WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES

Volume 3, Issue 2, 1204-1221. Review Article ISSN 2278 – 4357

VITAMIN D DEFICIENCY AND RENAL FAILURE DISEASES IN SAUDI ARABIA: A COMPREHENSIVE REVIEW

***Mohammed Kuddus**

College of Medicine, University of Hail, Hail-2440, Kingdom of Saudi Arabia.

Article Received on
02 December 2013,
Revised on 28 December 2013,
Accepted on 29 January 2014

***Correspondence for Author:**
Dr. Mohammed Kuddus
College of Medicine,
University of Hail, Hail-2440,
Kingdom of Saudi Arabia.

ABSTRACT

Vitamin D is produced by skin exposed to ultraviolet B radiation (Sunlight) or obtained from dietary sources. Now the scientists proved that the vitamin D has preventive effect on broad range of health disorders. It is required not only for bone health but also for regulation of a large number of physiological functions and for better human health. Deficiency of vitamin D in individual occurs due to limited oral intake, impaired intestinal absorption or inadequate sun exposure and can be determined by measuring serum level of 25(OH)D. Vitamin D deficiency may causes decline in renal function which is directly related to cardiovascular mortality. This review article includes worldwide status of vitamin D level in population with special reference to Saudi Arabia and some general background of vitamin D, including sources, benefits, deficiencies, dietary requirements especially in renal failure diseases and prevention/treatment of vitamin D deficiency.

Keywords: Vitamin D deficiency; Sunlight; 25(OH)D; ergocalciferol; cholecalciferol; Saudi Arabia.

INTRODUCTION

Vitamin D is a vital fat-soluble vitamin occurring in several forms, especially vitamin D_2 (1,25-dihydoroxyvitamin D) or vitamin D_3 (25-hydroxyvitamin D), which is required for the maintenance of musculoskeletal health especially for normal bone and tooth structure. Vitamin D is obtained either through dietary sources or synthesized in the skin by ultraviolet radiation from the Sun. The socio-economic status, latitude and season are important determinants for vitamin D level. Productions of vitamin D are also affected by mutations in

vitamin D receptor, low daily calcium intake, obesity, aging, skin pigmentation and smoking.[1-3] The consequence of vitamin D deficiency is reflected by the high prevalence of rickets in many countries which is reviewed by many authors.[4-6] Vitamin D deficiency not only causes rickets among children, but it also causes bone diseases among adults. In addition, it is associated with decreased immune function and an increased risk of cardiovascular disease, diabetes, chronic kidney disease, polycystic ovary syndrome, and many types of cancer such as breast, colon, and prostate cancers.[7-8] It was found that men have a better vitamin D status than women; and adolescents, young adults and older persons carry a high risk for vitamin D insufficiency.

Now-a-days, deficiency or insufficiency of vitamin D becomes a common international problem.[7,9] A number of studies have shown that in the past decade the prevalence of vitamin D deficiency, in both children and adults, has increased rapidly worldwide especially in the United Arab Emirates, Turkey, Australia, Lebanon and India.[7, 10-14] In context to Saudi Arabia, deficiency or insufficiency of vitamin D is normally not an expected problem due to abundance of sunlight throughout the year. However, studies showed a high prevalence of vitamin D deficiency in both the genders and all age groups. The studies also concluded that the concentrations of vitamin D are significantly lower in those Saudi Arabian women who lived in apartments and whose average exposure to sunlight was less than 30 minutes/day.[15-19] Vitamin D deficiency in pregnant women increases the risk for rickets in their offspring.[6] Recent literatures confirmed that chronic kidney disease is also related to deficiency or insufficiency of vitamin D.[20-21] Chronic kidney disease (CKD) refers to a condition related to irreversible kidney damage that can further progress to end stage renal disease. CKD and deficiency/insufficiency of vitamin D is a major public health problem worldwide and extensive epidemiological research are available for both. However, little is known about the relationship between deficiency/insufficiency of vitamin D and CKD. The aim of the present review is to determine the prevalence of vitamin D deficiency in Saudi Arabians and its association with CKD. This review will be helpful in raising awareness as well as suggesting strategies to combat vitamin D deficiency and consequently in reducing the incidence of CKD.

VITAMIN D AND ITS POTENTIAL HEALTH BENEFITS

There is a vast study showing the health benefits of vitamin D such as it can improves muscle function, protect lung function, lower blood pressure, blunts your appetite and important for

bone health. It is also required for the regulation of a large number of physiological functions.[22] The major function of vitamin D is to increase the active absorption of ingested calcium and phosphate that helps in building bone at younger ages.[23] Additionally, adequate concentrations of vitamin D may be important in reducing the occurrence of autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, diabetes, prevent rickets in children and osteomalacia in adults, and some cancers.[24-27] An investigation in Saudi Arabia found that there is 95% improvement in chronic low back pain after treatment with vitamin D.[15] Vitamin D deficiency is associated with cardiovascular disease,[28] cortical bone loss,[29] insulin resistance,[30] development of autoimmune disease, predisposing to osteoporosis,[31] and colon, breast and prostate cancers.[32-33] Vitamin D has different form such as vitamin D_2 or ergocalciferol (plant sources of vitamin D) and vitamin D_3 or cholecalciferol (animal sources of vitamin D). Vitamin D from all sources are turned into 25-vitamin D in the liver then carried to the kidneys where it is activated into 1,25-dihydroxyvitamin D or calciferol. Most of the patient with chronic kidney disease are not able to activate vitamin D into its active form of 1,25-dihydroxyvitamin D. The ability of activation is decreases with progression of kidney disease (www.davita.com/kidney-disease).

