SPECIAL PAPER

Vitamin D Deficiency in Critically Ill Children

Nizar Belal Said, MSc in Emergency and Critical Care Nursing/Pediatrics, BsN, RN
Department of Health Science, University of Oviedo, 33600, Spain

Corespondence: Nizar Belal Said, Department of Health Science, University of Oviedo, 33600, Spain
e-mail: Nizar_210@hotmail.com

Abstract

Background: Vitamin D has essential and important roles in the human body, some studies assumed its role as Skeletal and Extraskeletal functions. Also some studies connected the deviancy to the different body illness. It's important to keep vitamin D level within normal range in the body, exposure to sun light, food containing vitamin D, and supplements are the sources for vitamin D.
Aim: The aim of this review is to understand the associations between vitamin D deficiency and pediatric critical illness.
Design: Literature review of different articles and books related to vitamin D.
Method: Reviewing articles from different journals that were published since 2005, reports and books that concern about the topic with the following categories: Vitamin D Deficiency, Critical Illness and Pediatric.
Results: The results highlight that Vitamin D or 25-hydroxyvitamin D is important for growth and good health, also the lack of vitamin D is common between adult and children. It has a vital role in the body including skeletal in which it maintains calcium homeostasis for optimal skeletal health, and Extraskeletal roles like immune function, and other metabolic functions, thus the deficiency can affect the child health. Finally, vitamin D levels are lower in critically ill children.
Conclusion: Vitamin D is important for the body and its deficiency can affect different functions in the body, associated with pediatric critical illness.

Key words: vitamin D, deficiency, child, critical illness

Introduction

Vitamin D has a vital role in the body which includes skeletal and Extraskeletal roles like immune function and also it has a role in calcium homeostasis for optimal skeletal health. Vitamin D increases the intestinal efficacy of calcium absorption, and other roles for vitamin D in prevention of autoimmune diseases, prevention of falls, improves immunity, prevention of diabetes (Khazai, Judd & Tangpricha, 2008). In fact, vitamin D receptors are found in many tissues other than bone and the small intestine, such as in type 1 helper T cells, macrophages, the prostate, the brain, and other tissues. Some studies showed that Vitamin D levels are lower in critically ill children than in healthy controls.

Aims of the Review

- To understand the importance of Vitamin D for the body.
- To understand the associations between vitamin D deficiency and pediatric critical illness.

Methodology

Literature review of articles from different data bases that were published since 2005, reports and books that were related to Vitamin D and it's relation to human body and also the effect of its deficiency on pediatric illness.

Results

Vitamin D has important role in the body, it has different functions, some studies revealed the association of its deficiency and critical illness in children age. There is a need to keep this vitamin within normal range in the body and also it's important to nurses to educate mothers about this issue and to participate in public awareness about the topic.

Figure 1: Synthesis and Metabolism of Vitamin D in the Regulation of Calcium, Phosphorus, and Bone Metabolism. " Reprinted with permission from Holick M. Vitamin D deficiency. New England Journal of Medicine. 2007;35(7):266–281. Copyright © 2007 Massachusetts Medical Society. All rights reserved".

