CHAPTER 5

Requirements and Benefits of Vitamin-D for Optimal Health

5.1. Pre and Postnatal Vitamin D Benefits

One of the primary roles of vitamin D is the regulation of calcium and phosphorus absorption and metabolism for bone health. This role is especially important during pregnancy and lactation because bones develop rapidly during this period. Women have less skin pigmentation than men, a finding attributed to women's greater need for vitamin D during pregnancy and lactation (Jablonski NG., 2000). Insufficient vitamin D intake during infancy can result in rickets. The hallmarks of this disease are biochemical disturbances, reduced bone mineralization, slower growth, bone deformities, and increased risk of fracture (Pawley N., 2004). Indeed, rickets has been reported among breast-fed African-American infants in several southern states (Kreiter SR et al., 2000, Weisberg P., 2004). The relationship between maternal vitamin D/calcium intake and fetal bone development was reviewed (Specker B., 2004). Most of the papers reported an effect of maternal vitamin D status on both maternal and infant calcium homeostasis, but did not report whether infant Bone Mineral Density (BMD) was affected or not.
Low Birth Weight (LBW) appears to be a consequence of vitamin D insufficiency during pregnancy. The topic was reviewed by Fuller, who hypothesized that insufficient serum 25(OH)D levels disrupted calcium homeostasis, leading to intrauterine growth retardation, premature labour, and hypertension, all of which are risk factors for LBW infants (Fuller KE., 2000). Subsequent papers seem to support the hypothesis that African-American and Asian-Indian mothers have much higher rates of LBW infants in the United States than do European Americans or Hispanic Americans (Branum AM., 20002; Alexander GR et al., 2003). This may be in part because Hispanic Americans have a slightly higher consumption of vitamin D than African Americans, (Calvo MS., 2005) as well as lighter skin. Also, Koreans born in winter tend to have lower BMD than those born in summer (Namgung R., 2003). Children born prematurely are likely to have enamel defects in both primary and permanent teeth. Maternal vitamin D is required for proper fetal tooth development as well as adequate calcium. An additional benefit of vitamin D and calcium during pregnancy is good for maternal bone health. Studies report (Garland C et al., 1985, Grant WB., 2002) that bone density losses during pregnancy that are exacerbated by calcium and vitamin D deficiency. Maternal and infant 25 (OH) D sufficiencies also appear to be greatly reducing the risk of type 1 Diabetes Mellitus (DM). A study of vitamin
D supplementation during the first year of life found those receiving the highest amounts in Finland had an odds ratio of 0.2 of developing type 1 DM compared with those receiving no supplements. In further support of this hypothesis, mechanisms were investigated in a mouse model, (Zella JB, De., 2003) and vitamin D receptor (VDR) alleles have been associated with risk of type 1 DM (Motohashi Y et al., 2003). The VDR bind 1, 25-dihydroxy vitamin D$_3$ 1, 25(OH)$_2$D to its target cells and organs where it performs certain functions. The fact that VDR alleles are associated with a particular disease gives further support to vitamin D having an effect. In addition, there is an excess summer birth rate for those who develop type 1 DM (Willis JA et al., 2002). The most likely explanation is that maternal vitamin D insufficiency occurs during the second trimester of pregnancy, a time when the pancreas is likely to develop. Risk of type 1 DM related to vitamin D status should be considered when revising vitamin D guidelines (Harris SS., 2005). Maternal and infant 25 (OH) D sufficiencies is also linked to significant reduction of risk for Multiple Sclerosis (MS). Vitamin D is hypothesized to reduce the risk of MS by strengthening the immune system against viral infections, a theoretical etiological factor in MS. (Cantorna MT., 2000; Embry AF., 2004). Adequate serum 25(OH) D levels during pregnancy appear to reduce the risk of MS, as evidenced by seasonal variations in birth rate for those who later develop MS, with spring
being the season of greatest birth rate with MS. A recent paper suggests that vitamin D supplementation during pregnancy as a way to reduce the risk of fatal inclination toward MS (Chaudhuri A., 2005). A study in England found that vitamin D insufficiency also leads to by bipolar disorder. It strongly suggests that the risk of bipolar disorder can be reduced through sufficient vitamin D intake during pregnancy. The same can be said of anxiety neurosis, for which there is a very pronounced springtime excess birth rate; for example, in New South Wales (Parker G., 1978). It is likely several other mental disorders and birth defects associated with springtime excess birth rates will be linked to maternal vitamin-D deficiency earlier in pregnancy.

