaining normal calcium metabolism and obtaining maximum bone mass in older children and adults. Because of these facts, the blood 25(OH)D levels were used to assess vitamin D deficiency in this age group (>18 yrs and <55 yrs). Serum concentrations of 25(OH)D is not the only measure used to determine the Vitamin D status for the elderly (>60 yrs) (Institute of Medicine, 1997).

“Serum PTH concentrations are inversely related to 25(OH)D serum levels. Therefore, the serum PTH concentration, in conjunction with 25(OH)D, has proven to be a valuable indicator of vitamin D status” (Wootton, 2005).

The small number of studies pertaining to African Americans and Mexican Americans indicated that these two racial groups have decreased concentrations of 25(OH)D in the blood and increased blood concentrations of PTH and 1,25(OH)<sub>2</sub>D when contrasted with Caucasian populations (Institute of

Medicine, 1997). The most likely reasons for this difference is higher melanin pigmentation or darker skin color (which causes a decrease in the production of Vitamin D by the skin) and a lack of Vitamin D in the diet because of a high prevalence of lactose intolerance (Wootton, 2005).

### ***Serum Vitamin D***

Blood concentration of Vitamin D is not always an accurate measure of vitamin D status. This is because Vitamin D has a half-life that is considered to be fairly short. Not only that, the serum concentrations can range anywhere from 0 to over 250 nmol/liter, or 0 to 100 ng/ml, depending on the recent Vitamin D intake of the individual and any sun exposure that individual had (Institute of Medicine, 1997).

### ***Serum 1,25(OH)<sub>2</sub>D***

Likewise, the blood 1,25(OH)<sub>2</sub>D level is not a good indicator of vitamin D status because the hormone's blood levels are tightly controlled by a number of factors, such as the levels of blood calcium, phosphorus, parathyroid hormone, and more (Institute of Medicine, 1997).

Measurement of Vitamin D by immunoassay will stay the method of choice for several very specific reasons: convenience, speed, turnaround, and perhaps the biggest reason of all, cost. However, at the moment the most commonly used generations of commercial assays have difficulty determining the Vitamin D status of individuals who are currently being treated with Vitamin D<sub>2</sub>. Fortunately this problem has been identified and hopefully the performance of the assays will improve with the development of better ones. Because of the problems caused by Vitamin D<sub>2</sub> discussed above, it may also be appropriate to suggest a change from using D<sub>2</sub> to using D<sub>3</sub> instead in prescriptions or supplements (Wootton, 2005).

There are ongoing efforts to enhance laboratory procedures and vigilance by making quality assurance programs mandatory (Wootton, 2005). Those laboratories that do offer Vitamin D tests are

expected to take part in local and international programs that help standardize Vitamin D assays. The founding and maintenance of reference assays for Vitamin D are mandatory and have been backed by the AACB (Wootton, 2005). An HPLC procedure and method has been created in order to determine an approximation of both Vitamin D2 and Vitamin D3 metabolite concentrations in blood samples “so that the performance of routine immunoassays on quality assurance samples containing mixtures of these metabolites can be monitored” (Wootton, 2005).

The levels of 25(OH)D in the blood is currently thought to be the best indicator for determining the adequacy of Vitamin D intake for a person (Institute of Medicine, 1997). This is because 25(OH)D levels represent the total amount of Vitamin D produced in the skin and the oral intake of either of the Vitamin D forms: Vitamin D2 or Vitamin D3 (Institute of Medicine, 1997). The healthy range of blood 25(OH)D concentrations in an individual is determined by figuring out the average blood concentrations of 25(OH)D  $\pm 2$  standard deviations (SD) from a collection of individuals who are in good health. The lower-level of the healthy Vitamin D concentration could be as low as 20 nmol/liter (8 ng/ml) in the blood and could have a concentration as high as 37.5 nmol/liter (15 ng/ml). The serum concentration depends on factors such as the geographic location of the individual and the skin pigmentation of the person (Institute of Medicine, 1997).

#### CURRENT RECOMMENDATIONS FOR VITAMIN D INTAKE:

The Daily Recommended Intake (DRI) values are reference numbers that can be used for preparing and assessing diets of healthy populations and for countless other purposes. “The DRI replaces the periodic revisions of the Recommended Dietary Allowances (RDA)”. The DRI includes the Estimated Average Requirement (EAR), the Recommended Dietary Allowance (RDA), the Adequate Intake (AI), and the Tolerable Upper Intake Level (UL) (Institute of Medicine, 1997).

As has been common practice with dietary recommendations in the past, the DRI is most appropriately applied to a generally healthy population of individuals. As for RDAs and AI, these recommendations are the nutrient levels that should lower the risk of developing a condition related to that specific nutrient and linked with a negative functional outcome. Oral intake of the nutrient in question at the level of the RDA or AI wouldn't automatically be expected to restore individuals who were previously deficient to a healthy state, neither would it be a sufficient intake amount for an individual with a disease state requiring increased intake of the nutrient. Though there are instances when the reference intakes can act as the basis for recommendations for numerous situations, each situation should be reviewed and individually adapted by a qualified professional (United States Department of Agriculture, 2009).

