Non-Bone Effects of Vitamin D in Children, Adolescents, and Young Adults

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Additional information is available at the end of the chapter

Abstract

Vitamin D, also known as "sunshine vitamin", has long been established as an essential component for the maintenance of adequate bone health. Large number of studies are available which demonstrate the various biochemical pathways of vitamin D in bone physiology and its important role in musculoskeletal health. In last five decades, data regarding the non-bone effects of vitamin D have started to emerge, and now many important non-bone physiological processes are explained by the biochemical pathways and functions of vitamin D. However, majority of the data regarding extra-skeletal effects of vitamin D are available regarding adult population. In this chapter, we try to focus on the role of vitamin D in aging and various diseases which are frequently seen in children, adolescents, and young adults such as cancer, type 1 diabetes mellitus, allergies, asthma, and various autoimmune diseases.

Keywords: vitamin D, autoimmune disease, aging, diabetes, cancer, children

1. Introduction

Vitamin D, also known as "sunshine vitamin", is considered essential for maintenance of bone health along with many other key roles in metabolic processes of the body. About 10,000–20,000 IU of vitamin D3 is produced in our skin from the sun's ultraviolet light (UVB) after full body exposure for 15 min [1]. Complexion or skin phototype, use of sunblock, smog, cloud cover, latitude, time of day (10:00 am to 02:00 pm), and season are some of the factors that affect our body's ability to produce vitamin D [2]. Latitudes from 0 to 35° north or south allow yearlong production of vitamin D in our body, but as latitude increases the amount of vitamin

D production will decrease [3]. The latitude of Pakistan is 32.0162°N which is suitable for yearlong production of vitamin D.

Recommended daily intake of vitamin D in the first year of life is 400 IU and 600 IU for everyone above 1 year of age [4]. Vitamin D is essential for proper bone growth and bone remodeling by the action of osteoblasts and osteoclasts [5]. Vitamin D insufficiency or deficiency can lead to osteoporosis by decreasing calcium absorption from intestine and kidney [6]. Harinarayan et al. have showed that normal homeostasis of bone has been seriously affected by decreased intake of calcium and vitamin D in diet [7]. In children, inadequate mineralization of the growing skeleton leading to rickets is an established fact [8]. Välimäki et al. discussed that vitamin D deficiency is common in young men, especially in winter, and this deficiency may have detrimental effects on the acquisition of maximal peak bone mass [9]. Gait disturbances and myopathy have also been associated with severe vitamin D deficiency [10]. Discovery of the vitamin D receptor (VDR) expressed in the cell nuclei of muscle cells and its association with muscle cell contractility has been documented by Bischoff-Ferrari et al [11]. Meta-analysis done by Papadimitropoulos et al. concluded that adequate levels of vitamin D decrease the rate of vertebral and non-vertebral fractures [12].

1.1. Prevalence of vitamin D deficiency

Studies from around the world have shown pandemic of vitamin D deficiency or insufficiency [13]. In last decade, various studies from Pakistan have found critically low levels of vitamin D in diverse groups of population. Work done by Siddiqui and Rai [14] in Hazara division of Pakistan showed that nutritional rickets resulting from vitamin D deficient diet is a predisposing factor for different childhood illnesses such as pneumonia, diarrhea, and delayed motor milestones. They attributed lack of sun exposure, malnutrition, and various antenatal factors as important causes for vitamin D deficiency. Similarly, Anwar et al. [15] found that 99.5% of women and 97.3% of neonates from urban population sample and 89% of women and 82% of neonates from rural population sample had below 50 nmol/l levels of vitamin D. Jamal et al. [16] and Qamar et al. [17] have also found insufficient/deficient vitamin D levels in more than 90% children included in their studies. A study done in our laboratory including 5- to 11-year-old children with intellectual disability also showed extremely low levels of vitamin D (12.08 ± 9.06 ng/ml) in 85% of study sample. These numbers are consistent with another population-based study done in Karachi by Iqbal et al. [18] who found that vitamin D was deficient in 73.7% and insufficient in 13.8% study subjects.

In last two decades, lot of studies came out from around the world reporting lower or deficient levels of vitamin D; however, few questions remained ambiguous: How much vitamin D is needed to achieve desirable health outcomes and how much of vitamin D is too much? In 2011, a new public health report on dietary intake requirements for calcium and vitamin D authored by the committee from the Institute of Medicine (IOM) gave their recommendations regarding above queries. The committee concluded that serum 25OHD levels of 16 ng/ml (40 nmol/l) cover the requirements of approximately half of the population, and levels of 20 ng/ml (50 nmol/l) cover the requirements of at least 97.5% of the population. The IOM committee also highlighted the fact that data for the upper cutoff limit were scarce and long-term effects of

chronically high concentrations of vitamin D, and a margin of safety for public health recommendations was prudent. Thus, serum 25OHD levels above 50 ng/ml (125 nmol/l) should raise concerns among clinicians about potential adverse effects [4].