SOURCES OF VITAMIN D

As mentioned above there are two form of vitamin D *viz.* vitamin D_2 occurring in plants and vitamin D3 occurring in humans and animals. Both the forms have been synthesized commercially but also found in naturally.

Dietary sources of vitamin D

Some of the foods are naturally good sources of vitamin D. The best food sources for vitamin D are fatty fish (eg. herring, mackerel, sardines, tuna, salmon) eggs and fortified foods. Many foods, such as some breakfast cereals and milk, are fortified with vitamin D. Voluntary fortification of other foods also occurs, however, overall, dietary intake of vitamin D is low. As per Australian NHMRC and New Zealand Ministry of Health, the recommended daily intakes of vitamin D that may be achieved purely through dietary means, particularly in those at high risk are presented in table 1. The maximum dietary intake level of vitamin D for infants (0–12 months) and adults (including pregnant or lactating women) are 1000 and 3200 IU/day, respectively.

Table 1. Adequate daily dietary intake of vitamin D by age

Age	Adequate dietary intake (IU)
0-12 months	200
1-18 years	400
19-50 years	200
51-70 years	400
More than 70 years	600
Pregnant and lactating women, breastfed child	200
Pregnant women with limited sunlight	400

Vitamin D from Sunlight exposure

Sunlight exposure is considered as main source of vitamin D. Approximately 90% of vitamin D is obtained from sun exposure that maintain adequate 25(OH)D serum levels in most of the people. In this process, skin uses ultraviolet B radiation to form previtamin D_3 from its immediate precursor 7-dehydrocholesterol. Previtamin D_3 then converted to vitamin D_3 which varies from 10000 to 20000 IU/day.[34] The production of vitamin D in the skin depends on the amount of UVB radiation, amount of skin exposed to sunlight, duration of exposure and skin type. The serum levels of 25(OH)D varied in different season, with maximum at the end of summer and minimum at winter. It also fluctuates at various latitudes such as at latitudes greater than 35 degrees, UVB radiation is unable to produce vitamin D during the winter season.[35]

Hypovitaminosis D and Vitamin D deficiency/insufficiency

Low levels of 25(OH)D are defined as hypovitaminosis D.[29] In the recent literature it is often defined as vitamin D insufficiency when the level falls between 10 and 20 ng/ml, and as vitamin D deficiency when the level falls below 10 ng/ml.[36] It was found that the people with sun avoidant behavior, coeliac disease, chronic idiopathic musculoskeletal pain, osteoporosis therapy, refugees, housebound, pregnant women are at risk of significant vitamin D deficiency.[37-39] To determine whether a person is vitamin D sufficient, deficient, or intoxicated we have to measure the circulating concentrations of 25(OH)D which is produced in the liver.[35] Its half-life in the circulation is ~2 wk, and it is a measure of vitamin D status. The upper limit of 25(OH)D concentrations for most commercial assays is ~125 nmol/L (50 ng/mL) but there is ambiguity. It is known that lifeguards and sunbathers can

have blood concentrations of 25(OH)D of ~ 250 nmol/L (100 ng/mL), and they are not vitamin D intoxicated. The lower limit of the normal range for 25(OH)D assays is also suspicious but considered as ~78 nmol/L (30 ng/mL).[40-43] The literature suggested that concentrations of at least 50 nmol/L are required to satisfy minimum body's vitamin D requirement and the preferred concentrations is 30 ng/mL.[41,43-45]

Factors that affects Vitamin D status

There are various factors that affect vitamin D level. Along with traditional factor, vitamin D status is also affected by the objects which control dermal synthesis rate of vitamin D. In various region of the world, UVB radiation does not penetrate the atmosphere during winter season, and this prevents the production of vitamin D3 by the skin. Moreover, production of dermal vitamin D is also depends on UVB intensity, latitude, season, and time of the day. The study showed that at latitudes above 35°, winter sunlight does not contain sufficient amounts of UVB radiation, so the skin could not produce vitamin D_3.[2] Air pollution, especially in urban areas, also reduces the amount of UVB radiation reaching the earth's surface.[35] Cultural practices/lifestyle such as covering the skin with clothe also minimize or completely block vitamin D production. Furthermore, studies showed that daily use of sunscreen also reduces/blocks vitamin D synthesis,[3,46] however, it was opposed by other researchers.[35,47] Some other factors that lead to decreased vitamin D syntheses include obesity,[48] smoking,[49] age,[50] skin pigmentation,[51] and mobility or institutionalization of elderly people. Along with the above mentioned factors, Saudi people have an exclusive condition that affects vitamin D level. In Saudi Arabia, temperatures often rise above 50 C° in the summer. So, Saudis usually spend less time to outdoors during day time and women cover their bodies to block sunlight by using dark veils for cultural and religious reasons.