5.2. Vitamin D Benefits in Adulthood

Vitamin D levels in adulthood are important for maintaining BMD. The primary risk factors for low BMD, osteoporosis, and osteopenia are vitamin D insufficiency, inadequate calcium intake, lack of exercise, and other dietary factors. Serum 25(OH)D levels have been directly related to bone health in men and women of all ages. It was recently reported that tanners who had robust levels of 25(OH)D (>40ng/ml) had higher bone density (Tangpricha V et al., 2004). Inflammatory bowel diseases (IBD), such as Crohn’s disease, can reduce the absorption of dietary vitamin D, especially with resection of
the duodenum and jejunum, which are the sites of vitamin D absorption. The decreased vitamin D levels and increased risk of osteoporosis in IBD are associated not only with poor absorption of vitamin D but also with use of corticosteroids (Vestergaard P., 2004) which are also frequently prescribed for the treatment of such conditions as collagen vascular diseases, bronchial asthma, and skin conditions. Other medications, including anticonvulsants, heparin, warfarine and methotrexate also contributes to low BMD (Hansen LB., 2004). Therefore, adequate vitamin D and calcium consumption and exercise should be maintained to combat both primary and secondary risk factors for low BMD during adulthood.

Sufficient vitamin D levels in adults may significantly reduce the risk for many types of cancer. The interest in vitamin D as a reduction factor for cancer began in 1980 when Cedric and Frank Garland looked at maps of cancer mortality rates in the United States and noticed colon cancer rates were lowest in the southwest. In trying to determine a mechanism, they reasoned that the primary physiological effect of exposure to sunlight, other than inducing tanning, was the production of vitamin D. A few years later they demonstrated, using sera stored for another purpose, that colon cancer risk was inversely associated with pre-diagnostic serum 25(OH) D levels. It was soon demonstrated that breast, ovarian, and prostate cancers also had inverse correlations with
solar UV-B radiation. (Hanchette CL., 1992). By the late 1990s, the mechanism whereby vitamin D reduces the risk of cancer were fairly well known (Lampecht SA., 2003). It include facilitation of calcium absorption (colon cancer) increased cell differentiation and apoptosis and reduction of both metastasis and angiogenesis. Calcium has been shown to decrease proliferation and induce differentiation in epithelial cells. In addition, it was discovered that most organs have VDRs and that various alleles of the gene for VDRs affect the risk of cancer (Ingles SA, Garcia DG, Wang W, et al., 2000; Ikuyama T et al., 2002, Slattery ML et al., 2004). It is now thought that UVB and vitamin D reduce the risk of 17 types of cancer (Grant WB.2004). This determination was made using cancer mortality rate data from the Atlas of Cancer Mortality Rates in the United States (Devesa SS et al., 1999) and UVB data for July from the Total Ozone Mapping Spectrometer (TOMS) (Leffell DJ., 1996). The TOMS data provide a convenient index for vitamin D production from UV-B irradiation, but are somewhat limited because they cover only one month. Both July UV-B irradiation and cancer mortality rates have highly asymmetrical distributions in the United States UV-B levels are highest in the southwest and lowest in the northeast; whereas, the opposite holds for many types of cancer. The reason for the asymmetry in UVB irradiation is that, as the westerly winds prepare to cross the Rocky Mountains, the
air masses push up the tropopause west of the Rockies, thereby reducing the thickness of the stratospheric ozone layer. The edge of the ozone absorption band occurs in the UV-B region (290-315 nm); therefore, variations in ozone column amounts affect the UV-B transmission.