1.2. Vitamin D status and skin complexion

Complexion or skin phototype is another important factor that determines amount of vitamin D production in our body. Individuals with darker complexion have higher chances of developing vitamin D deficiency than fair-skinned people [19]. The deficiency in circulating levels of 25-hydroxyvitamin D in individuals with darker skin complexion is mediated largely by melanin which protects the skin from ultraviolet light rays. By blocking the sun's ultra violet rays, melanin greatly reduces the skin's ability to convert 7-dehydrocholesterol to cholecalciferol, the precursor of 25(OH)D, in the skin [20]. In 2011, Signorello et al. investigated the association between 94 single nucleotide polymorphisms (SNPs) in five vitamin D pathway genes (*GC*, *VDR*, *CYP2R1*, *CYP24A1*, *CYP27B1*) and serum 25-hydroxyvitamin D (25(OH)D) levels among 379 African American and 379 Caucasian participants, and they found that common variation in vitamin D pathway genes predicts circulating 25-hydroxyvitamin D levels among African Americans having darker complexion [21].

Vitamin D supplementation is considered as an important factor in improving the poor bone health of people with both fair and dark skin complexions. Studies have shown that people with both dark and white skin color appear to have similar capacities to synthesize vitamin D in the skin, but vitamin D synthesis is less efficient among blacks at usual levels of sun exposure as compared to white people [22]. Recently, a study done by Gallagher et al. demonstrated that despite having lower levels of vitamin D at baseline, the increase in serum vitamin D after supplementation in African American women was similar to that seen in the Caucasian women. Furthermore, 97.5% of both dark- and white-colored women on 800 IU/daily for 12 months reached a level of 20 ng/ml. They also concluded that because absorption and metabolism of oral vitamin D are similar in both dark and fair complexioned people, lower levels of serum 25OHD in African Americans must be due to lower production of vitamin D in skin [23].

1.3. Is Vitamin D synthesis gender specific?

Data regarding the association of gender with vitamin D synthesis are inconsistent and scarce. There are number of conflicting hypotheses which indicate that differences in the amount of adipose tissue in males and females and in their skins may lead to the variation in vitamin D synthesis. Number of studies has demonstrated decreased bioavailability of fat soluble vitamin D3 from cutaneous and dietary sources because of its deposition in body fat [24–27]. This may point toward decreased vitamin D levels in women because of their excessive adiposity as compared to men. On the other hand, it has also been hypothesized that the lighter color of female skin permits synthesis of relatively higher amounts of vitamin D3 during pregnancy and lactation [28]. On the contrary, data from a recent study in mice have demonstrated that androgens decrease the synthesis of vitamin D induced by ultraviolet rays in the skin of a male mice by an enzymatic mechanism [29].

1.4. Physiology of non-bone effects of vitamin D

Initially, it was thought that vitamin D has a restricted role in calcium homeostasis, but it is only now that the pleiotropic actions of vitamin D with their clinical significance are becoming apparent. Recently, 2776 genomic positions occupied by the vitamin D receptor (VDR) and 229 genes showing significant changes in expression in response to vitamin D have been identified [30]. VDR has been identified in wide variety of tissues other than small intestine, kidneys, and bone such as brain, heart, stomach, pancreas, activated T and B lymphocytes, skin and gonads [31]. One hydroxylase activity has also been identified in cultured cells from skin, colon, prostate, breast, lung, and brain [1, 32, 33]. Addition of vitamin D in our diet in the form of supplementation or food fortification can reduce the risk of asthma, influenza, respiratory tract infections, autoimmune diseases, diabetes, and cancer and improve bone and overall health [2]. This evidence points to the diverse functions of vitamin D and its implicated role in various diseases related to wide distribution of vitamin D receptors in many tissues.

In the following sections of this chapter, recent review of literature regarding physiological role of vitamin D in various non-bone effects is given.