The current DRI for healthy adults for Vitamin D is 5ug/d or 200 IU (United States Department of Agriculture, 2009). However, this number is based on the absence of adequate exposure to sunlight. Numbers estimated from the US Third National Health and Nutrition Examination Survey, 1988-1994, showed median values that were above the adequate intake of 5 micrograms/d (ug/d) (200 IU) for children between the ages of 6-11; however, the average intake tends to be below the adequate intake level for female subjects  $\geq 12$  y of age and men  $\geq 50$  yrs (Calvo, 2004).

As of 1997, the United States Dietary Reference Intake Tolerable Upper Intake Level (UL) for Vitamin D was recommended to be 2,000 IU (50 ug/d), however this intake level is no longer considered to be relevant and is exceedingly restrictive (Grant and Holick, 2005). A risk assessment performed in 2007 recommended that 10,000 IU/day (250 ug/d) of Vitamin D should be the recommended as the new UL for the U.S. Other sources point to the maximum intake for Vitamin D toxicity being 20,000-24,000 IU/kg/d (500-600 ug/kg/d) (Grant and Holick, 2005).



## METHODS:

The American Dietetic Association's (ADA) Evidence Analysis Library is a compilation of nutrition research that helps to answer practice-based questions in an online library (American Dietetic Association, 2010). The Library has two main purposes: to provide review and analysis of numerous published research articles important to nutrition and to provide evidence-based practice guidelines. The first step in the review and analysis is to develop a question of interest. Then the research was gathered and classified by determining the inclusion and exclusion criteria and then including articles that fit the inclusion criteria. Once all the articles that fit the inclusion criteria have been found, they are critically appraised and reviewed. Then the articles are summarized in an overview table and evidence summary. Finally, a conclusion statement is developed for each article and a grade based on the strength of the supporting evidence is assigned to each article.

#### EVIDENCE-BASED CRITERIA:

The articles chosen to be included in the Literature Review section of this paper were determined by a set of inclusion criteria and any articles not meeting the inclusion criteria or which specifically had any of the exclusion criteria were not included in the review. Inclusion criteria are considered to be a set of conditions that must be met so that subject can be included in the study. While exclusion criteria are the conditions used to determine if a subject may not be used in the experiment or clinical trial.

The inclusion criteria for the Literature Review section were that the article had to come from a peer-reviewed journal and was published between January 1990 and December 2009. The participants in the articles also had to be human adults (>18 yrs) from any country, with either normal or deficient levels of Vitamin D in the blood and could only have diseases related to Vitamin D deficiency. The articles could also be considered meta-analyses. The exclusion criteria for the Literature Review were any articles that were not peer-reviewed, included no measure of Vitamin D levels, articles that were not primary research, included participants less than 18 years of age and had treatment trials of less than 8 weeks including the duration of the follow-up. Articles were also excluded if the treatment trial used less than ten subjects.

## METHODS (SCORING SYSTEM):

The article grading system used in this paper is based directly from the American Dietetic Association's (ADA) grading system used in the Evidence Analysis Library. Grades range from 1 to 5 (I-V) were assigned to articles on the basis of the strength of the results found through methodical reviews of published literature concerning the question being studied. For instance, determination that there is "Good" (Grade I) evidence that supports the conclusion that an intervention is effective basically shows that there is good quality research to support the conclusion (American Dietetic Association, 2010). Good quality research usually involves double-blind studies involving control groups, valid and reliable measuring tools, as well as very precise record keeping during the experiments. On the other hand, the decision that there is "insufficient evidence" (Grade V) to ascertain the efficiency of a specific intervention does not mean that the intervention does not work or is not effective in treating the disease, but rather shows that more research and experimentation is required to establish if the results are valid and reliable. (American Dietetic Association, 2010) (see Appendix C). The grades are assigned as follows:

**“Grade I: Good**—The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any serious doubts about generalization, bias, and flaws in research design. Studies with negative results have sufficiently large sample sizes to have adequate statistical power.

**Grade II: Fair**—The evidence consists of results from studies of strong design answering the question addressed, but there is uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of doubts

about generalization, number of participants, possible bias, research design flaws, or adequacy of sample size. On the other hand, the evidence consists solely of results from weaker designs for the questions addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

**Grade III: Limited**—The evidence consists of results from a limited number of studies of weak design for answering the questions addressed. Evidence from studies of strong design is either unavailable because no studies of strong design have been done or because the studies that have been done are inconclusive due to lack of generalization, bias, design flaws, or inadequate sample sizes.

**Grade IV: Expert Opinion Only**—The support of the conclusion consists solely of the statement of informed medical commentators based on their clinical experience, unsubstantiated by the results of any research studies. These articles are reviews of primary research articles and no actual experiment was performed.

**Grade V: Not Assignable**—There is no evidence available that directly supports or refutes the conclusion” (American Dietetic Association, 2010).

#### SEARCH TERMS, DEFINITIONS AND DATABASES USED:

##### *Search Terms and Definitions*

**Vitamin D**—“A fat-soluble vitamin needed for normal growth of bone. Vitamin D is produced when sterols in the body are irradiated by ultraviolet light” (National Institute of Health, 2009).