Statistically significant inverse correlations were found for bladder, breast, colon, oesophageal, gastric, ovarian, prostate, rectal, renal, uterine cancer and Non Hodgkin Lymphoma (NHL). This study was extended by including several additional cancer risk-modifying factors, including degree of urbanization, smoking, alcohol consumption, Hispanic heritage, and fraction of the population living below the poverty line, with all data averaged at the state level (Grant WB., 2004). The additional cancers found to be vitamin D sensitive are cervical, gall bladder, laryngeal, oral, pancreatic, and Hodgkin’s lymphoma. In most cases the association with UV-B irradiation for July is stronger than that for any other factor. The primary exceptions to this relation are cancers strongly linked to smoking. However, in multi-country comparisons, the fraction of energy derived from dietary animal products is the primary risk factor for breast (Grant WB., 1999; 2002) and colon cancer. The link between diet and cancer risk in such cases appears to be mediated through insulin-like growth factor-1 (IGF-1) (Kaaks R., 2004). Dietary factors do not vary greatly within the United
States. Vitamin D has been shown to counteract the growth-signalling effects of IGF-1 (Xie SP., 1999).

5.3. The Role of Vitamin D in Health

Vitamin D is known for playing a role in promoting a healthy skeleton by maintaining serum calcium and phosphorus levels within normal ranges and, thus, promoting bone mineralization (Holick MF., 1996). In response to low serum calcium levels, such as from low calcium intake, parathyroid hormone (PTH) is secreted by the parathyroid gland. Parathyroid hormone triggers the hydroxylation of 25(OH) D to 1, 25-(OH)₂D (Holick MF., 1994). This active form of vitamin D then acts on the small intestine and bone to normalize serum calcium levels. In the small intestine, 1,25(OH)₂D increases the efficiency of calcium and phosphorus absorption by the small intestine and acts as a steroid hormone (Groff JL., 1999). Vitamin D receptors on absorptive cells in the small intestine bind to 1, 25(OH)₂D and begin the process of intestinal calcium absorption (Holick MF., 1999). 1,25(OH)₂D stimulates changes in the brush border and results in the opening of voltage-gated calcium channels. As the body becomes vitamin D deficient, the efficiency of intestinal calcium absorption decreases from 30-50% to no more than 15% (Groff JL., 1999).
1,25(OH)_2D also acts on bone to regulate blood calcium levels. In response to low serum calcium levels, 1, 25(OH)_2D first acts on the osteoblasts or bone forming cells, which in turn increase formation of osteoclasts, or bone resorbing cells. When osteoclast activity increases, bone is dissolved and calcium stores are released from bone and transported to the bloodstream where calcium levels are restored to normal ranges. When levels of vitamin D are inadequate to aid in calcium absorption from the bloodstream, humans are at risk of developing rickets and osteomalacia. Rickets occurs in children and osteomalacia can occur in both children and adults. Rickets is characterized by an interruption in the development and mineralization of the growth plate in bone (Rao DS., 1999). Osteomalacia and rickets result in softening of the bone and are characterized by biochemical markers including hypocalcaemia, elevated serum alkaline phosphatase, hypophosphatemia and decreased intestinal absorption of calcium and phosphorus (Rao DS., 1999). Rickets and osteomalacia are unlike other nutritional deficiencies in the respect that they are often asymptomatic and can go unnoticed. The best way to prevent prolonged vitamin D deficiency is through biochemical screening and assuring adequate dietary intake of vitamin D.

There have been recent studies on the other tissues of the body that possess receptor sites for the metabolite 1,25(OH)_2D (Holick MF.,
1998). These tissues include the brain, pancreas, stomach, and the skin. Many of the target tissues were discovered in experiments performed in vitro and the function of vitamin D in these tissues in humans is still unclear. In the newly discovered target tissues, the function of 1, 25(OH)₂D is not directly linked with serum calcium homeostasis. It would seem that the role of vitamin D is not necessary for the function of these tissues since the physiologic functions of these organs do not appear to be affected by vitamin D deficiency (Combs GF., 1998). Few researchers have investigated the effects of vitamin D intake during adolescence in the United States. Adolescence and puberty are important times of growth and bone metabolism in children (Outila TA., 2001). During adolescence the goal is to maximize peak bone mass during the critical time of skeletal development. Aksnes and Aarskog discovered that during puberty the conversion of 25(OH) D to 1,25(OH)₂D increases. This increase correlated with periods of growth for both girls and boys, with the girls' conversion rate increasing between 11 and 12 years and the boys increasing between 13 and 14 years. The increase in circulating 1,25(OH)₂D levels increases the efficiency of intestinal calcium absorption to supply the rapidly growing skeleton (Food and Nutrition Board., 1997).
5.4. Optimal Level of Vitamin-D in Serum to Support Health