2. Vitamin D and aging

It has been long known that aging decreases the capacity of human skin to produce vitamin D3 (7-dehydrocholesterol). This is evident from the classic study done by McLaughlin and Holick in 1985 in which they exposed the skin samples from various age groups to ultraviolet rays and compared the amount of previtamin D3 produced in the skin samples from 8- to 18-year-old subjects with the amount produced in the skin samples from 77- to 82-year-old subjects. The results revealed that aging can decrease the capacity of the skin to produce previtamin D3 by greater than twofold [34].

In humans, aging represents the accumulation of changes in a human being over time, encompassing physical, psychological, and social change. Telomeres, the DNA-protein structures located at the ends of chromosomes, have been proposed to act as a biomarker of aging [35]. A cross-sectional analysis of the Nurses' Health Study (NHS) data done by Liu et al. [36] demonstrated the association between vitamin D and telomere length in peripheral blood leukocytes by using plasma biomarkers of both 25(OH)D and 1,25(OH)2D. They found that higher plasma 25(OH)D levels are associated with longer telomeres, and this association may be modified by calcium intake. The difference in telomere length between those with high (vitamin D sufficient) and low (vitamin D insufficient) levels of vitamin D corresponded to 5 years of aging. The shortening of telomeres is thought to be caused by decreasing inflammatory mediators and cell proliferation [37]. Changes in the expression of VDR leading to vitamin D resistance with aging have also been elaborated in recent literature. Several studies have reported association of aging with decrease in the expression of VDR in bone, intestine, and muscle tissues [38–40]. Various factors that decrease with aging have been identified to influence VDR such as estrogen, growth hormones, and vitamin D itself [11, 41]. On the other hand, the expression of TNF alpha which increases with aging has been shown to downregu-

late the expression of VDR [42, 43]. An animal study has also demonstrated a decrease in number of vitamin D receptors in addition to decreased binding of active metabolite of vitamin D with VDR in aged rat intestinal subcellular fractions [44]. Association of premature aging phenotype with too high and too low vitamin D levels has also been demonstrated in mice [45]. A recent study found that individuals in the highest quartile of serum vitamin D had the longest lifespan compared to those in the lowest quartile [46]. Above evidence and already established associations of several common aging-associated diseases such as osteoporosis, hypertension, and diabetes with vitamin D deficiency point us to consider vitamin D levels as a biomarker for aging.

3. Cancer in children

Although cancer in children is rare, it is the leading cause of death by disease past infancy among children in the United States. The most common types of cancer diagnosed in children and adolescents are leukemia, brain and other central nervous system tumors, lymphoma, rhabdomyosarcoma, neuroblastoma, Wilms tumor, bone cancer, and gonadal (testicular and ovarian) germ cell tumors [47]. Pakistan is a developing country with a population of about 180 million people out of which 39% are under 15 years of age. Although malnutrition and communicable diseases are still the major killers, cancer is becoming an important cause of morbidity and mortality in children. Cancer among children is fortunately less common than in adult accounting for 3–5% of all cancers. Based on Karachi Cancer Registry, it is estimated that about 7000–7500 children get cancer every year in Pakistan [48]. A limited number of small studies have examined the vitamin D status of pediatric oncology patients, and the results indicate an increased prevalence of hypovitaminosis D [49, 50].

3.1. Role of vitamin D in cancer

Specific vitamin D receptors found in nearly all tissues produce 1,25(OH)2D in the presence of 25(OH)D. This 1,25(OH)2D is recognized to cause activation of VDR resulting in heterodimerization with the retinoid X receptor and binding to cognate vitamin D response elements (VDREs) in target genes involved in cellular differentiation, cell growth, apoptosis, inflammation, and immune modulation [51, 52]. Formation of 1 alpha hydroxylase enzyme in cancer cells has also been demonstrated [53, 54]. In last decade of twentieth century, number of studies came out that highlighted the association of decreased vitamin D levels in individuals living at high latitudes and increased risk of dying of colon, breast, prostate, and ovarian cancer [55–57].

Polymorphism of VDR gene has been associated with high risk of cancer. Women with mutations of VDR gene have higher risk of breast cancer [58]. Results of a hospital-based case-control study conducted by our department demonstrated that the *Bsm*I polymorphism in the *VDR* gene may be associated with an increased breast cancer risk in Pakistani women negative for *BRCA1/2* germline mutations [59].

Vitamin D-liganded VDR displays antiproliferative activities in many tumor types, as do activated members of the p53 family, through the induction of cell cycle arrest, senescence, differentiation, and apoptosis [60]. Several metabolites of vitamin D which do not cause hypercalcemia show antitumor activity in a subset of cancer patients with high VDR expression and are associated with good prognosis [61]. Some transcription factors repress VDR gene expression in human colon cancer cells. In human colon cancers, elevated expression of transcription factors correlates with downregulation of VDR [62]. The malignant cells are capable of annulling the antiproliferative activity of vitamin D by increasing the expression of transcriptional factors.