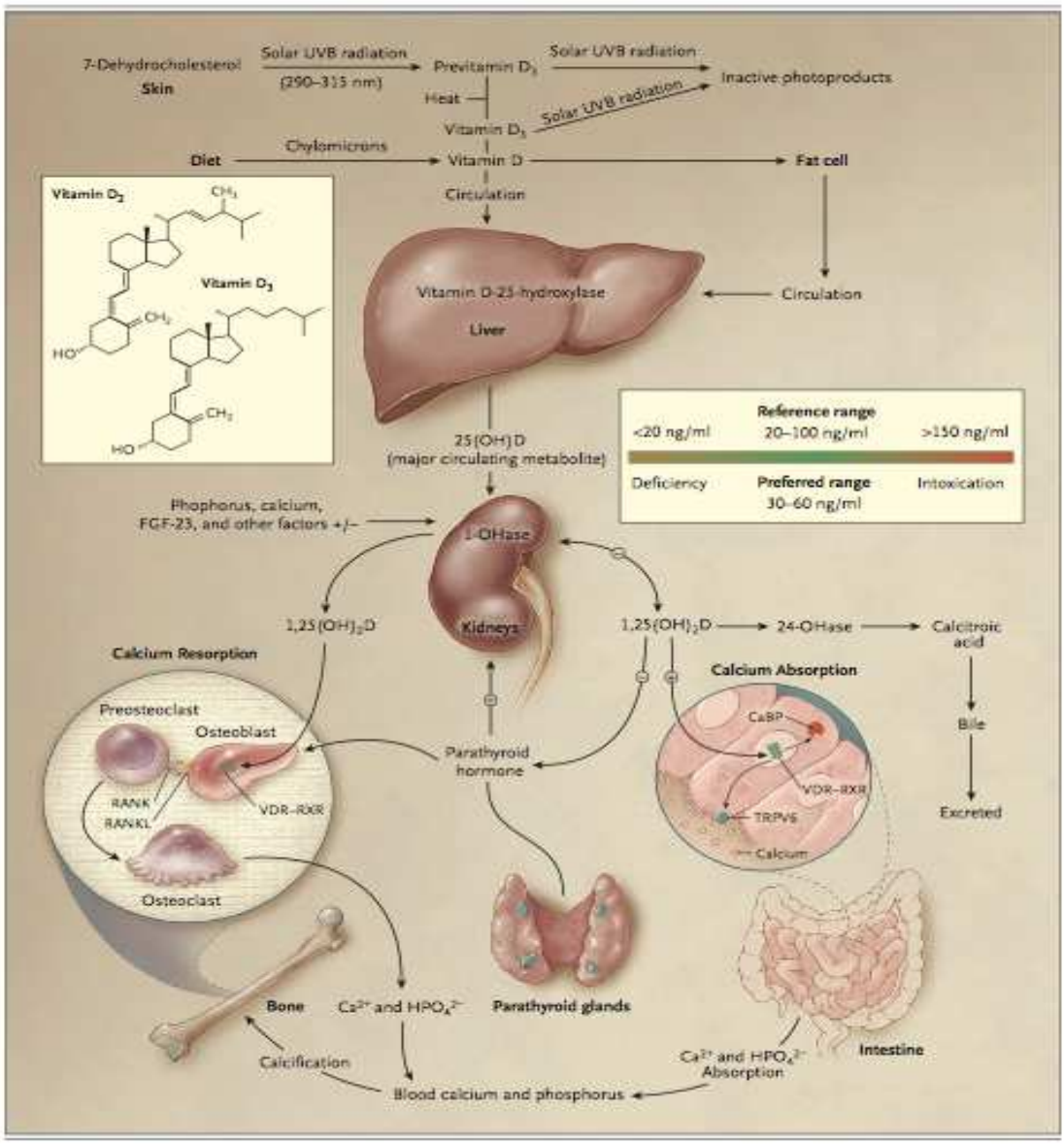


Figure 2: Metabolism of 25-Hydroxyvitamin D to 1,25-Dihydroxyvitamin D for Nonskeletal Functions. " Reproduced with permission from Holick M. Vitamin D deficiency. New England Journal of Medicine. 2007;35(7):266–281. Copyright © 2007 Massachusetts Medical Society. All rights reserved".