Vitamin D deficiency and related diseases

Vitamin D deficiency has been associated with various diseases, such as rickets, ostemalacia, osteoprosis, osteoarthritis, cognitive issues, kidney disease, respiratory concerns, diabetes, PCOS, gastrointestinal issues, cardiovascular disease, variety of immune system disorders and many types of cancer, and also associated with muscle weakness and pain in both adults and children.[2,7-8, 52-53]

EPIDEMIOLOGY OF HYPOVITAMINOSIS D

One of the recent reviews indicates that the hypovitaminosis D is widespread and re-emerging as a major health problem globally.[54] Hypovitaminosis D is diseases caused by

deficiency of vitamin D. There is no general agreement on optimal levels of 25(OH)D concentration, but recently it has been re-defined by most of the researchers by a cut-off of <20 ng/ml, for both children and adults.[55] In recent publications it is often defined as vitamin D insufficiency when the level falls between 10 and 20 ng/ml, and as vitamin D deficiency when the level falls below 10 ng/ml.[36] However, some of the studies such as vitamin D deficiency in the Middle East by Fuleihan[55] had predated such definitions and have used variable cut-offs. When serum levels of 25(OH)D are >150 ng/ml, the condition is known as vitamin D intoxication. To determine the vitamin D status in a person, measuring of 25(OH)D concentration is the best method. A large amount commercial assay includes various radioimmunoassay[56] and most significantly liquid chromatography–tandem mass spectroscopy.[57]

The status of vitamin D has been studied throughout the world and according to a PubMed search (January 2014) around 21,246 epidemiological studies have been conducted. These studies concluded that deficiency of vitamin D was prevalent across all the age-groups and geographic regions.[22,58] Some of the studies concluded that 40 to 100% of U.S. and European elderly men and women are deficient in vitamin D along with children and young adults who are also potentially at high risk for vitamin D deficiency.[3] The community who are exposed to direct sunlight without any sun protection and living close to the equator have healthy levels of 25(OH)D that is above 30 ng per milliliter.[3] However, vitamin D deficiency is common even in the sunniest areas, when the body is protected from the sun. The studies conducted in Australia, India, United Arab Emirates, Saudi Arabia, Turkey and Lebanon concluded that 30 to 50% of children and adults had 25(OH)D levels under 20 ng/ml.[10-12,59] Also 73% of the women and 80% of their infants were vitamin D deficient (<20 ng/ml) at the time of birth.[60] Another recent study on vitamin D status in Eastern Province of Saudi Arabia concludes deficiency of vitamin D among 28 to 37% of 200 randomly selected healthy men.[61] Further study in the eastern regions of Saudi Arabia, showed low concentrations of 25(OH)D in serum among both males (25.25 nmol/L) and females (24.75 nmol/L) even though >65% of participants had sufficient exposure to sunlight.[62] These findings recommended that near about entire world is facing today a new endemic disease. The actual number of vitamin-D-deficient people in the world may be far greater than reported.

EPIDEMIOLOGY OF RENAL FAILURE DISEASES IN KSA

A pilot community-based screening program was conducted to estimate the prevalence of CKD and its associated risk factors in the Saudi Arabian adult population. The studies concluded that the overall prevalence of CKD in the Saudi population was 5.7% and 5.3% determined by using the MDRD-3 and CKD-EPI glomerular filtration equations, respectively.[63] The prevalence of CKD in the young Saudi population was around 5.7%. The study also showed that CKD was significantly higher in the older age groups and patients with higher serum glucose and blood pressure.

VITAMIN D METABOLISM IN NORMAL AND DISEASED KIDNEY

Normal vitamin D metabolism

Vitamin D_3 is synthesized in the skin in response to UVB radiation from sunlight. It can also be obtained from the diet or from the food supplements. However, vitamin D_2 is obtained from some plants. Both forms of vitamin D undergo identical metabolism (Fig. 1). Though, some data shows that vitamin D_2 may be metabolized more rapidly than vitamin D_3.[64-65] In normal vitamin D metabolism conditions, 1,25-dihydroxy vitamin D (calcitriol) is synthesized passing through a series of reactions. Initially, ultraviolet light converts 7-dehydrocholesterol to previtamin D_3, which is then converted to vitamin D_3 (cholecalciferol). Only 10-15 minutes of sun exposure is required to synthesize vitamin D_3 more than any known dietary source.[66-67] However, in the absence of sun exposure, vitamin D_3 can also be obtained naturally from the diet or from the fortified foods.[3,68-69] Physically vitamin D_3 is more potent than vitamin D_2 which is an alternative form of vitamin D supplement derived from plants.[64] Vitamin D (D_2 and D_3) is transported in the blood by the vitamin D binding protein to the liver where these are converted into 25-hydroxy vitamin D (calcidiol), the major circulating form of vitamin D.[70-71] In order to be biologically active and affect metabolism and other diverse physiological functions vitamin D must be converted to its active form. In the kidney by enzyme 1-α-hydroxylase, calcidiol is hydroxylated into 1,25-dihydroxyvitamin D (calcitriol), which is the only biologically active form of vitamin D.[72-74] The activity of enzyme 1-α-hydroxylase is regulated by parathyroid hormone, which stimulates enzyme activity, and phosphate/fibroblast growth factor 23 (FGF-23), which inhibit the enzyme activity.[75-77] It was found that non-renal tissues also convert calcidiol to calcitriol using locally produced 1-α-hydroxylase.[78-79] The characteristics of 1,25-dihydroxyvitamin D are those of a hormone, and consequently vitamin D is a prohormone

rather than a true vitamin. The structure of 1,25-dihydroxyvitamin D is similar to that of other steroid hormones.[80]