Several preclinical trials have demonstrated the antiproliferative effects of active form of vitamin D in various tumor types. The mechanisms by which vitamin D can exert antitumor effects may include inhibition of tumor angiogenesis, induction of apoptosis, regulation of different signaling pathways in tumor cells, and arrest of tumor cells in G0/G1 phase of cell cycle. Preclinical data indicate that maximal antitumor effects are seen with pharmacological doses of $1\alpha,25(OH)2D3$ and can be safely achieved in animals using a high-dose, intermittent schedule of administration [60]. Some clinical trial data indicate that $1\alpha,25(OH)2D3$ is well tolerated in cancer patients within a proper dosing schedule. Data support the hypothesis that vitamin D compounds may have an important role in cancer therapy and prevention, and merit further investigation [63].

Despite the presence of wealthy data regarding vitamin D and cancer, only a handful of studies have assessed vitamin D status in pediatric patients with malignancy, and all included relatively small numbers of patients [50]. This may point to the need of continuing elaborative research to identify the role of vitamin D in cancer, especially in populations with younger age groups.

4. Diabetes and vitamin D

Vitamin D deficiency and diabetes have one major trait in common: both are pandemic. The International Diabetes Federation estimated the number of people with diabetes worldwide to be nearly 415 million out of which three-quarters (75%) live in low- and middle-income countries. In Pakistan, prevalence of diabetes is 8.1%, whereas number of new cases of type 1 diabetes per 100,000 children per year is 0.5 [64]. Studies from different populations throughout the globe have reported high rates of vitamin D deficiency in children with type 1 diabetes [65–70]. Also several studies suggest that vitamin D deficiency correlates with the severity and frequency of type 1 diabetes in children as well as that vitamin D supplementation may reduce the risk of developing type 1 diabetes in younger age groups [71–73]. An analytical cross-sectional study conducted in our department demonstrated that offsprings of type 2 diabetics were severely deficient in vitamin D and its levels were inversely correlated with most of the components of metabolic syndrome [74]. Researchers have also explored the geographical variation in childhood diabetes. In study done by Mohr et al. in 2008, incidence rates of type 1 diabetes in children aged <14 years during 1990–1994 in 51 regions worldwide were assessed

by using multiple regression. This study found an association between low ultraviolet B irradiance and high incidence rates of type 1 childhood diabetes after controlling for per capita health expenditure. Incidence rates of type 1 diabetes approached zero in regions worldwide with high UVB irradiance, adding new support to the concept of a role of vitamin D in reducing the risk of the disease [75]. Similarly, data from sixth edition of diabetes atlas showed that incidence of type 1 diabetes is higher in countries that are located furthest from the equator as compared to countries located closest to equator. Staples et al. in their another study, which specifically examined the latitude gradient within Australia's territories, found childhood diabetes to be positively related to latitude. There was a strong threefold increase in prevalence of type 1 diabetes moving from the most northern territory to the most southern territory of Australia [76]. The above discussion positively points toward the association of incidence of childhood type 1 diabetes with latitudinal location.

Type 1 diabetes mellitus results from a cellular-mediated autoimmune destruction of the beta cells of the pancreas [77]. Studies on mice suggest that vitamin D inhibits IL-12 production and pancreatic infiltration of T helper cells along with the increase in number of CD4 positive and d CD25 positive regulatory T cells in pancreatic lymph nodes which may help in limiting the immunological progression and preventing the clinical onset of type 1 diabetes [78, 79]. There is evidence that vitamin D is important in the prevention of islet cell death and might be useful in improving the survival of islet cell grafts [80]. The presence of VDR and vitamin D-dependant calcium binding protein on beta cells of pancreas has also been reported. The effects of vitamin D on beta cells may be by its regulation of extracellular calcium and calcium flux through the beta cell or through calcium-independent pathways. Vitamin D deficiency may also impair insulin secretion through its associated increase in parathormone levels. It may reduce insulin resistance by its immunomodulatory and antiinflammatory effects [61]. Above evidence suggests that vitamin D may play a role in the prevention and treatment of type 1 diabetes mellitus in children; however, definitive and conclusive evidence regarding the potential role of vitamin D in alleviating the increasing menace of diabetes needs to be further studied through its action on systemic inflammation, insulin secretion, and resistance.