- **Cholecalciferol**: “Vitamin D is a fat-soluble vitamin that helps maintain blood levels of calcium, by increasing absorption from food and reducing urinary calcium loss. Both functions help keep calcium in the body and therefore spare the calcium that is stored in bones” (Nutrition Data, 2009).

**Double Blind Study**—“double-blind procedure: an experimental procedure in which neither the subjects of the experiment nor the persons administering the experiment”. (Princeton University, 2010).

**D.R.I.**—“Dietary Reference Intake (DRI) is a system of nutrition recommendations from the Institute of Medicine (IOM) of the U.S. National Academy of Sciences. The DRI system is used by both the United States and Canada and is intended for the general public and health professionals” (United States Department of Agriculture, 2009).

**A.I.**—“the consumption and absorption of sufficient food, vitamins, and essential minerals necessary to maintain health” (United States Department of Agriculture, 2009).

**Clinical trials**—“A clinical trial is a research study designed to test the safety and/or effectiveness of drugs, devices, treatments, or preventive measures in humans. Clinical trials can usually be divided into four categories or "phases"” (Washington University, 2010).

**Deficiency**—“Nutritional deficiency (malnutrition) involves a lack of one or more nutrients essential for normal body function” (Washington University, 2010).

**Primary Research Article**—“Another term for scholarly journal, indicating that the articles published in the journal have been reviewed by appropriate subject scholars to determine the validity and value of the publication”. (University of Kentucky, 2009).

*Databases*

IBIDS - International Bibliographic Information on Dietary Supplements Database

PubMed

AGRICOLA

Medline

## LITERATURE REVIEW:

There has been a recent resurgence of Vitamin D research due to the increased prevalence of Vitamin D deficiency over the past ten years (Ray et al., 2009). The current Daily Recommended Intake (DRI) for Vitamin D for healthy adults age 19 – 50 years is 5µg per day or 200 IU per day (U.S. Department of Agriculture, Agricultural Research Service, 2009). However, this amount may not be adequate to prevent a Vitamin D deficiency. This section will examine and critique research articles regarding the recommendations for Vitamin D intake to maintain normal levels in the blood and the recommended intake to restore deficient levels of Vitamin D to normal levels.

For the portion of this review dealing with the topic of required vitamin D intake needed in order to maintain a healthy status, over 35 articles were either initially reviewed or skimmed in order to determine which might meet the criteria. Of these first 35 articles, 26 seemed appropriate and were thoroughly reviewed. It was determined that a total of 15 articles of these 26 articles might meet the criteria for the portion of this review dealing with the topic of required Vitamin D intake needed in order to maintain a healthy status. Of those initial 15 articles, 6 articles met the inclusion criteria for this review. Finally of the 6 articles reviewed and used, 4 of them received a Grade I and 2 of the articles received a Grade II. None of the articles used received a grade of III, IV or V. Grades were assigned based on the overall study design, how well records and data were kept, and whether or not a control group was used. The actual list of studies used can be found in **Table 1**.

For the portion of this paper dealing with the required Vitamin D intake needed in order to restore a person from a deficient status to a healthy status, a total of 11 articles were originally read and reviewed. Of those initial 11 articles, 5 articles met the inclusion criteria for this review. Finally of the 5 articles reviewed and used, 3 of them received a Grade I and 2 of the articles received a Grade II. None of

the articles used received a grade of III, IV or V. The grades were assigned based on the same reasons as were the articles listed in **Table 1**. The actual list of studies used can be found in **Table 2**.

**Table 1:** Summary of Literature Review to Maintain *Normal* Levels of Vitamin D in the Blood

Articles	Study Design	Subjects	Country	Publication Date	Healthy Subjects	Deficient Subjects	Included	Rating of Article
Glerup H, et al.	Original Research	Adult Women	Middle East and Denmark	2000	Yes	No	Yes	Grade I
Barger-Lux MJ, et al.	Original Research	Adult Males	United States	1998	Yes	No	Yes	Grade I
Calvo et al.	Original Research (meta-analysis)	Adult Men and Women	United States	2004	Yes	No	Yes	Grade II
Moore et. al	Original Research	Adult Men and Women	United States	2004	Yes	No	Yes	Grade II
Vieth, et al.	Original Research (randomized double blind)	Adult Men and Women	United States	2007	Yes	No	Yes	Grade I
Hollis et al	Original Research	Adult Women	United States	2004	Yes	No	Yes	Grade I

In the study performed in 2000 by Glerup, Mikkelsen, Poulsen, Hass, Overbeck, Thomsen, Charles and Eriksen, it was shown that veiled Arab women displayed extremely low values of 25-hydroxyvitamin D compared with ethnic Danish Moslems and Danish controls. The vitamin D intake (which included supplementation from food) was very low amongst Arab women in general. The oral intake of vitamin D amongst veiled Danish Moslems was approximately 600 IU but even they were still



vitamin D-deficient. The results of the study indicate that the daily oral intake of vitamin D in sunlight-deprived individuals should exceed 600 IU and really should be 1000 IU per day to maintain normal levels of 25-hydroxyvitamin D in the blood (Glerup, Mikkelsen, Poulsen, Hass, Overbeck, Thomsen, Charles and Eriksen, 2000).