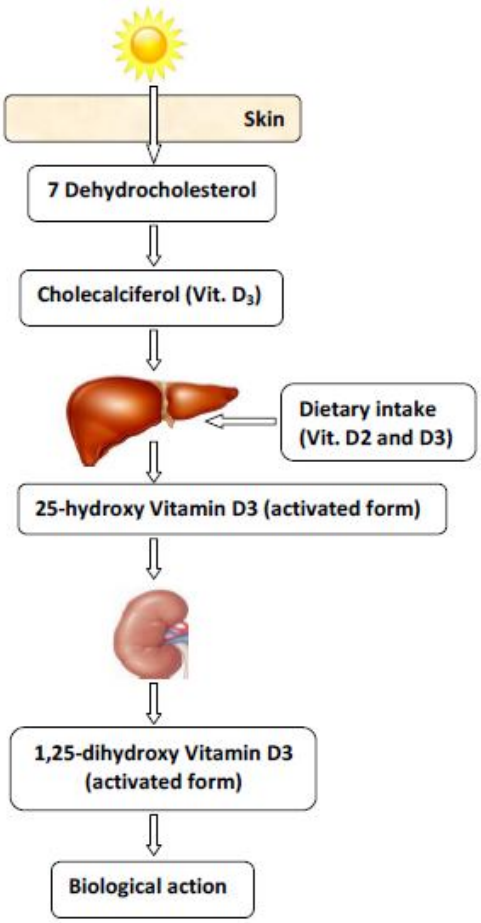

Figure 1. Vitamin D metabolism

Altered vitamin D metabolism in kidney disease

A loss of kidney function due to renal disease such as CKD leads to a decline in circulating 1,25-dihydroxyvitamin D concentrations.[81-82] Several mechanisms are involved in the decreased levels of 1,25-dihydroxyvitamin D during altered kidney function. The quantities of 1-α-hydroxylase, responsible for active vitamin D production, are decreases due to decrease in renal mass. Also reduction in glomerular filtration rate may reduce production of 1,25-dihydroxyvitamin D by the kidney due to limited delivery of substrate to the 1-α-hydroxylase.[83-86] In conclusion, as GFR declines, there is a limitation of substrate delivery that can compromise the ability of the failing kidney to produce 1,25-dihydroxyvitamin D.[87] This leads to decreased levels of 25-hydroxyvitamin D which is common feature in kidney patients.[88] Recent literatures suggested that fibroblast growth factor-23 (FGF-23) is also accountable for suppression of 1-alpha hydroxylase activity. Fibroblast growth factor-23 increases in the course of kidney disease and can directly decrease 1-α-hydroxylase quantity

that may be an additional factor to limits the ability of failing kidney to maintain 1,25-dihyroxyvitamin D levels along with progresses of kidney disease.[89-90] Additionally, 1-α-hydroxylase activity may also be directly suppressed by phosphate retention and hyperphosphatemia.[71]

GENETIC DETERMINANTS OF VITAMIN D INSUFFICIENCY

The quantity of circulating 25-hydroxyvitamin D is depends on its synthesis by the skin in the presence of sun light and its dietary intake. Moreover, the role of common genetic variants in the regulation of circulating 25(OH)D levels is also studied that suggested that the genetic determinants of 25-hydroxyvitamin D also play a major role due to its high heritability. The recent literatures recommended that genes involved in cholesterol synthesis (*DHCR7*), hydroxylation (*CYP2R1, CYP24A1*), and vitamin D transport (*GC*) influence vitamin D status.[91] Another studies also suggested that the genetic factors contribute substantially to variability in 25(OH)D with estimates of heritability as high as 53%.[92-93] However, further study is needed to determine whether this genetic predisposition modifies the response to sun exposure/dietary intake or not. Furthermore, these variants might serve as useful genetic tools for studies in vitamin D insufficiency and in a variety of chronic diseases along with better understanding of the regulation of vitamin D metabolism.

VITAMIN D DEFICIENCY AND RENAL FAILURE DISEASES

Recent literatures verified that there is strapping association between chronic kidney disease and nutritional vitamin D insufficiency or deficiency.[21] Patients with CKD have an exceptionally high rate of severe vitamin D deficiency that is further exacerbated by the reduced ability to convert 25(OH)D into the active form 1,25 dihydroxy-vitamin D.[94] The mechanism of altered vitamin D metabolism in kidney disease is described in previous section. The death rate of patients with chronic kidney disease is inversely proportional to their renal function and along with deterioration of renal function the activity of 1-α-hydroxylase is declined. The enzyme 1-α-hydroxylase is responsible for converting 25(OH)D2 to 1,25-dihydroxyvitamin D3 (calcitriol).[95] The epidemiological studies showed that vitamin D reduced the risk of cardio vascular disease deaths in the patients with chronic kidney disease.[96] The incidence of 25-vitamin D deficiency increases with succession of chronic kidney disease and approaches 80% in stage 5 of chronic kidney disease patients.[97] Another study showed that 50,000 units of cholecalciferol weekly for 12 weeks was safe and effective in repleting 25-vitamin D levels in stage 3 and 4 chronic kidney disease patients.[98]

