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Vitamin D3

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Introduction

Vitamin D is the only vitamin that is free. It can be easily obtained from exposure to sunlight and yet more than 60% of Americans are Vitamin D deficient (Ginde et al., 2009; *Bones, Vitamin D, and Calcium*, n.d). The significance of Vitamin D can't be emphasized enough and is often overlooked. Some its profound effects are apparent in the prevention of various diseases such as cancer, multiple sclerosis, and cardiovascular disease et cetera. Many lives can be spared each year just by taking Vitamin D. From cancer alone, 23,000 deaths can be attributed each year to a lack of Vitamin D (Grant, 2002; Reichrath, 2008). Vitamin D deficiency in America is an epidemic that needs to be addressed.

Vitamins:

Vitamins are required for the well being of the human body, in essence in achieving homeostasis. Vitamins are organic substances (coenzymes) that can't be synthesized by the human body. Vitamins are divided into two discrete categories: water-soluble and lipid-soluble vitamins. Water soluble vitamins can be eliminated easily from the body in the form of urine and sweat. On the other hand, an excess intake of lipid soluble vitamins can be fatal. They can't be easily excreted as a waste, due to their hydrophobic properties. Vitamin D is one such lipid soluble vitamin that is stored in adipose tissue.

Vitamin D_3 Background

Vitamin D is a steroid hormone despite it being classified as a vitamin. The molecular structure of Vitamin D closely resembles typical steroid hormones, which have the same cyclopentanoper-hydrophenanthrene root carbon ring structure. This suggests that Vitamin D reacts similarly to other steroid hormones. There are various forms of Vitamin D, but the naturally occurring form is cholecalciferol, also known as Vitamin D_3. The primarily and most abundant source of Vitamin D is obtained during the presence of sunlight. It can also be naturally obtained from several food sources, however, in minute amounts.

BiochemistryA cholesterol molecule, 7-Dehydrocholesterol functions as a precursor to Vitamin D. The highest concentrations are found in the epidermis, particularly the stratum basale and stratum spinosum layers. In conjunction with sunlight, in the form of Ultra-violet B radiation, cholecalciferol is synthesized. The most effective wavelength is found between the range of 270-290 nm. This absorption excites the double bonds, allowing the B-ring to open, thereby making it into a more flexible structure. Once produced, cholecalciferol (D_3) the inactive form of Vitamin D_3 is then transported to the liver by the plasma transport protein, Vitamin D–binding protein (DBP) or also known as transcalciferin (TC). In the endoplasmic reticulum of hepatocytes, cholecalciferol is hydroxylated at the Carbon-25 position to yield 25-

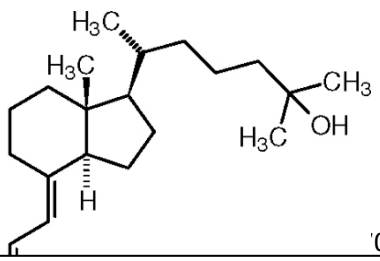

Figure 1. 1α,25-dihydroxycholecalciferol [1,25-$(OH)_2D_3$] also known as Vitamin D_3. Source: IUPAC. (Dixon, 1982)

hydroxycholecalciferol (Calcidiol) by the enzyme 25-hydroxylase. It is then successively transported by DBP to the proximal tubules of the kidney where it is catalyzed by the enzyme 1α-hydroxylase. The hydroxyl is placed on Carbon 1 or 24 to yield the following, 1α,25-dihydroxycholecalciferol [1,25-$(OH)_2D_3$] and 24*R*,25-dihydroxyvitamin D_3 [24,25$(OH)_2D_3$] respectively (Dixon, 1982). Finally, by a means of diffusion (Hollis et al., 2008), DBP transports both steroids to their target tissues, where 1α,25-dihydroxycholecalciferol or also known as calcitriol, is considered to be the hormonally active form of Vitamin D_3 (Figure 1). The inactive form 24, 25$(OH)_2D_3$, is chemically degraded and eventually excreted as either calcitroic acid or as 23-carboxyl derivatives. In comparison to its inactive isomer 24,25$(OH)_2D_3$, the affinity of calcitriol to Vitamin D_3 receptor sites is over 1000 times more than to its isomer. (Norman, 1990; 1998; MacDonald & Sutton, 2003)