Serum levels of 25(OH) D are considered the best measure of overall Vitamin D status (Food and Nutrition Board, 1997, Holick MF., 2002). When vitamin D is hydroxylated to 25(OH) D, the reaction is in response to vitamin D synthesized in the skin and consumed in the diet. The reaction is poorly regulated and not limited (Coombs GF., 1998). Little of the 25(OH) D formed in the liver stays in the liver, and little 25(OH) D are absorbed by extra hepatic tissues (Groff JL., 1999). The blood is therefore the largest pool because 25(OH) D is not stored in the cells. The serum half-life of 25(OH) D is longer than vitamin D or 1, 25(OH)\textsubscript{2}D (Holick MF., 2002). The half-life of serum 25(OH)D is about 3 weeks as compared to the half-life of circulating vitamin D, which is about 24 hours, and the half-life of 1, 25(OH)\textsubscript{2}D is only 4 to 6 hours (Utiger RD., 1998). The optimal serum levels of 25(OH) D to maintain a healthy skeleton and reduce disease may differ with each age group and the latitude at which each person lives, particularly during the winter months. Wide ranges of serum levels of 25(OH) D have been seen in adults and children, from 20nmol/L (8ng/ml) to 150nmol/L (60ng/ml) (Malabanan A., 1998). Levels of 25(OH)D between 20 and 2nmol/L (8 and 10ng/ml), or lower, are typically considered a sign of vitamin D deficiency, and increased PTH activity and bone mobilization of calcium
stores occur at or below these levels (Holick MF., 1990). Outila et al. 2001 studied 178 healthy females aged 14-16 years in Helsinki, Finland during the winter. They found that serum 25(OH)D concentrations \(>40\text{nmol/L (16ng/ml)} \) were adequate to keep serum PTH concentrations at normal levels for optimal health (Outila et al., 2001). Similarly, Malabanan et al. 1988 found that adults over the age of 49 needed serum 25(OH) D levels \(>50\text{nmol/L (20ng/ml)} \) to sustain PTH at optimal levels. Adults who had serum 25(OH) D levels greater than 50nmol/L (20ng/ml) had no significant change in their circulating concentrations of PTH after receiving vitamin D therapy. Based on this study, the recommended minimum level of serum 25(OH)D should be 50nmol/L (20ng/ml), and levels below this may indicate deficiency and put an individual at risk for developing secondary hyperparathyroidism, rickets or osteomalacia, or worsen osteoporosis (HolickMF.,1990).

### 5.5. Recommended Intake and Sources of Vitamin D

The amount of UV-B irradiation required for sufficient vitamin D can be calculated from the amount of vitamin D produced from one minimal erythemal dose (MED) 10,000-25,000IU of oral vitamin D (Holick MF., 2004). If 10,000 IU of vitamin D is produced from exposure of the full body to one MED, exposing the full body to 25 percent of the MED would produce 2,500 IU. In order to achieve 1,000
IU, 40 percent of the body should be exposed to 25 percent of the MED; if production is more efficient, less of the body need be exposed. For pale skin, the exposure time for one MED in the summer noonday sun in the southern United States is about 4-10 minutes; for dark skin, such as for African Americans, the corresponding time is 60-80 minutes. (Holick MF., 2003; 20004). Exposure times should be 25-50 percent of the MED. The length of time varies with geographical location, skin pigmentation, percent body fat, and age.