VITAMIN D TREATMENT IN RENAL FAILURE DISEASES

In patients of chronic kidney diseases, serum levels of vitamin D reduced and cause vitamin D deficiency. Since vitamin D does not occur naturally in most of the foods and due to protection to restrict sun exposure, the use of vitamin D supplements is now required universally.[3,94,99] Vitamin D3 or D2 may be given in oral form to fulfill required quantity. Vitamin D3 or cholecalciferol and Vitamin D2 or ergocalciferol is the natural and synthetic form of the vitamin D, respectively. In chronic kidney diseases, supplementation with 25(OH)D is suggested at the initiation of the disease. Recent literatures recommended that 4,000 IU may be required daily to maintain optimum levels of vitamin D in normal populations and higher doses may be required in CKD patients.[3,94,99-100] Hemodialysis patients will be given a prescription medicine intravenously during their dialysis treatment. Those not on dialysis or on peritoneal dialysis will be prescribed an oral form of activated vitamin D or generic calcitriol. The treatment of vitamin D deficiency with vitamin D receptor activators (calcitriol, paricalcitol, or doxercalciferol) has also been shown to reduce mortality in dialysis and non-dialysis renal failure patients.[101]

FUTURE PROSPECTIVE

As the deficiency of vitamin D is a global problem, more organized future studies are needed to evaluate the serum level of 25(OH)D in patients with chronic kidney diseases. An efficient epidemiological study will affect future recommendation of vitamin D intake levels. Further studies are required to understand better the role of 25(OH)D and 1-α-hydroxylase enzyme on cardiac function and to characterize the gene-environment interactions that influence 25(OH)D and 1,25(OH)D level.[100] In conclusion, more attention should be paid to determine status of vitamin D in the world population and intake of vitamin D in patients suffering from renal diseases. The people should involve in more outdoor activity during the daytime in order to increase their exposure to sunlight especially women who live in houses such as Saudi women. The consumption of food having good source of vitamin D such as fatty fishes, dairy products and eggs should also be increased. Patient suffering from renal and cardio-vascular diseases should consume additional amounts of vitamin D after proper consultation with doctor. Also, more education is needed in the area of vitamin D deficiency to make the public more aware of this serious problem.

REFERENCES

[1] Kamycheva E, Joakimsen RM, Jorde R. Intakes of calcium and vitamin D predict body mass index in the population of northern norway. J Nutr, 2003; 133: 102–106.

[2] Wolpowitz D, Gilchrest B. The vitamin D questions: How much do you need and how should you get it? J Acad Dermatol, 2005; 54:301-317.

[3] Holick MF. Vitamin D Deficiency. N Engl J Med, 2007;357:266-81

[4] Lips P, Hosking D, Lippuner K, Norquist JM, Wehren L, Maalouf G, Ragieis S, Chandler J. The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation, J Intern Med, 2006; 260: 245–254.

[5] Kuchuk NO, van Schoor NM, Pluijm SM, Chines A, Lips P. Vitamin D status, parathyroid function, bone turnover, and BMD in postmenopausal women with osteoporosis: global perspective. J Bone Miner Res, 2009; 24: 693–701.

[6] Lips P. Worldwide status of vitamin D nutrition. J Steroid Biochem Mol Biol, 2010; 121: 297–300.

[7] Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes Am J Clin Nutr, 2006; 84:18-28.

[8] Gissel T, Rejnmark L, Mosekilde L, Vestergaard P. Intake of vitamin D and risk of breast cancer- A meta-analysis. J Steroid Biochem Mol Biol, 2008; 11:195-199.

[9] Bandeira F, Griz L, Eufrazino C, Bandeira C, Freese E. Vitamin D deficiency: a global prospective. Arq Bras Endocrinol Metab, 2006; 50:640-646.

[10] Fuleihan GE, Nabulsi M, Choucair M, Salamoun M, Hajj Shahine C, Kizirian A, Tannous R. Hypovitaminosis D in healthy school children. Pediatrics, 2001; 107:E53.

[11] McGrath JJ, Kimlin MG, Saha S, Eyles DW, Parisi AV. Vitamin D insufficiency in south-east Queensland. Med J Aust, 2001; 174:150–151.

[12] Marwaha RK, Tandon N, Reddy DR, Aggarwal R, Singh R, Sawhney RC, Saluja B, Ganie MA, Singh S. Vitamin D and bone mineral density status of healthy schoolchildren in northern India. Am J Clin Nutr, 2005; 82:477–482.

[13] Rajpathak SN, Rimm EB, Rosner B, Willett WC, Hu FB. Calcium and dairy intakes in relation to long-term weight gain in US men. Am J Clin Nutr, 2006; 83:559–566.

[14] Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and Associations of 25-Hydroxyvitamin D Deficiency in US Children: NHANES 2001–2004. Pediatrics, 2009; 124:e362–e370.

[15] Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. Spine, 2003; 28:177-179.

[16] Elidrissy AT, Sedrani SH, Lawson DE. Vitamin D deficiency in mothers of rachitic infants. Calcif Tissue Int, 2006; 36: 266-268.