Vitamin D_3 similarly to other steroid hormones, binds to intracellular ligand-dependent transcription receptors. Being hydrophobic it is easily able to penetrate the phospholipid membrane of target cells. Once in the cytosol of the cell, Vitamin D_3 binds to a receptor protein known as the Vitamin D receptor (VDR), which prompts a cascade of macromolecular interactions leading to the transcription of certain genes. Promoted by Vitamin D_3 the Vitamin D receptor forms a heterodimer complex with the retinoid-X receptor (RXR), a category of class II nuclear receptors. Class II receptors are known as transcription factors which regulate the expression of specific genes .In contrast to class I receptors, class II receptors are found in the nucleus of the cell. With the correspondence of Vitamin D_3 the active receptor protein complex enters the nucleus and initiates a series of molecular interactions, where the activation and suppression of specific modification of genes occurs. The specific sequences of genes that it seeks are known as the Vitamin D-responsive elements. Finally the transcription of these genes is executed and an mRNA strand is produced, where it is translated into specific proteins by ribosomes (Norman, 1998; Campbell & Reece, 2001; Holick, 2004).

Regulation: Parathyroid Hormone

Parathyroid hormone (PTH) is necessarily mentioned here on the basis that it plays a crucial role in the regulation of Vitamin D_3. The rate limiting step of Vitamin D_3 production occurs in the kidney and is accomplished by the enzyme 1α-hydroxylase. The parathyroid hormone plays an active role in directly either inhibiting or by the activation of the enzyme 1α-hydroxylase, which in turn produces l,25$(OH)_2D_3$. Also to be noted the half-life of Vitamin D_3 is only approximately 3-4 hours. Due to its short half life, its production is tightly regulated as a means of conserving it, where PTH essentially serves as this control point in the production of Vitamin D_3 (Bowen, n.d.).

Receptor Sites:

Calcitriol targets a wide range of tissues. Until recently VDR sites for l,25$(OH)_2D_3$ were only known to be located on bones, intestines and in the kidneys. New research formulates that VDR receptors are localized in cancer cell lines, the pituitary gland, the skin, hematopoietic cells, leukocytes including T and B lymphocytes, reproductive organs, ß-islet cells of the pancreas, and nerve cells. This suggests the additional roles and involvement of Vitamin D_3 , in the functioning and regulation of the immune system (Holick, 2004; Norman, 1990).

Roles:

Vitamin D_3 has been recognized for maintaining adequate levels of calcium in the serum. Additionally, it has been associated with keeping bones strong, as we know drinking milk as a source of Vitamin D_3, has been highly encouraged over the past years by the statement "Got Milk". Vitamin D_3 has been evident in preventing rickets in children and osteoporosis (osteomalacia) in adults. Moreover, recent evidence has established that Vitamin D_3 has extraordinary properties that go beyond strong bones, to such an extent that it has been reputed as a preventive medicine. It is apparent that it functions and is highly involved in the immunological system. It has been proven to prevent an extensive range of diseases including, multiple sclerosis, cardiovascular disease, diabetes, and most forms of cancer (*Vitamin D Science*, n.d.; Zittermann, 2003).

Calcium

Calcium (Ca^{2+}), a key element required for the human survival. A minor drop in calcium levels can be fatal and lead to cardiac arrest. Calcium is associated with maintaining and keeping the strength and rigidity of bones. Additionally, it is also responsible for the propagation of action potentials across nerve synapses. Release of neurotransmitters (exocytosis) into the synaptic cleft is prompted by calcium ions, which consecutively are transmitted along and received by adjacent dendritic cells in the post synaptic region. In addition, calcium plays a pivotal role in muscle contraction such as of the skeletal and cardiac muscles (Tortora, Grabowski, & Roesch, 1996, p. 125).

One of the essential attributions of Vitamin D_3 is for promoting calcium absorption. One way this is achieved is by the absorption of calcium from the lumen of the small intestine, primarily in the duodenum and jejunum. Calcitriol activates specific gene factors in DNA that translate into carrier proteins known as Vitamin D-dependent calcium binding proteins .These act as a vector for transporting proteins across the small intestine and into the blood. The most commonly known of these calcium transporters is calbindin (Norman, 1990; Tortora et al., 1996, pp. 525-527). Calcium absorption also occurs in the distal convoluted tubule (DCT) of the nephron. In concert with parathyroid hormone, production of $1,25(OH)_2D_3$ results in changes in gene expression that eventually results in the re reabsorption of Ca^{2+}in the tubule (Lajeunesse & Brunette, 1991).