The 1998 article *Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men* by Barger-Lux M.J., Heaney R.P., Dowell S., Chen T.C., and Holick M.F. studied the quantitative relationships between graded oral dosing with vitamin D<sub>3</sub>, 25(OH)D<sub>3</sub>, and 1,25(OH)<sub>2</sub>D<sub>3</sub> for short periods and changes in circulating levels of these substances within the blood stream. There were 116 healthy men used in the study and they subjects were distributed among nine open-label treatment groups: vitamin D<sub>3</sub> (25, 250 or 1250 micrograms/day for 8 weeks), 25(OH)D<sub>3</sub> (10, 20 or 50 micrograms/day for 4 weeks) and 1,25(OH)<sub>2</sub>D<sub>3</sub> (0.5, 1.0 or 1.0 microgram/day for 2 weeks). The results of the study were that the three groups treated with vitamin D<sub>3</sub> had increased circulating blood values of vitamin D<sub>3</sub>. The same was true for the groups taking 25(OH)D. As for treatment with 25(OH)D<sub>3</sub>, it also increased circulating blood levels (Barger-Lux, Heaney, Dowell, Chen, and Holick, 1998).

In the article *Efficacy and safety of vitamin D<sub>3</sub> intake exceeding the lowest observed adverse effect level* by Reinhold Vieth, Pak-Cheung R Chan and Gordon D MacFarlane, the research teams took 61 adult men and women and randomly assigned them to groups receiving either 1000 or 4000 IU/d (25 or 100 µg/d) of Vitamin D for 2-5 months. The results showed that the 4000 IU/d (100-µg/d) dosage of vitamin D<sub>3</sub> successfully raised the levels of 25(OH)D to high-normal concentrations in virtually all adults used in the study and blood levels of 25(OH)D stayed inside the physiologic range (Vieth, Chan and Gordon, 2007).

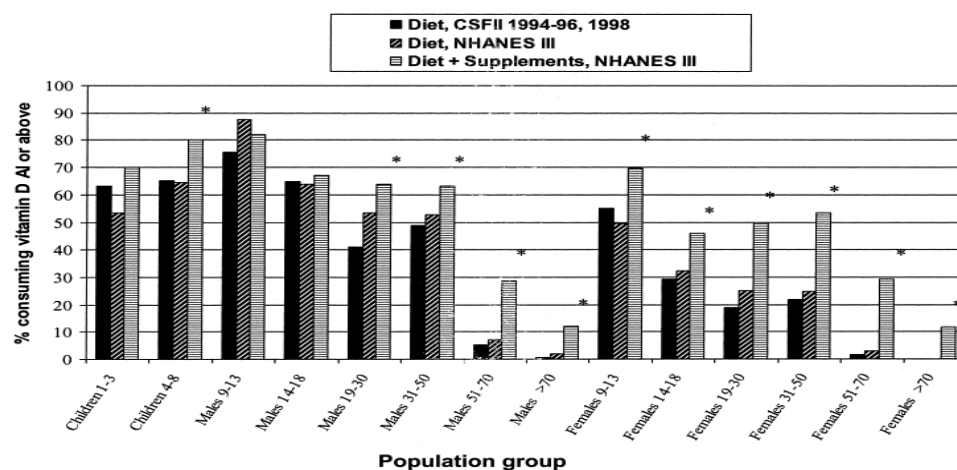
In yet another study done in 2004 by Hollis it was found that the daily recommended intake of 400 IU/d was subjectively set. In this experiment the “effect of high-dose maternal vitamin D<sub>2</sub> supplementation on the nutritional vitamin D status of mothers and nursing infants” (Hollis, 2004). In the

Hollis study 18 fully lactating women were enrolled after one month post-birth and were randomly put in one of two experimental groups that were watched over a 3 month study period. The first group received 1600 IU/d vitamin D2 and vitamin D3 (prenatal vitamin) while the second group received 3600 IU/d vitamin D2 and 400 IU/d Vitamin D3. The results were that these high-doses of vitamin D2 safely increased the serum vitamin D (Hollis, 2004). As for the African American in each of the groups, they received 2000 IU/d or 4000 IU/d. The research found that the antirachitic action of the lactation from mothers getting the 2000 IU/d supplement indicated that the Vitamin D concentration rose by 34.2 IU/L in the blood; the activity in the 4000 IU/d group increased by 94.2 IU/L. With an increase that high it could be possible to attain a large improvement in maternal as well as neonatal vitamin D status (Hollis, 2004).