[17] Khoja SO, Khan JA, Maimani AR, Berry JL, Lanham-New SA. Influence of diet on bone health in Saudi Arabian women. ICS Elsevier, 2007; 1297:296-302.

[18] Siddigui AM, Kamfar HZ. Prevalence of vitamin D deficiency rickets in adolescent school girls in Western region, Saudi Arabia. Saudi Med J, 2007; 28:441-4.

[19] Al Turki HA, Sadat Ali M, Al Elg AH, Al Mulhim FA, Al Ali AK. 25-Hydoxyvitamin D levels among healthy Saudi Arabian women. Saudi Med J, 2008; 29:1765-8.

[20] Gonzalez EA, Sachdeva A, Oliver DA, Martin KJ. Vitamin D insufficiency and deficiency in chronic kidney disease: A single center observational study. Am J Nephrol, 2004; 24: 503–510.

[21] LaClair RE, Hellman RN, Karp SL, Kraus M, Ofner S, Li Q, Graves KL, Moe SM. Prevalence of calcidiol deficiency in CKD: A cross-sectional study across latitudes in the United States. Am J Kidney Dis, 2005; 45: 1026–1033.

[22] Alshishtawy MM. Vitamin D Deficiency: This clandestine endemic disease is veiled no more. SQU Med J, 2012; 12: 140-152.

[23] Mason RS, Sequeira VB, Gordon-Thomson C. Vitamin D: the light side of sunshine. Eur J Clin Nutr, 2011; 65:986–93.

[24] Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: A birth-cohort study. Lancet, 2001; 358:1500–1503.

[25] Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Vitamin D intake is inversely associated with rheumatoid arthritis: Results from the Iowa Women's Health Study. Arthritis Rheum, 2004; 50:72–77.

[26] Willer CJ, Dyment DA, Sadovnick AD, Rothwell PM, Nurray T, Ebers GC. Timing of birth and risk of multiple sclerosis: Population based study. BMJ, 2005; 330:1-5.

[27] Garland CF, Gorham ED, Mohr SB, Garland FC. Vitamin D for cancer prevention: Global perspective. Ann Epi, 2009; 19:468–83.

[28] Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. Prog Biophys Mol Biol, 2006;92:39–48.

[29] Parfitt AM, Gallagher JC, Heaney RP, et al. Vitamin D and bone health in the elderly. Am J Clin Nutr, 1982;36:1014–31.

[30] Chiu KC, Chu A, Go VLW, Saad MF. Hypovitaminosis D is associated with insulin resistance and b cell dysfunction. Am J Clin Nutr, 2004;79:820–5.

[31] Ebeling PR. Megadose therapy for vitamin D deficiency. Med J Aust, 2005; 183:4–5.

[32] Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr, 2004; 79:362-371.

[33] Schwalfenberg G. Not enough vitamin D – health consequences for Canadians. Can Fam Physician, 2007;53:841–854.

[34] Cannell JJ, Hollis BW, Zasloff M, Heaney RP. Diagnosis and treatment of vitamin D deficiency. Expert Opin Pharmacother, 2008; 9: 107–118.

[35] Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr, 2004; 80: 1678– 88

[36] Lips P. Vitamin D status and nutrition in Europe and Asia. J Steroid Biochem Mol Biol, 2007; 103: 620–625.

[37] Scott EM, Gaywood I, Scott BB. Guidelines for osteoporosis in coeliac disease and inflammatory bowel disease. Gut, 2000; 46 :1–8.

[38] Munns C, Zacharin MR, Rodda CP, et al. Prevention and treatment of infant and childhood vitamin D deficiency in Australia and New Zealand: a consensus statement. Med J Aust, 2006;185:268–72.

[39] Benson J. Hiding from the sun: vitamin deficiency in refugees. Aust Fam Physician, 2007;36:355–7.

[40] Chapuy MC, Schott AM, Garnero P, et al. Healthy elderly French women living at home have secondary hyperparathyroidism and high bone turnover in winter. J Clin Endocrinol Metab, 1996;81:1129 –33.

[41] Chapuy MC, Preziosi P, Maaner M, et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int, 1997;7: 439–43.

[42] Glerup H, Mikkelsen K, Poulsen L, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. J Intern Med, 2000; 247: 260–268.

[43] Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. Am J Med, 2002;112: 659–62.

[44] Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet, 1998;351:805– 6.

[45] Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. Jam Coll Nutr, 2003; 22: 142– 146.

[46] Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. Am J Public Health, 2006; 96:252-261.

[47] Marks R, Foley PA, Jolley D, et al. The effect of regular sunscreen use on vitamin D levels in an Australian population. Arch Dermatol, 1995; 131:415-421.

[48] Parikh SJ, Edelman M, Uwaifo GI, et al. The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. J Clin Endocrinol Metab, 2004; 89:1196-1199.

[49] Lamberg-Allardt CJ, Outla TA, Karkkainen MU, Rita HJ, Valsta LM. Vitamin D Deficiency and Bone Health in Healthy Adults in Finland: Could This Be a Concern in Other Parts of Europe? J Bone Miner Res, 2001; 16:2066-2073.

[50] McKenna MJ, Freaney R. Secondary hyperparathyroidisism in the elderly: a means to defining hypovitaminosis D. Osteoporos Int, 1998; 8:S3-S6.