A drop in serum calcium levels (normal reference range is 8.5 - 10.5 mg/dL), induces the parathyroid gland to secrete parathyroid hormone (PTH) in an attempt to restore normal calcium levels back to normal. PTH brings about the release of calcium from the bones by osteoclast formation, thereby reducing bone density. Excess PTH can lead to fragile bones, a condition known as osteoporosis. However, when Vitamin D is present, calcium is obtained by the alternative means such discussed above, conserving bone density by leaving bones intact and strong. Additionally, Vitamin D has been shown to interact with PTH, activating osteoclasts and subsequently the release of calcium. However, Vitamin D stimulates intestinal calcium uptake and excess calcium is restored to bones by osteoblast formation. Therefore, this accounts for a net gain of calcium, strengthening and maintaining the bone matrix (Tortora et al., 1996).

Cellular Differentiation

All cells originate from pluripotent stem cells, as they divide and mature they reach a climax state, where differentiation isn't possible anymore. In contrast to differentiated cells, immature cells proliferate rapidly, as evident in embryos and infants. Alternatively, aging accounts for the

lack of stem cells, brought about by terminal differentiation (*Cell Differentiation*, n.d; Oberley et al., 1980). Being that cancer cells are similar to embryonic tissues, and are relatively undifferentiated, they have a high growth rate potential (Sell, 2004). Furthermore, stem cells are present in malignant tumors, this evidently substantiates their similarity in their differentiation state and growth pattern (Farkas et al., 2009; Kopper & Hajdú, 2004; *Tumor Stem Cells*, n.d).

Vitamin D_3 via gene expression factors induces the differentiation of osteoblasts. Osteoblasts, derived from osteoprogenitor cells, secrete collagen and other essential organic components required in bone formation and maintenance. Additionally, many genes are directly involved in the cell cycle and influence proliferation, differentiation, and apoptosis in distinctively every cell. This speculates that Vitamin D_3 deficiency can consequently result in a low degree or lack of cellular differentiation (Kadakia et al., 2010; Samuel & Sitrin, 2008; Tortora et al., 1996, p. 144).

Immunology

Vitamin D_3 plays an exceptional role in the immune system. Vitamin D deficiency is an unrecognized epidemic among both children and adults in the United States. Vitamin D deficiency not only accounts for rickets among children and osteoporosis among adults but is also highly associated with increased risks for Multiple Sclerosis (MS), malignant cancers, cardiovascular disease, and both types of diabetes mellitus but primarily type 1 (Holick, 2004).

Multiple Sclerosis

Multiple Sclerosis, also known as MS, is a chronic autoimmune disease that affects the central nervous system (CNS). The CNS consists of the brain and the spinal cord. On a cellular level, neurons continuously transmit and receive signals, each being a minute, yet a necessary part of the intricate CNS orchestration, that culminate in the actions, sensations, thoughts and emotions that comprise the human experience. Normally, the path over which a nerve signal or action potential travel is protected by an insulation of fibrous material known as the myelin sheath or white matter. This is essential for efficient nerve conduction and propagation. In MS, the myelin sheath is eroded, which diminishes the ability of neurons to properly transmit signals.

It is believed that the loss of myelin is the result of mistaken attack of white blood cells. In MS something goes awry; white blood cells infiltrate the CNS, cross the blood brain barrier, seek out and destroy the myelin. As an ongoing inflammation of nerve tissue occurs, nerve signals are disrupted, leading to an array of symptoms; ranging from numbness or tingling to blindness and paralysis (*Multiple Sclerosis*, n.d.).

In MS an unknown trigger activates helper T cells (CD-4), which correspondingly recognize myelin as an antigen. Once activated, helper T cells reproduce and release cytokines such as interleukin-2. Subsequently B cells and cytotoxic T cells (CD-8) become stimulated, enabling them to cross the blood brain barrier. Once in the cerebrospinal fluid (CSF), B-cells produce immunoglobulins or antibodies that bind to myelin and oligodendracytes (cells of CNS that synthesis myelin). Cytotoxic T cells and macrophages are involved in the destruction of myelin. (Hellings, 2008)

Currently about 350,000 people in the United States and over 2 million people worldwide are affected by MS (Dangond, n.d.). Statistics have revealed that there is a higher incidence of MS in regions where inadequate sunlight exists. As a trend, the risk of developing multiple sclerosis usually increases with the distance from the equator (Figure 2). Astonishingly, regions near the equator are risk free or have a 0 MS risk coincidence. The risk of acquiring MS increases dramatically with latitude and is inversely related to sunlight. For instance, in Canada 240 out of 100,000 people have MS, compared to a mere of 9 in Mexico (*Atlas of MS Database*, n.d.). In the United States, the prevalence rate of MS below the 37th parallel is 57 to 78 out of 100,000 people. On the other hand, above the 37th parallel, the prevalence rate of MS is 110 to 140 per 100,000 people, approximately twice the rate as below the 37th parallel. An insufficient level of Vitamin D transpires under low sunlight conditions, which make one more susceptible to MS (*Nursing Home Care*, n.d.).