5. Allergies and asthma in children

Asthma and allergies are common chronic diseases in developed world [81–83]. CDC reports from national surveys in United States show the prevalence of asthma in children as 8.3% in 2013. The highest rates were observed among children aged 5–14 years, boys of less than 18 years, and people below 100% of poverty level [84]. Epidemiology of allergies and asthma is not well documented in Pakistan. A survey conducted in the city of Karachi among school children of age 3–16 years reported the prevalence of asthma at 15.8% and that of allergic rhinitis at 28.50% [85]. Another two-stage community-based representative cross-sectional survey conducted in Karachi from March 2012 to April 2013 reported overall prevalence of asthma among study participants as 10.2% [86].

5.1. Role of vitamin D in allergies and asthma in children

Many potential reasons have been reported in literature that could account for the pattern of increased burden of allergic diseases and asthma in developing as well as developed world. In last couple of decades, several studies have proposed pandemic of vitamin D deficiency as an important candidate that could explain a significant proportion of increased prevalence of allergic disease and asthma [87]. Potential mechanisms of how vitamin D can affect the risk of developing asthma and allergies include genetic pathways, role of vitamin D in prevention of bacterial infections, immune system effects, and effects on lung development and functions [88]. Significant associations between polymorphisms in the VDR gene and asthma have been reported by number of studies [89–91]. It has been proposed that asthmatics with bacterial and viral infections are at higher risk of more severe symptoms [92, 93]. Vitamin D induces the production of the antimicrobial polypeptide cathelicidin which has both antibacterial and antiviral effects [94, 95], and supplementation with vitamin D in asthmatics demonstrated decreased incidence of cold or influenza symptoms [96]. Studies done in mice have shown that vitamin D deficiency *in utero* leads to decreased lung volumes by affecting lung development [97]. Similarly, vitamin D also appears to affect *in utero* immune system development that begins to exert its effects in early life. Work done by Chi et al. [98] showed that cord blood vitamin D levels were inversely associated with the proportions of CD25(+), CD25(Bright), and CD25(+) FoxP3 cells to total CD4(+) T cells. While the clinical consequence of this inverse association remains unclear, it supports the notion that *in utero* vitamin D levels affect immune development and may influence immune regulation early in life. The number of studies has shown that maternal supplementation with vitamin D during pregnancy may eventually decrease the risk of allergies and wheezing in their children [99–101]. Other studies have investigated the association between vitamin D levels and asthma and allergies in the post-partum period. Several case-control studies from different parts of the world have found greater prevalence of vitamin D deficiency among asthmatic children than in controls [102–104]. In a recent work done in our department, an inverse relation of vitamin D levels with severity of asthma has been found (Lone Unpublished data).

Although more studies have shown a beneficial effect of vitamin D on asthma and allergies than studies showing negative results, definitive clinical trials are lacking and the optimal dose and level of vitamin D for decreasing the burden of asthma and allergies in children remain unknown.

6. Autoimmune diseases in children and vitamin D

There are at least 80 recognized human autoimmune diseases with new diseases frequently added to the list [105]. Autoimmune diseases are generally rare in children; however, when they occur, they can be challenging to diagnose and difficult to treat because most of the autoimmune diseases that are common in children have not cured yet. Besides type 1 diabetes mellitus, other autoimmune diseases which commonly occur in children include celiac disease,

lupus (SLE), juvenile dermatomyositis, scleroderma, juvenile idiopathic arthritis (JIA), and multiple sclerosis (MS) [106].

The effects of vitamin D in the immune system translate into an enhancement of innate immunity associated with a multifaceted regulation of acquired immunity [107]. Vitamin D supplementation is considered as an appealing therapy in pediatric autoimmune diseases. The diverse effects of vitamin D may minimize disease-related comorbidities resulting from bone weakening and infections in addition to attenuation of immune hyperactivation that is characteristic of pediatric SLE [108]. The SLE Disease Activity Index scores were found to be significantly higher in children who had 25(OH)D level less than 20 ng/ml [109]. Work done by Robinson et al. [110] demonstrated that low serum 25(OH)D level in children with SLE is associated with proteinuria and urinary vitamin D binding protein. Animal models have also shown that vitamin D and calcium supplementation can inhibit lupus activity [111, 112]. An incidental finding of an association between vitamin D deficiency and SLE nephritis has also been reported [113], but studies evaluating this relationship are lacking. Juvenile dermato-myositis (JDM) is a photosensitive rheumatic disease, treated commonly with sun avoidance, corticosteroids, methotrexate, and hydroxychloroquine. JDM shares many similarities with pediatric SLE in photosensitivity and methods of treatment, but it is not associated with proteinuria, making this an ideal comparison group for SLE. Robinson et al. [110] also reported that vitamin D deficiency is associated with disease activity in children with JDM.