The best time of the day for vitamin D production is near solar noon, when the ratio of UVB to UVA is highest. Typically, vitamin D3 can be produced from 10 a.m. to 3 p.m. during the spring and summer fall. Because UVB radiation occurs at shorter wavelengths than UVA, it experiences greater attenuation from atmospheric scatter than UVA. Also, UVB is absorbed by ozone. Thus, the exposure time required for a given level of vitamin D photo production is lowest near solar noon. In addition, basal cell carcinoma (BCC) and cutaneous malignant melanoma (CMM) are probably more susceptible to UVA irradiation than UVB irradiation, (Armstrong BK., 2001; Wang SQ et al., 2001) so that minimizing UVA rather than UVB exposure may be appropriate. For these two reasons, midday solar UV irradiation, short of erythema, will reduce the risk of both BCC and CMM. BCC and CMM are also linked more to intermittent UV exposure, such as during a vacation in a
sunny location, than to occupational exposure, which seems to be protective (Kennedy C et al., 2003; Berwick M et al., 2005; Gandini S et al., 2005). This protective effect of regular exposure may be via vitamin D production (Millen AE et al., 2004) or perhaps through conditioning of the skin for higher UV radiation. BCC is the most common form of skin cancer for those with lightly pigmented skin, whereas CMM is the most deadly. On the other hand, actinic keratosis (AK) and squamous cell carcinoma (SCC) are more likely related to total lifetime UVB irradiation. SCC, although a rare form of skin cancer, is more deadly than BCC and accounts for most non-melanoma skin cancer deaths in the United States. Thus, sunscreens, which have much greater protection against UVB than UVA radiation, appear to protect against AK and SCC but not BCC (Green A et al., 1999) and CMM (Dennis LK, 2003).

In addition, indoor tanning using artificial lamps with a UV spectral output that mimics that of solar UV radiation reaching the Earth’s surface near summer time noon at mid latitude (3-5% UV-B, 95-97% UV-A) can also be used to produce vitamin D (Tangpricha V, Turner A, Spina C, et al., 2004). Lower fractions of UV-B, such as 1.5 percent in France and Sweden, are associated with increased risk of melanoma (Autier P., 2004). However, those who do not tan easily should not use such lamps since they are less well protected against free
radical formation. Higher fractions of UV-B may be more beneficial, but research on this topic has not been conducted. The vitamin D production potential of both the sun and artificial UV-B sources can be determined by various means (Terenetskaya I., 2004).

5.5.1. Recommended Intake of Vitamin D

The main sources of vitamin D for humans are exposure to sunlight and consumption of food products containing vitamin D (Davies PS et al., 1999). The recommended Adequate Intake (AI) for children and adults up to 50 years of age set by the Food and Nutrition Board of the Institute of Medicine in 1997 is 5μg per day, or 200 International Units (IU). The amount of 5μg per day is based on the minimum requirement of 2.5μg (100 IU) to keep blood levels of vitamin D at adequate levels, and doubled to cover needs regardless of exposure to sunlight (Food and Nutrition Board., 1997). As the age of the individual increases, the dietary requirement (AI) for vitamin D increases. This increase may be due a decrease in the amount of time spent outside, more concern about their skin resulting in the use of sunscreen and clothing to prevent ageing and cancer, and a decrease ability of the skin to make vitamin D (Food and Nutrition Board., 1997, Holick MF., 1999). Between the ages of 51 and 70 years, the AI is 10μg (400IU) and for individuals over 71 years of age, the AI is 15μg.
(600IU). Amounts of vitamin D are expressed either as International Units (IU) or micrograms (μg). One μg of vitamin D is biologically equivalent to 40IU.