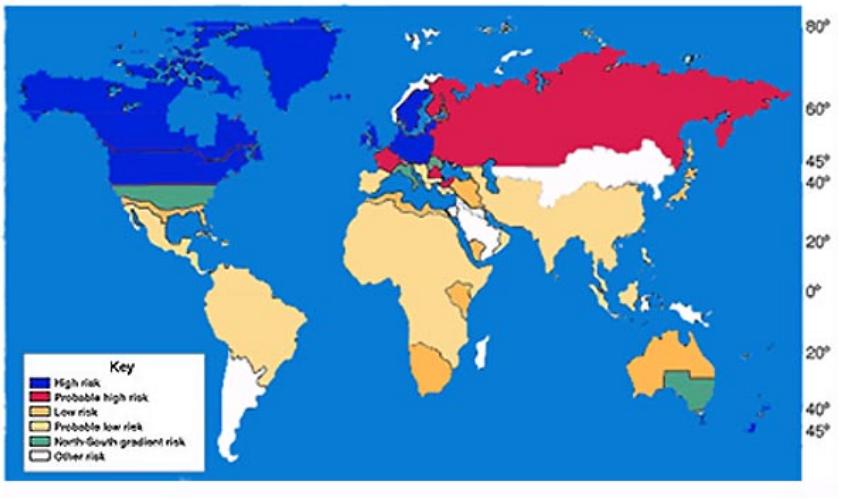

Figure 2. Epidemiology of Multiple Sclerosis: World map showing that risk (incidence) for MS increases with greater distance from the equator. Source: Multiple Sclerosis International Federation. (*Atlas of MS Database*, n.d).

In a case conducted study, a group of researchers at the Harvard School of Public Health accessed serum samples of more than 7 million military personnel. Two hundred and fifty seven of them were diagnosed with MS and had blood samples taken prior to diagnoses. Each had their serum level compared to at least two other control subjects that were disease free. They were matched on the basis of common characteristics such as age, serum collection date etc. They were then ranked into five groups based on their Vitamin D levels. Predictability, those with MS fell disproportionately into the lowest-ranking groups. Those in the highest compared to the lowest-ranking group, had a lower risk of developing MS by a staggering rate of 62 percent. (Munger et al., 2006)

Based on a study, pregnant women are encouraged to obtain Vitamin D. In this study the mothers of approximately 35,000 nurses provided information regarding their diet during pregnancy. After a span of 16 years, 199 out of these nurses developed MS. It was concluded that the mothers that consumed Vitamin D during pregnancy, gave birth to daughters with a 45 percent less risk of developing MS in years to come (Langer-Gould et al., 2010). Additionally, babies born in northern countries during the month of

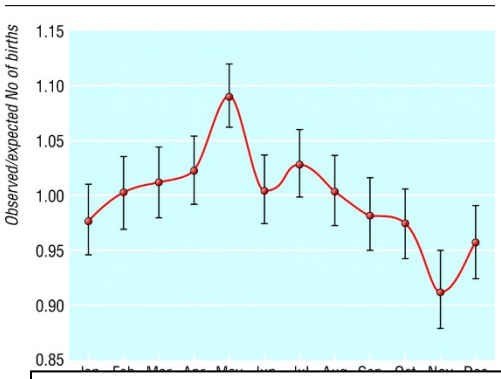

Figure 3. Pooled analysis of observed births in people with multiple sclerosis. Source: British Medical Journal. (Willer et al., 2005)

November have shown a decreased risk of developing multiple sclerosis later on in life (Figure 3). This study was based on 42,000 people and those that were born in November had a 19% decreased risk of developing multiple sclerosis over those that were born in May. Mothers pregnant during sunny months have higher levels of Vitamin D in their serum, which apparently is gets passed on to their developing baby (Willer et al., 2005).