Numbers estimated from the US Third National Health and Nutrition Examination Survey, 1988-1994 (NHANES III), showed the median intakes are generally below the adequate intake level for female subjects  $\geq 12$  y of age and men  $\geq 50$  y (Calvo, 2004). The NHANES III survey was used by Calvo et al. to approximate the Vitamin D intakes for specific age and gender groups (Calvo, 2004). The study consisted of female and male subjects 6-11 years of age (female: n = 1553; male: n=1581), 12-19 years of age (female: n = 1599; male: n = 1462), 20-49 years old (female: n = 4546; male: n = 4199), and  $\geq 50$  years of age (female: n = 3554; male: n = 3271). The results of Calvo's experiment were consistent with the NHANES III survey in that only the age category from 6-11 years had adequate intake, meaning that males and females  $\geq 18$  years old were deficient in Vitamin D.

Another study done by Dr. Carolyn Moore found that young male adults were the most likely to have the recommended levels of vitamin D; while the lowest dietary intakes were found in female adults (Moore, Murphy, Keast, and Holick, 2004) (Figure 7.) Figure 7 indicates that less than 10% of older adults (51 to 70 years old) and no more than 2% of the elderly, older than 70 years old, met requirements for vitamin D from food sources alone (Moore et al., 2004).

**Figure 7:** Percentages of US populations with usual intake of vitamin D from diet alone or diet plus supplements at or above the Vitamin D Adequate Intake (AI), Continuing Survey of Food Intakes by Individuals (CSFII 1994–1996, 1998) and the Third National Health and Nutrition Examination Survey (NHANES III) (Moore et al., 2004).



**Table 2:** Summary of Literature Review to *Restore* Deficient Levels of Vitamin D in the blood to Normal Levels

Articles	Study Design	Subjects	Country	Publication Date	Healthy Subjects	Deficient Subjects	Included	Rating of Article
Goswami R, et al.	Original Research (Randomized, double-blind, temporal)	Adult	India	2008	No	Yes	Yes	Grade I
Mastaglia	Original Research	Adult	Argentina	2006	No	Yes	Yes	Grade I

Mastaglia SR, et al.	Original Research (Longitudinal study)	Adult Women	Argentina	2006	No	Yes	Yes	Grade I
Diamond TH, et al.	Original Research	Adult Women and Men	Australia	2005	No	Yes	Yes	Grade II
Vieth, et al.	Original Research (meta-analysis)	Adult Men	United States	1999	No	Yes	Yes	Grade II
Ilahi et al	Original Research	Adult Men and	United States	2008	No	Yes	Yes	Grade I

In an experiment by Goswami et al., a group of 28 Asian-Indian subjects were given 60,000 IU/d (1500 µg/d) cholecalciferol for 8 weeks as a treatment for vitamin D deficiency. The end results and conclusion of this experiment were that 8 weeks of cholecalciferol supplementation in subjects with continuous vitamin D deficiency, the blood levels would be normalized during those 8 weeks. Unfortunately, this type of quick, and not long lasting supplementation would not maintain their 25(OH)D levels in the sufficient range for 1 year. For sustained improvement in 25(OH)D levels vitamin D supplementation has to be much more long term (Goswami, Gupta N, Ray, Singh, and Tomar 2008).

A study done in 2006 by Mastaglia et al. examined 38 postmenopausal and osteoporotic women were randomly separated into 3 groups. The control group (n=13): no vitamin D2, the 125 ug /day (n=13) and 250 ug /day (n=12) of vitamin D2 groups. Each of the groups were monitored for at least 3 months. The results of this study indicated that was approximately 250 ug/d was the most affective at raising blood Vitamin D levels back up to normal (Mastaglia, Mautalen, Parisi, and Oliveri, 2006).

In the Ilahi et al. study, group one (30 subjects) was given a single oral dose of 100, 000 IU (2500 ug) of cholecalciferol or Vitamin D3. The second group (10 subjects) acted as a control group to assess

the seasonal change of calcidiol in the blood. Serum calcidiol levels were monitored for 4 months. The subjects were healthy adults with little sun exposure ( $\leq 10$  h/wk) and little milk consumption ( $\leq 0.47$  L daily) in their daily diets. The results of the study were that blood calcidiol levels rose quickly after cholecalciferol dosing from an average ( $\pm$ SD) baseline of  $27.17 \pm 7$  ng/ml to a concentration peak of  $42.0 \pm 9.1$  ng/ml. 7% of the supplemented (trial) group failed to attain the 32.1 ng/ml blood concentration at any time point. The highest reached concentration in any subject used in the study was 64.2 ng/ml. The control group of 10 subjects showed a non significant change from baseline of  $-0.72 \pm 0.80$  ng/ml during the 4 months of the experiment. Based off of these results it appears that a single dose of cholecalciferol (100,000 IU) is a safe, effective, and simple way to increase calcidiol levels in the serum of a deficient person. The dosing interval should be  $\leq 2$  months to ensure continuous blood calcidiol levels above baseline (Ilahi, Armas and Heaney, 2008).