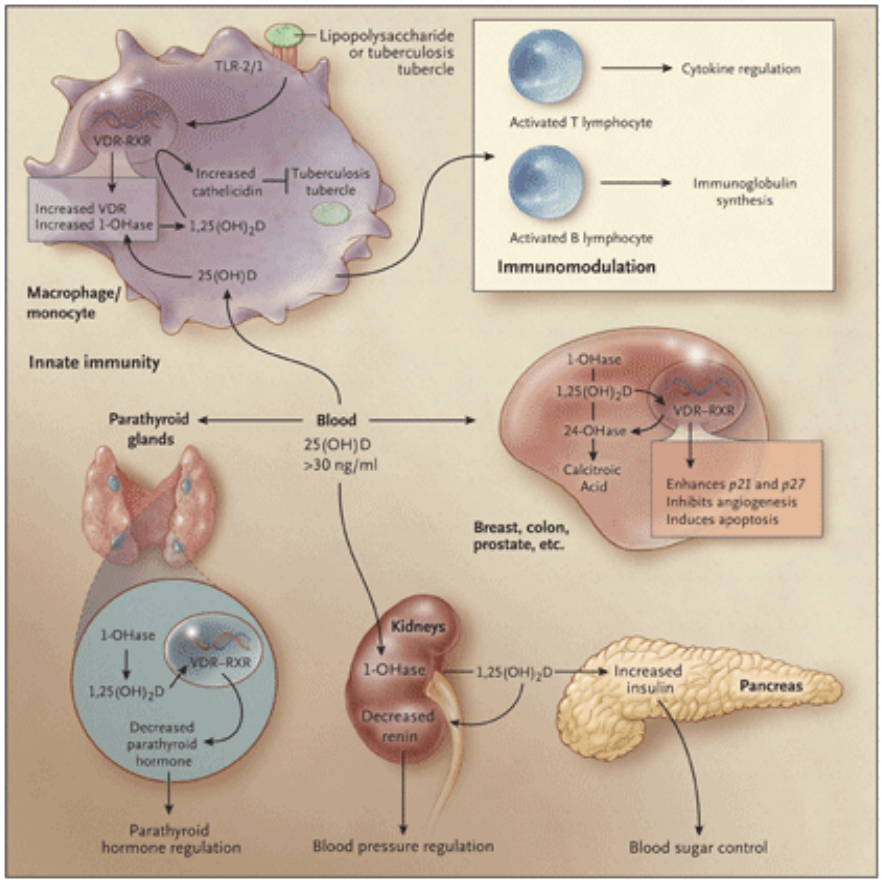
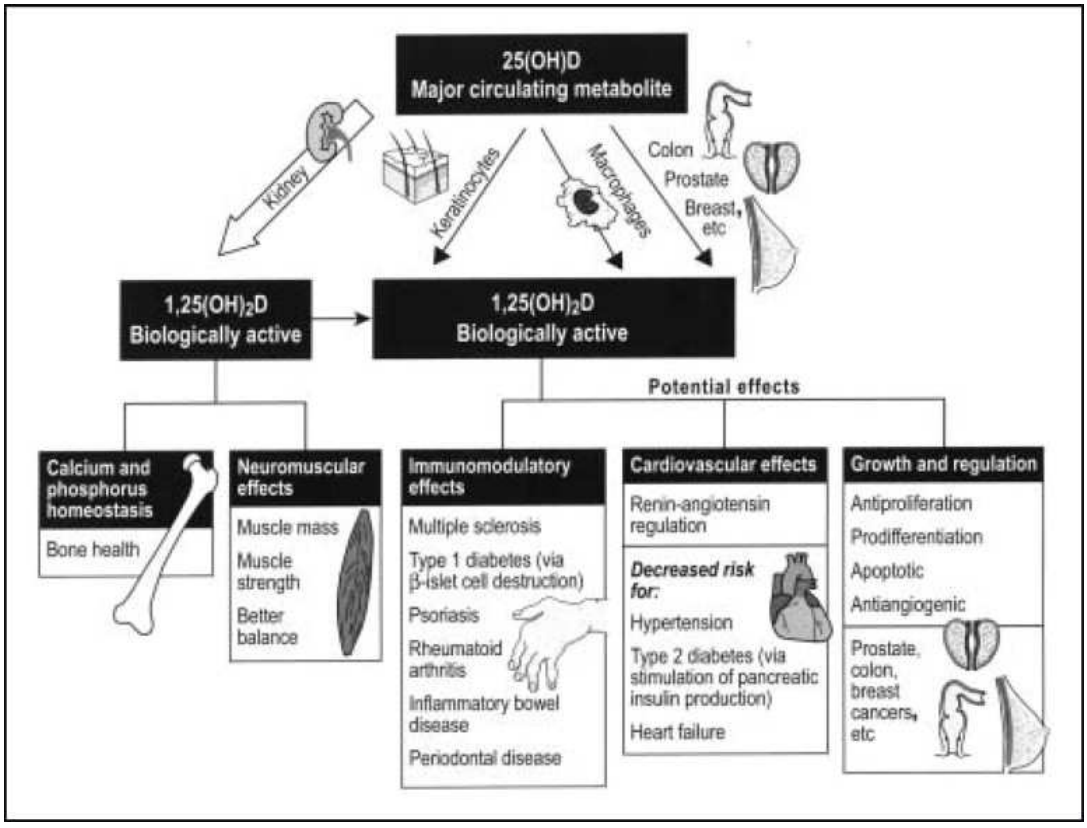