MS patients often experience and/or are prone to bone fractures. MS is also associated with a high frequency of osteoporosis. The bone mass density (BMD) of the lumbar spine and femoral neck was found to be one to twofold lower in women with MS against controls. Low circulating levels of Vitamin D that were found in MS patients, can account for this direct relationship. (Siokaa et al., 2009; Van der Mei et al., 2007; Correale et al., 2009; Nieves et al., 1994) .Additionally, MS patients with a high Vitamin D level has shown a lesser relapse rate than controls. A dosage of 15 ng per mL, which is equivalent to 2000 international units (IU) has been shown to cut the relapse rate by half (Correale et al., 2009; Mowry et al., 2010).

Cancer

In between 1970 to 1994, cancer mortality rates in the US were approximately twice as high in the northeast compared with the southwest. An examination of 506 regions found a close inverse relationship between cancer mortality rates and levels of sunlight in the form of UV-B radiation. Annually, 21,700 premature deaths result due to a lack of Vitamin D. These results were obtained by comparing UV-B data in various regions and by using regression analysis based methods (Figure 4). This study surveyed and concluded that Vitamin D is associated with the prevention of most forms of cancers, including breast, colon, ovarian, prostate, lung, pancreatic, stomach, non-Hodgkin lymphoma, et cetera (Grant, 2002; Reichrath, 2008).

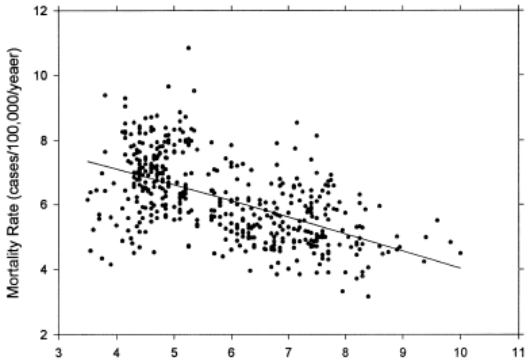

Figure 4. Annual mortality rates for breast carcinoma in white females (1970-1994) versus DNA-weighted ultraviolet (UV) radiation for July 1992. Source: American Cancer Society (Grant, 2002)

A four year randomized study conducted by the Creighton University School of Medicine revealed that Vitamin D can reduce cancer risks by a dramatic 60 to 77 percent. The subjects were 1,179 randomly selected healthy women over the age of 55. Participants were free of known cancers for a minimum of ten years prior to entering the study. Each group was either given 1,400-1,500 mg supplemental calcium, 1,400-1,500 mg supplemental calcium plus 1,100 IU of Vitamin D_3 (nearly three times the Recommended Daily Amount) or just placebos. Over the course of four years there was no statistically significant difference in cancer incidence between participants taking placebos and those just taking calcium supplements. However, those in the Vitamin D_3/Calcium group demonstrated a remarkable 60 percent cancer risk reduction, than to the placebo group alone.

On the premise that some women entered the study with undiagnosed cancers, the first year was eliminated from the study. During the last three years, the results became even more apparent in signifying the effects of Vitamin D_3 on Cancer. In those three years alone, the calcium/Vitamin D3 group exhibited a startling 77 percent cancer-risk reduction. These results were based on the

notion that calcium intervention had no significant difference in cancer reduction and were primarily due to the positive effects of Vitamin D_3. The significance of this study was that it was population based and subjects were randomly selected. Additionally, the study had a low dropout rate of less than 3.5 percent, due to the high level of treatment adherence, which applauds to the positive effects of Vitamin D_3. This provides strong evidence that Vitamin D_3 is the most effective medicine against cancer, far more than any other drug (Lappe, 2007).

There has been some controversy, however, in the role of Vitamin D_3 in the prevention of cancer. In a study conducted between 1995 and 2005, the Women's Health Initiative (WHI) gathered over 36 thousand participants, making it the largest randomized clinical trial of calcium and Vitamin D ever done. The subjects were divided into two groups and were administered twice daily either, 500 mg of calcium plus 200 IU Vitamin D_3 or just placebo alone. Participants were required to make clinical visits annually and answer a series of questions every six months, in order to determine the effects of the pills. Over an average span of seven years, a total of 322 women were diagnosed with invasive colorectal cancer. In comparison to participants who took the active Ca-D supplements with those who took placebo pills, there was no substantial difference in the rate of colorectal cancer diagnoses, prompting evidence that Vitamin D_3 may not play a role in cancer prevention (Wactawski-Wende et al., 2006).