[51] Clemens TL, Adams JS, Henderson SL, Holick MF, Increased skin pigment reduces the capacity of skin to synthesize vitamin D3. Lancet, 1982; 1:74–76.

[52] Berdanier CD, Zempleni J. Advanced nutrition: macronutrients, micronutrients, and metabolism. 1st ed. CRC Press: Taylor & Francis Group, 2009.

[53] Schwalfenberg G. Improvement of chronic back pain or failed back surgery with vitamin D repletion: a case series. JABFM, 2009; 22:69-74.

[54] Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, El-Hajj Fuleihan G, Josse RG, Lips P, Morales-Torres J. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int, 2009; 20(11):1807-20.

[55] Fuleihan GE. Vitamin D deficiency in the Middle East and its health consequences for children and adults. Clinic Rev Bone Miner Metab, 2009; 7:77–93.

[56] Binkley N, Krueger D, Cowgill CS et al. Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization. J Clin Endocrinol Metab, 2004*;* 89*:* 3152–3157.

[57] Holick MF. Photobiology of vitamin D. In: Feldman D, Pike J, Glorieux F, eds. Vitamin D, 2nd edition. New York: Elsevier Academic Press; 2005:37-46.

[58] Yetley EA. Assessing the vitamin D status of the US population. Am J Clin Nutr, 2008; 88:558–64.

[59] Sedrani SH. Low 25-Hydroxy vitamin D and normal serum calcium concentrations in Saudi Arabia: Riyadh region. Ann Nutr Metab, 1984; 28:181–185.

[60] Lee JM, Smith JR, Philipp BL, Chen TC, Mathieu J, Holick MF. Vitamin D deficiency in a healthy group of mothers and newborn infants. Clin Pediatr, 2007;46:42-44.

[61] Sadat-Ali M, AlElq A, Al-Turki H, Al-Mulhim F, Al-Ali A. Vitamin D levels in healthy men in eastern Saudi Arabia. Ann Saudi Med, 2009; 29:378–82.

[62] Elsammak MY, Al-Wossaibi AA, Al-Howeish A, Alsaeed J. High prevalence of vitamin D deficiency in the sunny Eastern region of Saudi Arabia: a hospital-based study. East Mediterr Health J, 2011; 17:317–22.

[63] Alsuwaida AO, Farag YMK, Al-Sayyari AA, Mousa D, Alhejaili F, Al-Harbi A, Housawi A, Mittal BV, Singh AK. Epidemiology of chronic kidney disease in the Kingdom of Saudi Arabia (SEEK-Saudi Investigators) – A pilot study. Saudi J Kidney Dis Transplant, 2010; 21(6):1066-1072.

[64] Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R. Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. Am J Clin Nutr, 1998; 68(4):854-858.

[65] Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab, 2004;89(11):5387-5391.

[66] Holick MF, Siris ES, Binkley N, et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab, 2005; 90*:*3215*–24.*

[67] Holick MF. Vitamin D and the skin: photobiology, physiology and therapeutic efficacy for psoriasis. *In*: Heersche J, Kanis J, eds. Bone and Mineral Research. Amsterdam: Elsevier; 1990:313-366.

[68] Holvik K, Meyer HE, Haug E, Brunvand L. Prevalence and predictors of vitamin D deficiency in five immigrant groups living in Oslo, Norway: the Oslo Immigrant Health Study. Eur J Clin Nutr, 2005;59:57-63.

[69] van der Meer IM, Boeke AJ, Lips P, et al. Fatty fish and supplements are the greatest modifiable contributors to the serum 25-hydroxyvitamin D concentration in a multiethnic population. Clin Endocrinol (Oxf), 2008;68:466-472.

[70] Prosser DE, Jones G. Enzymes involved in the activation and inactivation of vitamin D. Trends Biochem Sci, 2004;29:664-673.

[71] Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol, 2005;289:8-28.

[72] Slatopolsky E, Hruska K, Rutherford WE. Current concepts of parathyroid hormone and vitamin D metabolism: perturbations in chronic renal disease. Kidney Int Suppl, 1975;90-96.

[73] Brunette MG, Chan M, Ferriere C, Roberts KD. Site of 1,25(OH)2 vitamin D3 synthesis in the kidney. Nature, 1978;276:287-289.

[74] Akiba T, Endou H, Koseki C, et al. Localization of 25-hydroxyvitamin D3-1 alpha-hydroxylase activity in the mammalian kidney. Biochem Biophys Res Commun, 1980;94:313-318.

[75] Yoshida T, Yoshida N, Monkawa T, Hayashi M, Saruta T. Dietary phosphorus deprivation induces 25-hydroxyvitamin D(3) 1alpha-hydroxylase gene expression. Endocrinology, 2001;142:1720-1726.

[76] Armbrecht HJ, Hodam TL, Boltz MA. Hormonal regulation of 25-hydroxyvitamin D3-1alpha-hydroxylase and 24-hydroxylase gene transcription in opossum kidney cells. Arch Biochem Biophys, 2003;409:298-304.

[77] Liu S, Tang W, Zhou J, et al. Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. J Am Soc Nephrol, 2006;17:1305-1315.