In a 1999 study by Reinhold Vieth, it was found that for adults, the 200 IU (5 ug) vitamin D recommended dietary allowance may be able to inhibit the development of osteomalacia in the absence of sunlight, but a higher intake is required to help prevent osteoporosis and secondary hyperparathyroidism in deficient individuals. Fully-body exposure to sunlight effortlessly provides the comparable amount of 10,000 IU (250 ug) vitamin D/d if it were taken orally, indicating that this could be the human body's physiological limit. Vieth assembled data from numerous Vitamin D supplementation studies and created a curve for vitamin D dose versus serum 25-hydroxyvitamin D [25(OH)D] response to those varying doses that is astonishingly flat up to 250 ug (10 000 IU) Vitamin D/d concentration. Vieth then goes on to recommend that in order to guarantee that blood 25(OH)D concentrations are higher than 100 nmol/L, a total Vitamin D intake of 4000 IU (100 ug) per day is needed (Vieth, 1999). Vieth also noted that there is a lack of evidence as to what the adverse effects of blood 25(OH)D concentrations  $< 140$  nmol/L are. In order to reach these levels, it would require a daily Vitamin D intake of which requires 10,000 IU (250 ug) (Vieth, 1999).

In the article, *Annual intramuscular injection of a megadose of cholecalciferol for treatment of vitamin D deficiency: efficacy and safety data* by Diamond TH, Ho KW, Rohl PG, and Meerkin M., 50 subjects (45 women and 5 men) who were given a single therapeutic intramuscular injection of 600 000 IU (15 mg or 1500 ug) cholecalciferol (vitamin D3) in order to see if it could return them to normal levels and if that dose would maintain the healthy levels. The results of the study indicated that the yearly intramuscular injection of 600,000 IU of Vitamin D is an effective treatment for Vitamin D insufficiency (Diamond, Ho, Rohl and Meerkin, 2005).

#### RESULTS:

Based on the amount of the research that has been done and the literature published about it, it is believed that there needs to be at least 50-80nmol/l of 25(OH)D in the blood to prevent deficiency. There are a few articles stating that the minimum levels of 25(OH)D needed to be between 70-80 nmol/l. In order to maintain those blood levels, there needs to be an intake of 800-1000 IU of Vitamin D a day (Dawson-Hughes, Heaney and Holick, 2005). In addition to the research used in this paper, the Linus Pauling Institute also recommends that serum levels of 25(OH)D be maintained at 80 nmol/L (Linus Pauling Institute, 2010). There have also been a handful of other studies done in other countries that have found that 80 nmol has been correlated with a lowered risk of breaking bones, cancer, and type 1 diabetes. Therefore, due to the increasing prevalence of vitamin D deficiency, it appears that the DRI for this vitamin needs to be increased above 200 IU/d (5 ug/d) for adults. However, how much it should be increased is not conclusive and needs further research, though the consensus is approximately 1000 IU/d (25 ug/d), and needs further research (Mosekilde, 2008).

Based on the current research, the lowest dose that resulted in returning levels to normal was 10,000 IU (250 ug) Vitamin D a day for as long as the person is deficient (Vieth, 1999 and Dawson-Hughes et al., 2005). The highest intake studied was 600,000 IU (15,000 ug) given in a singular shot (Diamond, Ho, Rohl and Meerkin, 2005). The consensus appears to be that a person needs to have an intake of over 10,000 IU (250 ug/d) to restore healthy blood levels of Vitamin D and it appeared that intakes of approximately 100,000 IU (2,500 ug) given approximately every 2 months was the most effective (Ilahi, 2008).

#### CONCLUSIONS:

Maintaining healthy levels of Vitamin D is no easy task when there are numerous reasons for a person to be Vitamin D deficient. An individual's exposure to sunlight, the amount of Vitamin D in the diet, the color of an individual's skin, and other health factors such as obesity can have an unpredictable and substantial impact on body Vitamin D levels. If a person does not have the recommend levels of Vitamin D intake over time due to their dietary and lifestyle choices, such as being a vegan or being obese, they alter their normal levels. If a person limits their exposure to the sun because they live at northern latitudes or prefer to wear long sleeved tops and long pants they will also have altered Vitamin D levels. It has even been shown that the darker a person's skin color is the more likely they are to be deficient because the hormone melanin decreases the skin's ability to produce Vitamin D (Scientific Advisory Committee on Nutrition, 2007).

Based on the amount of the research that has been done and the literature published about it, it is believed that there needs to be at least 50-80 nmol/l of 25(OH)D in the blood to prevent deficiency. There are a few articles stating that the minimum levels of 25(OH)D needed to be between 70-80 nmol/l. In order to maintain those blood levels, there needs to be an intake of 800-1000 IU (20-25 ug) of Vitamin D a day (Dawson-Hughes et al., 2005). In addition to the research used in this paper, the Linus Pauling Institute recommends that serum levels of 25(OH)D be maintained at 80 nmol/L (Linus Pauling Institute,

2010). There have also been a handful of other studies done in other countries that have found that 80 nmol has been correlated with a lowered risk of breaking bones, cancer, and type 1 diabetes. Therefore, due to the increasing prevalence of vitamin D deficiency, it appears that the DRI for this vitamin needs to be increased above 200 IU/d (5 ug/d) for adults. However, how much it should be increased is not conclusive and needs further research, although the consensus is approximately 1000 IU/d (25 ug/d) (Mosekilde, 2008).