However there are many flaws in this study, considering scientists' estimate that it may take at least 10 to 20 years for colorectal cancer to develop and the study was limited to an average of 7 years. Additionally, the WHI based its report on colorectal cancer incidence but failed to account for the many other predominant forms of cancers. The highly significant inverse relationship between Vitamin D_3 and the risk incident for all cancers was reported in the Creighton study. Nevertheless, it was observed in the WHI study that the participants with lowest quartile of serum had an overall colorectal cancer incidence that was 253 percent of the incidence in the highest quartile. Furthermore, a much lower dose of Vitamin D3 was used in the study than in the Creighton study. A dose of 400 IU was administered, which is inadequate in promoting the health benefits of Vitamin D_3 to the full potential. It is now generally recommended that 1000 IU of Vitamin D_3 daily is necessary to attain proper levels in order to achieve optimal prevention of cancer and other crucial benefits such as calcium absorption and bone strength (Holick et al., 2003). Finally, all the subjects in the study had Vitamin D insufficiency prior to the start of the trial and also during the trial based on the criterion given above (Holick, 2006).

The best source of evidence that significantly demonstrates that a higher dose of 1000 IU of Vitamin D_3 is advisable for preventing colorectal cancer, besides for other cancers, is based on a Quantitative meta-analysis pool of data from an extensive range of studies that were conducted between January 1966 and December 2004. The five studies that were surveyed contained serum collections from a wide variety of healthy volunteers who were closely monitored for periods ranging from two to twenty five years. There were a total of 1,448 total participants, 535 in the pooled analysis and 913 controls. The researches established that 1000 IU of Vitamin D_3 is associated with a 50 percent, or half of a risk reduction, of developing colorectal cancer, rather than the 400 IU of D_3 that was seen in the WHI study. The results were obtained by dividing the pooled results into quintiles with median values. Odds ratios were calculated by quintile, with the lowest as the reference group. Based on the odds for each quintile of the pooled data, a dose response curve was plotted. Data were abstracted and analyzed in 2006. It has also concluded that public awareness is needed to increase the Vitamin D_3 intake of to 1000 IU per day (Holick et al., 2007; Holick et al., 2005).

To validate the effects of Vitamin D_3 deficiency and cancer, mice with lacking VDR receptor sites were assessed. Vitamin D effects are mediated through VDR receptors, a ligand-dependent transcription factor. In comparison to normal wild type mice, the VDR knockout mice exhibited accelerated growth and heavier mammary glands. This supported the hypothesis that Vitamin D_3 inhibits proliferation and induces differentiation. Additionally, this study demonstrated that VDR absent mice were more prone and sensitive to mammary tumors that were induced due to a disruption of Vitamin D_3 (Welsh, 2004). To further determine the effects of Vitamin D and cancer proliferation, two groups of mice were fed different diets. The first group was fed a Vitamin D deficient diet for three months. The other was fed the same diet but with supplemental Vitamin D for the same duration. The mice were then injected with MC-26, a colon cancer cell line. The tumors were measured daily for an interval of twenty days. The result: the Vitamin D sufficient mice had forty percent smaller tumors than the Vitamin D deficient mice. In the Vitamin D sufficient mice the expression of the mRNA for the VDR and 1α-hydroxylase were measured and found to be 37- and 6-fold higher, respectively, in comparison to the Vitamin D absent mice. These results support the notion that Vitamin D_3 inhibits the proliferation of cancer (Tangpricha et al., 2005).

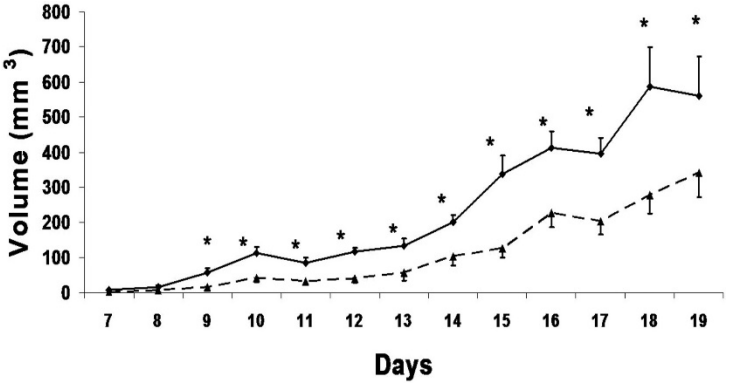

Figure 5. MC-26 tumor size in vitamin D–deficient (solid line) vs. vitamin D–sufficient (dashed line) mice.Source: Journal of Nutrition (Tangpricha et al., 2005)