[78] Lambert PW, Stern PH, Avioli RC, et al. Evidence for extrarenal production of 1 alpha ,25-dihydroxyvitamin D in man. J Clin Invest, 1982;69:722-725.

[79] Somjen D, Katzburg S, Stern N, et al. 25 hydroxy-vitamin D(3)-1alpha hydroxylase expression and activity in cultured human osteoblasts and their modulation by parathyroid hormone, estrogenic compounds and dihydrotestosterone. J Steroid Biochem Mol Biol, 2007;107:238-244.

[80] Thacher TD, Clarke BL. Vitamin D Insufficiency. Mayo Clin Proc, 2011;86(1):50-60.

[81] Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int, 2007;71:31-38.

[82] Zehnder D, Landray MJ, Wheeler DC, et al. Cross-sectional analysis of abnormalities of mineral homeostasis, vitamin D and parathyroid hormone in a cohort of pre-dialysis patients. The chronic renal impairment in Birmingham (CRIB) study. Nephron Clin Pract, 2007;107:c109-116.

[83] Leheste JR, Rolinski B, Vorum H, Hilpert J, Nykjaer A, Jacobsen C, Aucouturier P, Moskaug JO, Otto A, Christensen EI, Willnow TE. Megalin knockout mice as an animal model of low molecular weight proteinuria. Am J Pathol, 1999; 155: 1361–1370.

[84] Nykjaer A, Fyfe JC, Kozyraki R, Leheste JR, Jacobsen C, Nielsen MS, Verroust PJ, Aminoff M, de la Chapelle A, Moestrup SK, Ray R, Gliemann J, Willnow TE, Christensen EI: Cubilin dysfunction causes abnormal metabolism of the steroid hormone 25(OH) vitamin D(3). Proc Natl Acad Sci USA, 2001; 98: 13895–13900.

[85] Hilpert J, Wogensen L, Thykjaer T, Wellner M, Schlichting U, Orntoft TF, Bachmann S, Nykjaer A, Willnow TE: Expression profiling confirms the role of endocytic receptor megalin in renal vitamin D3 metabolism. Kidney Int, 2002; 62: 1672–1681.

[86] Willnow TE, Nykjaer A. Pathways for kidney-specific uptake of the steroid hormone 25-hydroxyvitamin D3. Curr Opin Lipidol, 2002; 13: 255–260.

[87] Andress DL. Vitamin D in chronic kidney disease: A systemic role for selective vitamin D receptor activation. Kidney Int, 2006; 69: 33–43.

[88] Al-Badr W, Martin KJ. Vitamin D and Kidney Disease. Clin J Am Soc Nephrol, 2008; 3: 1555–1560.

[89] Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T, Nakahara K, Fukumoto S, Yamashita T. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res, 2004; 19: 429–435.

[90] Perwad F, Zhang MY, Tenenhouse HS, Portale AA: Fibroblast growth factor 23 impairs phosphorus and vitamin D metabolism in vivo and suppresses 25-hydroxyvitamin D-1alpha-hydroxylase expression in vitro. Am J Physiol Renal Physiol, 2007; 293: 1577–1583.

[91] Wang T.J., Zhang F., Richards J.B., Kestenbaum B., van Meurs J.B., Berry D. et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet, 2010; 376(9736): 180–188.

[92] Shea MK, Benjamin EJ, Dupuis J, Massaro JM, Jacques PF, D'Agostino RB Sr, Ordovas JM, O'Donnell CJ, Dawson-Hughes B, Vasan RS, Booth SL. Genetic and non-genetic correlates of vitamins K and D. Eur J Clin Nutr, 2009; 63:458–464.

[93] Hunter D, De Lange M, Snieder H, MacGregor AJ, Swaminathan R, Thakker RV, Spector TD. Genetic contribution to bone metabolism, calcium excretion, and vitamin D and parathyroid hormone regulation. J Bone Miner Res, 2001; 16:371–378.

[94] Williams S, Malatesta K, Norris K. Vitamin D and chronic kidney disease. Ethn Dis, 2009;19:S5-8-11.

[95] Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med, 2004;351:1285–1295.

[96] Shoji T, Shinohara K, Kimoto E, et al. Lower risk for cardiovascular mortality in oral 1alpha-hydroxy vitamin D3 users in a haemodialysis population. Nephrol Dial Transplant, 2004; 19:179–184.

[97] Blair D, Byham-Gray L, Lewis E, McCaffrey S. Prevalence of vitamin D [25(OH)D] deficiency and effects of supplementation with ergocalciferol (vitamin D2) in stage 5 chronic kidney disease patients. J Ren Nutr, 2008;18:375–382.

[98] Chandra P, Binongo JN, Ziegler TR, et al. Cholecalciferol (vitamin D3) therapy and vitamin D insufficiency in patients with chronic kidney disease: a randomized controlled pilot study. Endocr Pract, 2008; 14: 10–17.

[99] Heaney RP. Vitamin D in health and disease. Clin J Am Soc Nephrol, 2008; 3(5): 1535–1541

[100] Artaza JN, Mehrotra R, Norris KC. Vitamin D and the cardiovascular system. Clin J Am Soc Nephrol, 2009; 4: 1515–1522.

[101] Patel T, Singh AK. Role of vitamin d in chronic kidney disease. Semin Nephrol, 2009; 29(2): 113–121.