Figure 3: Cutaneous production of vitamin D and its metabolism and regulation for calcium homeostasis and cellular growth. " Reprinted with permission from Holick , M. F. High Prevalence of Vitamin D Inadequacy and Implications For Health. Mayo Clinic Proceedings. 2006; 81(3), 353-373. Copyright © 2006 Elsevier".



Discussion

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods, and available as a dietary supplement. Also it's produced endogenously from sunlight which strike the skin and trigger vitamin D synthesis as result of the action of ultraviolet light on 7-dehydrocholesterol (WHO, 2013). In the liver converting vitamin D to 25-hydroxyvitamin D [25(OH) D], also known as calcidiol. The second occurs primarily in the kidney and forms 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as calcitriol (Yu et al., 2010).

Vitamin D Metabolism

There are 2 forms of vitamin D: D2 (ergocalciferol, synthesized by plants) and D3 (cholecalciferol, synthesized by mammals) (Wagner & Greer, 2008; Khazai, Judd & Tangpricha, 2008). Cholecalciferol is produced in skin or found naturally in fatty fish such as salmon or mackerel. Both forms of vitamin D can be used to fortify food; however, only cholecalciferol can be made endogenously in skin. When the skin is exposed to ultraviolet B (UVB) 7-dehydrocholesterol, a compound present in the skin, is converted to previtamin D3, which

isomerizes to form vitamin D3. The amount of vitamin D3 made in the skin can be affected by an individual's skin color, age, and other factors (Holick, 2007). Through the heat of the skin, previtamin D3 is transformed into vitamin D3, which then binds to the vitamin D–binding protein and is transported to the liver and converted to 25-hydroxyvitamin D (25-OH-D) by the action of 25-hydroxylase. 25-OH-D, the nutritional indicator of vitamin D, undergoes a second hydroxylation in the kidney and other tissues to become 1,25-dihydroxyvitamin D {1,25-OH2-D} (Wagner & Greer, 2008; Misra et al., 2008).

Figure 1 is explaining the Synthesis and Metabolism of Vitamin D in the Regulation of Calcium, Phosphorus, and Bone Metabolism (Holick, 2007).