Cell Cycle

Human development and maintenance requires billions of rounds of the cell cycle. The cell cycle is split into two stages, Interphase and Mitosis, respectively. Interphase accounts for approximately 95 percent of the cell cycle, making it the prominent stage in regards to cellular regulation. It consists of a sequence of three distinct phases in the order of the G_1, S, and G_2 (Figure 6). Mitosis is defined as the M phase. Depending on environmental and developmental signals, cells in the G_1 phase may temporarily or permanently cease division and enter into an arrested phase known as the G_0 resting phase .Highly differentiated cells, such as, nerve cells exist in the G_0 state (Tortora et al., 1996, p. 80) .A mishap in the cell cycle is believed to be an attribution for cancer. Simultaneously, Vitamin D is believed to be one of the crucial components responsible for cellular regulation and thus preventing cellular abnormalities that contribute for cancer.

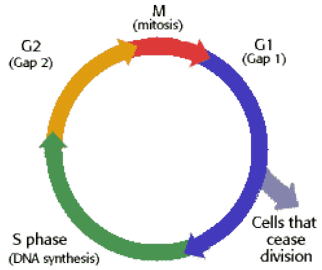

Figure 6. The cell cycle. Source: University of Arizona. (*The Cell Cycle*, n.d.).

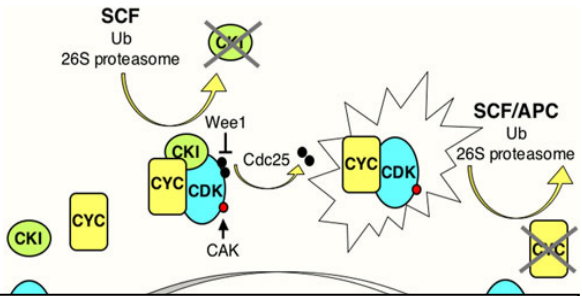

Figure 7. Model illustrating CDK regulation. Source: Harvard Medical School (Van den Heuvel, 2005).

In transition to consecutive phases, throughout the cell cycle there are several regulatory checkpoints. A group of protein kinase molecules known as Cyclin-dependent kinases (CDK's) trigger the transition of subsequent phases in the cell cycle (Figure 7). CDK's are in an active

state when bound to Cyclin proteins and by direct phosphorylation. Cyclin molecules are degraded as they progress through the cell cycle; in respect to time their concentration varies in a cyclical fashion. This ensures that cells only proceed up to the subsequent cycle. CDK's are kept in an inactive state through association with CDK-inhibitory proteins (CKIs) and by Wee1, inhibitory phosphorylation molecules. Activation requires ubiquitin-dependent proteolysis of the CKI, phosphorylation of the CDK by a CDK-activating kinase (CAK), and removal of the inhibitory phosphates by Cdc25 (**c**ell **d**ivision **c**ycle) phosphatase.

Interphase consists of several regulatory checkpoints. They ensure proper cell development, DNA replication and other critical processes that enable a cell to be error free. The G_1 checkpoint (G_1through S phase) is regulated by CDK-2, -4, and CDK6 proteins, which proper entry into the S phase. The G_2 checkpoint (G_2 to mitosis) is regulated by the CDK-1 protein, which promote M-phase progression. Identical DNA allows the cells to proceed through these checkpoints. However, the unexpected can occur, damaged DNA are often recognized and repaired. Nevertheless, unsuccessful repair attempts can result in cellular aptosis. Families of CDK kinase inhibiters (CKI) include classes of p21, p27, and p57 proteins. Their function is to inhibit a broad range of CDK's, including CDK-1, 2, 4, and CDK-6. In breast cancer cells, Vitamin D_3 impeded proliferation by preventing entry into the S-phase. Vitamin D_3 was identified to up-regulate p21 inhibiters through analogues. One such analogue is EB1089, a derivative of Vitamin D_3 with modified side chains. This targets and inactivates CDK-2 complexes, thereby terminating DNA synthesis and cell replication (Jeffrey et al., 1995; Liu et al., & Freedman, 1996; Jensen et al., 2001).