5.5.2. Dietary Sources of Vitamin D

Vitamin D occurs naturally in few foods such as fatty fish including salmon and fish oils including cod liver oil. Because of the low levels of vitamin D occurring naturally in foods, many countries, including the United States, fortify selected food products with vitamin D, and these foods are the major sources of dietary vitamin D for many people. Milk is the major food product fortified with vitamin D in the United States. Recently various other foods, such as some margarines, yogurts, cereals and cereal bars are fortified with vitamin D as well (Holick MF., 1999). Vitamin D fortification of cow's milk began in the early 1930's because the vitamin D content of unfortified cow's milk was quite low. Fortification of cow's milk with vitamin D resulted in the elimination of rickets as a key health concern for children in North America (Holick MF., 1992). The process began by adding the animal sterol 7- dehydrocholesterol and irradiating the milk, which would then form vitamin D₃ in the milk (The Dairy Practices Council., 1995). In 1937, the Council on Food and Nutrition of the American Medical Association determined the appropriate level of vitamin D fortification
for cow's milk to be 400 IU per quart. When the level of 400 IU was established, problems developed with the irradiation process. The main problem was maintaining continuous power input to the ultraviolet lamps to produce this level. This problem was compounded by the initiation of the use of high-temperature, short-time pasteurization. With these problems, there arouse the need to fortify milk directly with vitamin supplements. In the United States and Canada, direct fortification of homogenized cow's milk with vitamin D is currently the standard practice. To meet the requirements of the Code of Federal Regulations, each quart of fortified milk product must contain no less than 400 IU per quart and no more than 600 IU per quart (The Dairy Practices Council., 1995). With these requirements, the vitamin D content of cow's milk should not exceed 150% of the required level of vitamin D. Vitamin D is stable in homogenized milk and is not affected by pasteurization. Under normal shelf life there is no significant loss of vitamin D in the milk. Improper fortification of milk may occur during processing due to human error; either the amount of vitamin D added has been miscalculated or forgotten all together. A wide variation in the vitamin D content of fortified cow's milk exists (Holick MF., 1992, 1999, The Dairy Practices Council., 1995). In 1991, Holick et al.1992 investigated that vitamin D content of 42 containers of milk from 13 milk processors were purchased in 5 Eastern states in the United States.
The samples included 14 samples of whole milk, 10 samples of 2% milk, 4 samples of 1% milk and 14 samples of skim milk. When the milk was analyzed for actual vitamin D content, only 12 of the 42 samples contained 80 to 120% of the 400 IU of vitamin D stated on the label (320 IU to 480 IU). Twenty-six of the 42 samples contained less than 80% of the vitamin D claimed on the label of the 14 skim milk samples tested, 3 had no detectable amounts of vitamin D present (Holick MF., 1992). Chen et al. 1993 performed a follow up to the Holick et al. 1992 study between May 1992 and June 1993. Seventy-nine milk samples were purchased in seven Eastern states, including the five states where milk was purchased for the study in 1991. Eighty percent of the milk samples contained either 20% less or 20% more than the label stated. Fourteen percent of the 79 milks sampled had undetectable amounts (4%) of vitamin D as stated on the label. Over-fortification, above 120%, occurred in 29% of the samples. One sample of chocolate milk contained 914% of the amount of vitamin D stated on the label and another whole milk sample contained 382% of the acceptable limit of 400 IU per quart (Chen T et al., 1993).

The importance of optimal vitamin D at all stages of life, from fetal development to old age, dosage recommendations for vitamin D can be addressed. The most important consideration is serum 25(OH) D levels. Exposure to solar UV-B irradiation as it contributes to serum
25(OH)D levels depends on latitude, time of day, season, fraction of body exposed, whether one visits indoor tanning facilities, (Tangpricha V et al., 2004) skin pigmentation, body mass index, and amount of body fat (Wortsman J et al., 2003). Non-UVB factors include diet, vitamin D supplementation, and use of certain pharmaceutical drugs, such as glucocorticoids (Di Munno O et al., 2004).

The importance of vitamin D sufficiency for optimal health, and the fact that solar UV-B irradiation is the primary source of vitamin D for most people, it is imperative that guidelines for solar UV exposure can be revised in consideration of overall health, rather than only for reducing the risk of skin cancer and melanoma.

The guidelines currently in place in the United States recommend 5μg/day (200 IU/day) of vitamin D for children and younger adults, 400 IU/day for those ages 51-70, and 600 IU/day for those over age 70 (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes., 1997). These guidelines are based on maintaining the bone health. Since 1997, much has been learned about the non-calcemic benefits of vitamin D, essentially making these guidelines obsolete. From evaluation of vitamin D consumption among nurses and male health professionals in cohort and other studies, the mean intake of vitamin D at age 50 and older is approximately 320 IU/day in the United States, with about 200IU/day coming from dietary sources.