The Skeletal Role of Vitamin D

The major function of vitamin D is to optimize intestinal calcium and phosphorus absorption for proper formation of the bone mineral matrix. Since the Calcium is transported across the intestine through paracellular or transcellular pathway, the second pathway is highly regulated by 1,25(OH)2D. Several vitamin D–dependent calcium transport proteins regulate intestinal calcium absorption. Transient receptor potential cation channel V6 (TRPV6) which is a membrane calcium channel which is responsible for the first step in calcium absorption in the intestine and it's vitamin D dependent, that means is regulated by 1,25(OH)2D (Khazai, Judd & Tangpricha, 2008). Also Calbindin 9k which is calcium binding protein is involved in active intestinal calcium transport and it's mainly mediated by 1,25-dihydroxyvitamin D3 (Krisinger et al., 1991; Khazai, Judd & Tangpricha, 2008). These findings show that the function for vitamin D is to increase intestinal calcium absorption for proper mineralization of bone. Thus the need optimal vitamin D levels that is necessary to increase the efficiency of calcium absorption.

The Extraskeletal Role

Infants and young children who are vitamin D deficient may be imprinted for the rest of their lives with increased risks of type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and many common cancers (Holick, 2004). Also patient with vitamin D deficiency are at higher risk of insulin resistance and the metabolic syndrome (Chiu et al., 2004).

Muscle function and fall prevention

Severe vitamin D deficiency causes a reversible myopathy characterized by muscle weakness, wasting, and instability of gait. The etiology of this myopathy is multifactorial and it's attributed to secondary hyperparathyroidism, hypocalcemia, hypophosphatemia, and calcitriol deficiency itself, also the presence of vitamin D receptor (VDR) in skeletal muscle related to vitamin D deficiency which lead to myopathy (Holick, 2006).

Immune system

Many studies have shown that the relation of vitamin D on the pathogenesis of type 1 diabetes mellitus, multiple sclerosis and Crohn's disease and other diseases (Misra et al., 2008), which indicates the role of vitamin D in the pathophysiology of autoimmune diseases. Some experiments showed the capability of vitamin D to regulate chemokine (which are a family of small cytokines, or proteins secreted by cells) production, counteracting autoimmune inflammation and to induce differentiation of immune cells (Antico et al., 2012). Vitamin D could potentially reduce the inflammatory activity (Burton et al., 2010). Vitamin D intake has been associated with lower risk of developing MS (Khazai, Judd & Tangpricha, 2008). Vitamin D was shown to inhibit primarily production of the proinflammatory cytokines by adaptive immune cells and to decrease B-cell proliferation, plasma-cell differentiation and IgG secretion (Mora, Iwata, & von Andrian, 2008). It enhances the induction of the antimicrobial peptides cathelicidin and β-defensin which is present in body mucosal and epithelial tissues since these are the body's first line of defense against viral and bacterial pathogens (Watkinsa et al., 2011). Furthermore it has important role in regulation and functions of T-lymphocyte (Benrashida et al., 2012). Figure 2 is explaining Metabolism of 25-Hydroxyvitamin D to 1,25-Dihydroxyvitamin D for Nonskeletal Functions (Holick, 2007).

Sources of Vitamin D

The simplest way to obtain vitamin D is from moderate exposure to sunlight (Holick, 2004). Natural sources of vitamin D include oily fish such as salmon, mackerel, and sardines, cod liver oil, liver and organ meats. (Misra et al., 2008). Alternatively, multivitamin containing vitamin D and a vitamin D supplements (Holick, 2004).

Vitamin D Deficiency

Vitamin D deficiency is common between adult and children (Holick, 2007). According to WHO (2003) in many regions there is still sever deficiency of Vitamin D. It's associated with many acute and chronic illnesses such disorders of calcium metabolism, autoimmune diseases, and infectious diseases. It's recognized as a global pandemic (Wacker & Holick, 2013). Vitamin D deficiency is diagnosed when 25(OH)D <20 ng/mL (Ross & Institute of Medicine (U.S.), 2011). Also Sai et al. (2011) recommended to defined Vitamin D insufficiency as serum 25OHD less than 20 ng/ml. Measuring serum 25(OH)D and 1,25(OH)2D levels are important tests in order to refine the deficiency.