Sunscreens and Sunlight

People use sunscreen as a protective measure from the sun's rays. According to evident studies, sunscreens may do more harm than good. Sunscreens block Vitamin D production, which can contribute to far greater cancer deaths than it prevents (Dennis, Freedman, & VanBeek, 2003). Each year less than 1500 people die from skin related cancers while each day, 1500 people die from other cancers (Cancer Facts & Figures, n.d.; Skin Cancer Facts, n.d.). Sunscreens with an SPF of 8 or greater block both UVA and UVB rays (Hughes & Talbott, 2007). UVB rays are necessary to synthesize Vitamin D in the skin. Sun block may prevent skin cancer but at the same time, can be attributed to other major forms of cancer that are far more fatal.

Sunlight is often associated with promoting skin cancer but it has been demonstrated to the contrary in a San Diego study. During 1974 to 1984, there were 176 confirmed cases of melanoma that were identified in active-duty white male personnel enlisted in the US Navy. Occupations were grouped in three categories based on sunlight exposure, as indoor, outdoor or a combination of indoor/outdoor. Compared to the U.S. civilian population, those working indoor had a higher melanoma occurrence of 10.6 per 100,000 people. Those who worked in occupations that required spending time both indoors and outdoors had the lowest rate, of 7.0 per 100,000 people. Additionally, incidence rates of melanoma were higher on the trunk than on more common sunlight exposed areas, such as the head and arms. This establishes that moderate amounts of sunlight can prevent melanoma rather than cause it (Garland et al., 1990).

According to the CDC melanoma has been rising sharply for the last several decades ("Notice to Readers:," 2000). Yet, concurrently, as year's progress, less time is spent outdoors. In the early1900's more than 75% of the North American population worked outdoors compared to only 10% by the 1970's (Genius, 2006). This trend illustrates an inverse relationship between

sunlight and melanoma. Furthermore, the greatest increase of melanoma occurred after the introduction of sunscreens. Death rates in the US between the 1950's and 1990's doubled in men and nearly tripled in women (Garland et al., 1992,).

Analytic studies were performed on articles published in between 1966 to 2003 relating to melanoma and sunscreen use. Odds ratios were pooled across studies by using standard meta-analytic techniques. It was concluded however, that, no correlation was seen between melanoma and sunscreen use (Dennis, Freedman, & VanBeek, 2003). In between 1978-1992, cancer mortality rates were analyzed in Spanish provinces. The mortality rates of melanoma and other forms of cancer were significantly correlated with latitude. This concluded that melanoma occurs more frequently in northern latitudes versus lower latitude areas (Grant, 2007).

Although sun light has been proven to have positive effects, it has limits too. There is a common rule that applies to everything; "too much of a good thing is bad". There should always be a healthy balance between things. The recommended optimal daily intake of Vitamin D for an adult is approximately 1000 IU (international units). This can be achieved by spending approximately, depending on the day, about 15-20 minutes in the sun. Obviously, prolonged endurance in the sun requires one's discretion and application of sunscreen may be necessary (Vitamin D, n.d.).

Toxicity

In healthy individuals, Vitamin D blood levels are normally found in the range of 32 to 70 ng per mL. Vitamin D is a fat soluble molecule, making elimination difficult. An advantage to sunlight obtained Vitamin D is that it is automatically regulated by a negative feedback loop. An adequate threshold level of Vitamin D prompts the shutdown of further synthesis. This makes overdosing unattainable by regulating Vitamin D levels. However, Vitamin D obtained in supplemental form can pose a serious threat. Toxicity results from overdosing, which is about over 1,500 micrograms or 10,000 IU, ten times the recommended FDA daily dosage. Symptoms of overdosing include nausea, poor appetite, constipation, weakness, weight loss, confusion, heart rhythm abnormalities and Kidney stones.

Conclusion

The enormous positive effects of Vitamin D are vividly apparent. Its functions range from Calcium absorption to the suppression of tumors. A diet rich in Vitamin D is extremely encouraged. On the other hand, a deprivation of Vitamin D results in a multitude of consequences. It is no coincidence that in recent years Vitamin D emerged in the spot light of research, involving the formulation of numerous exceptional works.

Unfortunately, modern society encourages low levels of Vitamin D. People do not go out often and when they do are in cars. Pollution obscures some of the sun's beneficial rays. Furthermore, spending time in the sun is associated with significant sun block use. Sunlight shouldn't be averted; it is a benefactor to humans. As mentioned in the Bible of Genesis, when redemption will arrive, G-d will use the magnificent powers of the sun to heal the righteous.

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