According to Parfitt et al, “Vitamin D deficiency implies the existence of an anatomic, physiological, or biochemical abnormality that can be corrected by the administration of Vitamin D” (Parfitt, Gallagher, Heaney, Johnston, Neer and Whedon, 1982). There is however, much debate on what the exact intake amount needs to be and how frequently that amount needs to be ingested to restore Vitamin D levels to a healthy range (Wolpowitz and Gilchrest, 2006). Based on the current research, the lowest dose that resulted in returning levels to normal was 10,000 IU (250 ug) Vitamin D a day for as long as the person is deficient (Vieth, 1999 and Dawson-Hughes et al., 2005). The highest intake studied was 600,000 IU (15,000 ug) given in a singular shot and was able to restore deficient serum levels and maintain normal levels for 1 year (Diamond, Ho, Rohl and Meerkin, 2005). The consensus appears to be that a person needs to have an intake of over 10,000 IU (250 ug) a day to restore healthy blood levels of Vitamin D and it appeared that oral intakes of approximately 100,000 IUs (2500 ug) once every 2 months was the most effective (Ilahi et al., 2008). However, this is all dependent on the level of deficiency and whether or not there will be lifestyle changes to include more sun exposure and eating more Vitamin D fortified foods. A healthy person should have a Vitamin D intake somewhere within the range of 1000-2000 IU (25-50 ug) a day, getting it from either foods it naturally occurs in or from foods fortified with Vitamin D. None of the research used in this review indicated whether the intake needed to come from a natural source, a fortified source or supplements. It appears that it is the intake amount that is important and not the source of the vitamin. As for the required intake in addition to an adequate amount of sun exposure, the required intake would probably decrease to be between 800-1000 IU (20-25 ug). But none



of the research specifically addressed how much the intake would change if the person was receiving an adequate amount of sunlight.

#### LINUS PAULING INSTITUTE:

The mission of the Linus Pauling Institute on the campus of Oregon State University is to try and determine the function and roles of vitamins, minerals, phytochemicals, oxidative stress and inflammation on the human body. The Institute's primary areas of research deal with immune function, aging, cancer, neurodegenerative diseases, cardiovascular diseases and metabolic diseases. Several specific research projects being done at the Institute include Vitamin E metabolism and its biological functions, transplacental cancer chemo protection, oxidative stress in Alzheimer's disease, and Vitamin D in immune function (Linus Pauling Institute, 2009).

“The Linus Pauling Institute recommends that generally healthy adults take 2,000 IU (50 ug) of supplemental Vitamin D daily. Most multivitamins today contain 400 IU (10 ug) of vitamin D, and single ingredient Vitamin D supplements are available for additional supplementation. Sun exposure, diet, skin color, and weight have variable, and often substantial impact on body Vitamin D levels. To account for individual differences and ensure adequate body Vitamin D status, the Linus Pauling Institute suggests aiming for a serum 25-hydroxyvitamin D level of at least 80 nmol/L (32 ng/ml). Numerous observational studies have found that serum 25-hydroxyvitamin D levels of 80 nmol/L (32 ng/ml) and above are associated with reduced risk of bone fractures, several different types of cancers, multiple sclerosis, and type 1 (insulin-dependent) diabetes. As for older adults (> 50 years), the Linus Pauling Institute suggests that daily supplementation with 2,000 IU (50 ug) of Vitamin D is especially important for older adults because aging is associated with a reduced capacity to synthesize Vitamin D in the skin upon sun exposure” (Linus Pauling Institute, 2010).

#### AREAS FOR FUTURE RESEARCH:

There has been a large resurgence in the scientific community's interest in Vitamin D over the past ten years due to the increasing prevalence of disorders stemming from Vitamin D deficiency. Even with all of the new research being performed there are still concepts that need to be investigated. Some of

those concepts include assessing the differing Vitamin D intakes during the entire lifespan of an individual while also looking at the geographic location and skin pigmentation of those individuals (racial components) that represent the cultural mixture of the Australian, Eastern European, Asian, and American populations (Institute of Medicine, 1997). There also needs to be research done on how Vitamin D production in the skin at various geographic locations and among various races is affected by the use of sunscreen. There should also be research done to assess the effect of different Vitamin D intakes on blood levels of 25(OH)D and 1,25(OH)<sub>2</sub>D during the winter months because at this time of the year little to no Vitamin D is processed from the sun by the skin (Institute of Medicine, 1997). Along the same lines there needs to be much more research done that would evaluate differing doses of Vitamin D oral intake in young adults and middle-aged adults that are not exposed to sunlight. This is important because it is very problematic to find the reference values for Vitamin D in these two groups in the absence of sunlight since they are typically active outdoors and often get most of their Vitamin D from exposure to the sun (Institute of Medicine, 1997).