Children who have chronic fat malabsorption or even chronically taking antiseizure medications are risky to have vitamin D deficiency (Wagner & Greer, 2008). Some studies showed the role of vitamin D in the pathophysiology of autoimmune diseases, also Vitamin D exerts anti-inflammatory and immunoregulatory effects. Also several mechanisms explain vitamin D potentially beneficial effects on infectious diseases, and its role in initiating immunity against various infections (Wacker & Holick, 2013). Vitamin D deficiency has been shown to predispose children to respiratory infections, and lower levels of vitamin D are associated with reduced lung function (Chinellato et al., 2011). Figure 3 explains Endocrine and autocrine or paracrine functions of 1,25-dihydroxyvitamin D (1,25[OH]2D).

"The kidneys serve as the endocrine organ to convert 25-hydroxyvitamin D (25[OH]D) to 1,25(OH)2D. 1,25(OH)2D carries out its calcium-regulating functions for bone health by stimulating intestinal calcium and phosphorus absorption. The circulating levels of 1,25(OH)2D can also potentially influence the activity of other tissues and cells that have a vitamin D receptor (VDR) and have no function in regulating calcium homeostasis and bone health. These include, among others, the heart skeletal muscle, active T and B lymphocytes, breast, colon, and prostate. In addition, a multitude of in vitro studies with human and animal cells have shown that most tissues and cells not only express the VDR but also express the same 1α-hydroxylase as the kidney. Thus, it has been suggested that most cells, including lung, colon, prostate, and breast, locally produce 1,25(OH)2D3 to help regulate a variety of cellular functions including growth and differentiation. This may help explain the epidemiological evidence that sun exposure at lower altitudes and higher serum levels of 25(OH)D are related to a decreased risk of a wide variety of chronic illnesses. It has been speculated that when 25(OH)D levels are above 30 ng/mL this serves as the substrate for the external 25(OH)D3-1α-hydroxylase to produce 1,25(OH)2D in the colon, prostate, breast, and lung to modulate cell growth and reduce risk of the cells becoming malignant" as shown in Figure 3 (Holick, 2006, p. 363). Moreover, Wittkamp et al. (2012) did an observational study in 30 beds PICU for patients who had respiratory failure or/and shock that required vasopressors. They studied 25(OH)D in those patients comparing with a healthy group, considering deficiency less than 25 ng/ml, among critically ill patients, those with asthma had lower 25(OH)D levels than others, also they found that African-American in comparison to Caucasian race was associated with more 25(OH)D deficiency, finally they concluded that 25(OH)D levels are lower in critically ill children than the healthy children. Another study conducted by Madden et al., 2011. They studied the children who were admitted to PICU in one year, they measured plasma concentration of 25(OH)D as soon as they were admitted to PICU, they used Pediatric Risk of Mortality III score to determine the severity of illness within 24 hours, 511 were the total patients and they found vitamin D deficiency higher with older age and nonwhite race. Furthermore, it showed high prevalence of vitamin D deficiency in critically ill children, also it was significant with children who have sever septic shock , but unknown the relation between vitamin D deficiency and septic shock is due to

increased severity of infection with decrease levels of 25(OH)D, or due to cardiovascular effects of vitamin D. According to their conclusion the role of vitamin D in sepsis and hemodynamic instability needs more investigation. Furthermore, McNally et al. (2012) conducted a prospective cohort study from 2005-2006 in 6 units PICUs in Canada, included 326 critically ill children, found there are deficiency of vitamin D in critically ill children and also it's associated with the severity of critical illness.

Another new study which aimed to examine the association of patients outcome to vitamin D status in patients with sepsis, Nguyen et al. (2013) noticed the decrease the serum 1.25(OH)2D in non survivors comparing with survivors patients, as a result they concluded that low 1.25(OH)2D levels are associated with increased 30-day mortality in sepsis patients. It's necessary to correct the abnormalities in vitamin D metabolism, through correcting both serum 25(OH)D and 1,25(OH)2D levels by the administration of vitamin D and 1,25(OH)2D (Nguyen et al., 2013). A Meta-Analysis of Randomized Controlled Trials about vitamin D and respiratory tract infection provided that vitamin D supplementation has a protective effect against respiratory tract infection (Bergman et al., 2013). Thus the vitamin D supplements and sun lights are important in keeping vitamin D in the body.