Multiple sclerosis is an autoimmune disease of the central nervous system characterized by inadequate recognition of autoepitopes in myelinated nerve fibers by cells of the acquired immune system, generating an inflammatory immune response mediated by lymphocytes and macrophages, resulting in localized areas of inflammation and demyelination [114]. Some studies have also demonstrated the association of vitamin D deficiency and MS and its role not only in the reduction of relapse rates, but also in the prevention of its development [115, 116]. In MS, allelic variation in the MHC class II region exerts the single strongest effect on genetic risk. Environmental factors act at a population level. Sunlight or vitamin D is a key environmental factor in etiology and might interact with inherited factors in the MHC class II region [61]. A single MHC vitamin D response element (VDRE) gene has been identified as *HLA-DRB1*15* haplotypes. In a subgroup of individuals genetically predisposed to multiple sclerosis, deficiency of vitamin D may cause non-activation of histocompatibility genes necessary for differentiating between self and foreign proteins [117].

Despite the compelling evidence of low levels of vitamin D and its association with various autoimmune diseases, recently studies are coming out that challenge the assumption that serum levels of 25OH vitamin D are a sensitive marker of the autoimmune disease state [118]. Now many commentators are also advocating clinicians to stop costly measurements of 25OH vitamin D in asymptomatic patients [119–121]. The consideration of vitamin D as a marker for autoimmune diseases requires further sensitive evidence from randomized controlled clinical trials. The results then may elaborate the status of vitamin D as a marker for autoimmune diseases in future. Although more epidemiologic studies are needed to better understand the theory of vitamin D deficiency and its association with various auto immune diseases in

children, the compelling data pointing to a role for vitamin D in immune regulation suggest that special attention should be paid to these at-risk populations.

6.1. Role of sunlight in autoimmune diseases

The ultraviolet radiation in sunlight can induce the onset of, or exacerbate, the symptoms of certain autoimmune diseases. Work done by Fraser et al. suggested that ultraviolet light exposure triggers production of reactive oxygen species as normal by-products. If the cell does not quickly eliminate the reactive oxygen species, however, the buildup can cause cellular and DNA damage. The *GSTM1* gene normally codes for an enzyme, glutathione S-transferase, which rids the body of reactive oxygen species. Individuals who have the GSTM1 null genotype and are missing the enzyme may, therefore, be at an increased risk of DNA damage and can induce the onset of lupus [122]. Work done by Love et al. to study the distribution of myositis phenotypes and ultraviolet radiation exposure in the United States showed that ultraviolet radiation may modulate the clinical and immunological expression of autoimmune disease in women [123]. The above evidence points toward the stimulation and exacerbation of autoimmune process in specific disease, whereas, on the other hand, ultraviolet radiations can also prevent or reduce the symptoms of other autoimmune diseases by vitamin D formation in skin as elaborated in various parts of this chapter.

7. Conclusion

In last decade, the number of studies that have investigated the non-bone effects of vitamin D has increased tremendously. Many studies from around the globe have measured circulating 25-hydroxyvitamin D as a determinant of vitamin D status. However, several queries regarding the definitive place of 25OH vitamin D as a biomarker of vitamin D status and the exact level of 25OHD that determines optimal vitamin D status in children for majority of non-bone effects of vitamin D still remain elusive. Although the committee from Institute of Medicine has recommended that a 25OHD level of 50 nmol/l (20 ng/ml) should be considered sufficient, this recommendation was mainly based on studies of bone health and the committee acknowledged that studies in other disease states are sorely lacking [4]. There are number of authors who have dissenting opinion regarding the IOM recommendations of optimal vitamin D levels [124]. Furthermore, there are data that suggest that optimal circulating levels regarding adequate bone health as well as other non-bone effects are much higher than the current IOM recommendations [125]. Most of the studies done in children have only measured vitamin D level once at one point in time. It is known that vitamin D levels vary over seasons and likely over time. Future studies need to measure 25OHD at multiple time points in relation to the outcome of interest. Finally, there is a continuing need for further conclusive studies to define appropriate levels of vitamin D status and recommended daily allowance regarding adequate bone health and other non-bone effects of vitamin D, especially in children, adolescents, and young adults.

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