There are other areas of interest in Vitamin D research that need to be researched beyond how a lack of sun affects serum levels. These include such things looking at ways to evaluate alternative constraints of calcium metabolism in relation to Vitamin D status, while taking into account blood levels of PTH. This is important because it is difficult to determine exactly how much Vitamin D is sufficient to meet the body's need due to some evidence that adequate PTH levels require 50 nmol/liter concentration of 25(OH)D in the blood. While it may be possible to survive with lower limits, Vitamin D is also required in other functions in the body and greater serum concentrations may be required to maintain these normal functions (Institute of Medicine, 1997). Finally, it would be useful to develop methodologies that could measure any major changes in the body's stores of Vitamin D in order to accurately determine Vitamin D requirements in the absence of sun exposure (Institute of Medicine, 1997).

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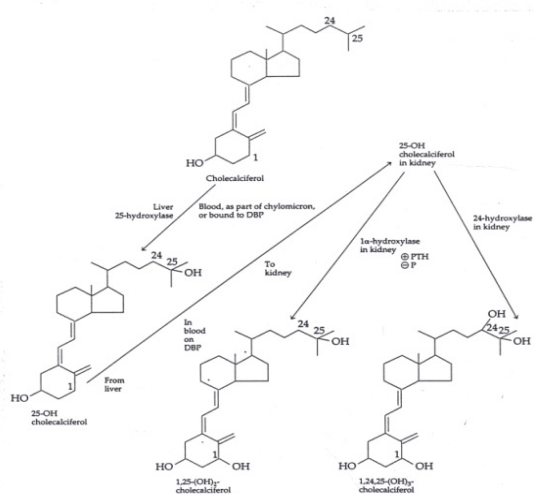
## APENDIX A

**Table 3:** Selected Food Sources of Vitamin D (USDA Nutrient Data Base, 2009).

<b>Food</b>	<b>IUs per serving</b>	<b>Percent DV</b>
Cod liver oil, 1 tablespoon	1,360	340
Salmon, cooked, 3.5 ounces	360	90
Mackerel, cooked, 3.5 ounces	345	90
Tuna fish, canned in oil, 3 ounces	200	50
Sardines, canned in oil, drained, 1.75 ounces	250	70
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	98	25
Margarine, fortified, 1 tablespoon	60	15
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Egg, 1 whole (vitamin D is found in yolk)	20	6
Liver, beef, cooked, 3.5 ounces	15	4
Cheese, Swiss, 1 ounce	12	4

## APENDIX B

**Figure 6:** synthesis of the active form of vitamin D (Gropner, 2005).



**FIGURE 10.15** Hydroxylation of vitamin D.

## APENDIX C

**Table 4:** Brief Definitions of ADA Grading Criteria (American Dietetic Association, 2010).

Conclusion Grading Table					
<b>Strength of Evidence Elements</b>	<b>Grades</b>				
	<b>I</b>  <b>Good/Strong</b>	<b>II</b>  <b>Fair</b>	<b>III</b>  <b>Limited/Weak</b>	<b>IV</b>  <b>Expert Opinion Only</b>	<b>V</b>  <b>Grade Not Assignable</b>
<b>Quality</b>  Scientific rigor/validity  Considers design and execution	Studies of strong design for question  Free from design flaws, bias and execution problems	Studies of strong design for question  with minor methodological concerns, OR  Only studies of weaker study design for question	Studies of weak design for answering the question  OR  Inconclusive findings due to design flaws, bias or execution problems	No studies available  Conclusion based on usual practice, expert consensus, clinical experience, opinion, or extrapolation from basic research	No evidence that pertains to question being addressed
<b>Consistency</b>  Of findings across studies	Findings generally consistent in direction and size of effect or degree of association, and statistical significance with minor exceptions at most	Inconsistency among results of studies with strong design, OR  Consistency with minor exceptions across studies of weaker design	Unexplained inconsistency among results from different studies OR single study unconfirmed by other studies	Conclusion supported solely by statements of informed nutrition or medical commentators	NA
<b>Quantity</b>  Number of studies  Number of subjects in studies	One to several good quality studies  Large number of	Several studies by independent investigators  Doubts about adequacy of	Limited number of studies  Low number of subjects studied	Unsubstantiated by published research studies	Relevant studies have not been done

	<p>subjects studied</p> <p>Studies with negative results have sufficiently large sample size for adequate statistical power</p>	<p>sample size to avoid Type I and Type II error</p>	<p>and/or inadequate sample size within studies</p>		
<p><b>Clinical Impact</b></p> <p>Importance of studied outcomes</p> <p>Magnitude of effect</p>	<p>Studied outcome relates directly to the question</p> <p>Size of effect is clinically meaningful</p> <p>Significant (statistical) difference is large</p>	<p>Some doubt about the statistical or clinical significance of the effect</p>	<p>Studied outcome is an intermediate outcome or surrogate for the true outcome of interest</p> <p>OR</p> <p>Size of effect is small or lacks statistical and/or clinical significance</p>	<p>Objective data unavailable</p>	<p>Indicates area for future research</p>
<p><b>Generalizability</b></p> <p>To population of interest</p>	<p>Studied population, intervention and outcomes are free from serious doubts about generalizability</p>	<p>Minor doubts about generalizability</p>	<p>Serious doubts about generalizability due to narrow or different study population, intervention or outcomes studied</p>	<p>Generalizability limited to scope of experience</p>	<p>NA</p>