Following mothers since pregnancy is important in decreasing the incidence of having babies with this deficiency, then following the babies after birth is also helpful, then any problem rises, the healthcare should have the proper plan to treat that defect, it's better always to have the treatment and correct the deficiency as soon as possible. Strategies could help to decrease the deficiency include; first, national health policies for screening and prevention of vitamin D deficiency such as periodical screening for people especially the children age, by this step if any sudden illness rises we are sure that the body has enough storage. Second, government supports for vitamin D supplementation especially for people who are not covered by health insurance. Third, public health awareness is important for addressing this issue. After that we can see the effect of previous strategies in decreasing vitamin D deficiency that has negative effects on different systems in the body.

Nursing Implications

Since nurses are always near the patients especially in postpartum care, it's important for nurses to encourage mothers for breast feeding and rich their food with vitamin D sources to ensure the optimal level of supplementation.

The nurses have to be cautious when administering the vitamin D supplements for the baby for the correct doses given, public health awareness, patients and families education through community, primary health care, and home nurses for the importance of adequate vitamin D intake to the maintenance of optimal vitamin D status and potential strategies to increase vitamin D intake.

Conclusion

Vitamin D is important for the body and has vital role in skeletal and Extraskeletal functions in the body. Attention should be more regarding the vitamin D levels in pediatric population. Prevention of vitamin D deficiency and achieving adequate intake of vitamin D throughout childhood may reduce the severity of illness.

From previous studies there is a strong relation between vitamin D deficiency and critical illness of children and also it appears more in nonwhite race. It's important that nurses have the role of education and public awareness to address the importance of vitamin D and its consequences in case of deficiency. More studies need to be conducted to determine whether vitamin D supplementation can reduce the risk of Extraskeletal diseases.

References

Antico, A., Tampoia, M., Tozzoli, R., & Bizzaro, N. (2012). Can Supplementation With Vitamin D Reduce The Risk or Modify The Course of Autoimmune Diseases? A Systematic Review of The Literature. *Autoimmunity Reviews*, 12, 127-136. doi:10.1016/j.autrev.2012.07.007

Benrashida, M., Moyersa, K., Mohtyb, M., & Savanic, B. N. (2012). Vitamin D Deficiency, Autoimmunity, and Graft-Versus-Host-Disease Risk: Implication for Preventive Therapy. *Experimental Hematology*, 40, 263-267. doi:10.1016/j.exphem.2012.01.006

Bergman, P., Lindh, A. U., Bjorkhem-Bergman , L., & Lindh, J. D. (2013). Vitamin D and Respiratory Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PLOS ONE*, 8(6), e65835. doi:10.1371/journal.pone.0065835

Burton, J. M., Kimball, S., Vieth, R., Bar-Or, A., Dosch, H. M., Cheung, R., Gagne, D., D'Souza, C., Ursell, M., & O'Connor, P. (2010). A Phase I/II Dose-Escalation Trial of Vitamin D3 and Calcium in Multiple Sclerosis. *Neurology*, 74(23), 1852-1859. doi:10.1212/WNL.0b013e3181e1cec2

Chinellato , I., Piazza, M., Sandri, M., Peroni, D. G., Cardinale, F., Piacentini, G. L., & Boner, A. L. (2011). Serum Vitamin D Levels and Exercise-Induced Bronchoconstriction in Children With Asthma. *European Respiratory Journal*, 37(6), 1366-1370. doi:10.1183/09031936.00044710

Chiu, , K. C., Chu, A., Go, V. L., & Saad, M. F. (2004). Hypovitaminosis D is Associated With Insulin Resistance and B Cell Dysfunction. *The American Journal of Clinical Nutrition*, 79(5), 820-825.

Holick , M. F. (2004). Vitamin D: Importance in The Prevention of Cancers, Type 1 Diabetes, Heart Disease, and Osteoporosis. *The American Journal of Clinical Nutrition*, 79(3), 362-371. Retrieved from http://ajcn.nutrition.org/content/79/3/362.full

Holick , M. F. (2006). High Prevalence of Vitamin D Inadequacy and Implications for Health. *Mayo Clinic Proceedings*, 81(3), 353-373. doi:10.4065/81.3.353

Holick, M. F. (2007). Vitamin D deficiency. *New England Journal of Medicine*, 357(3), 266-281.

Khazai, N., Judd, S. E., & Tangpricha, V. (2008). Calcium and Vitamin D: Skeletal and Extraskeletal Health. *Current Rheumatology Reports*, 10(2), 110-117.

Krisinger , J., Strom , M., Darwish, H. D., Perlman, K., Smith , C., & DeLuca, H. F. (1991). Induction Of Calbindin-D 9k mRNA But Not Calcium Transport in Rat Intestine By 1,25-Dihydroxyvitamin D3 24-Homologs. *Journal Of Biological Chemistry*, 266(3), 1910-1913.

Madden, K., Feldman, H. A., Smith, E., Gordon, C. M., Keisling, S., Sullivan, R., Hollis, B. W., Agan, A. A., & Randolph, A. G. (2011). Septic Shock And Vasopressor Requirement is Associated With Lower Vitamin D Levels in Critically Ill Children. *Critical Care*,15(3), P21. doi: 10.1186/cc10390

McNally, J. D., Menon, K., Chakraborty, P., Fisher, L., Williams, K. A., Al-Dirbashi, O. Y., & Doherty, D. R. (2012). The Association of Vitamin D Status With Pediatric Critical Illness. *Pediatrics*, 130(3), 429-436. doi:10.1542/peds.2011-3059

Misra, M., Pacaud, D., Petryk , A., Collett-Solberg , P., Kappy, M., & Drug and Therapeutics Committee of The Lawson Wilkins Pediatric Endocrine Society (2008). Vitamin D Deficiency in Children and Its Management: Review of Current Knowledge and Recommendations. *PEDIATRICS*, 122 (2), 398 - 417. doi:10.1542/peds.2007-1894

Mora, J. R., Iwata, M., & von Andrian, U. H. (2008). Vitamin effects on the immune system: vitamins A and D take centre stage. Nature Reviews Immunology, 8(9), 685-698. doi:10.1038/nri2378

Nguyen, H. B., Eshete, B., William Lau, K. H., Sai , A., Villarin, M., & Baylink, D. (2013). Serum 1,25-Dihydroxyvitamin D: An Outcome Prognosticator in Human Sepsis. *PLOS ONE*, 5(5), 1-10. doi:10.1371/journal.pone.0064348

Ross, A. C., & Institute of Medicine (U.S.). (2011). DRI, dietary reference intakes: Calcium, vitamin D. Washington, D.C: National Academies Press.

Sai, A. J., Walters, R. W., Fang, X., & Gallagher, J. C. (2011). Relationship Between Vitamin D, Parathyroid Hormone, and Bone Health. *The Journal of Clinical Endocrinology & Metabolism*, 96(3), 436-446. doi:10.1210/jc.2010-1886

Wacker, M., & Holick, M. F. (2013). Vitamin D—Effects on Skeletal and Extraskeletal Health and The Need for Supplementation. *The American Journal of Clinical Nutrition*, 5(1), 111–148.. doi:10.3390/nu5010111

Wagner, C. L., & Greer, F. R. (2008). Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents. *PEDIATRICS*, 122(5), 1142 -1152. doi:10.1542/peds.2008-1862

Watkinsa, R. R., Yamshchikovb, A. V., Lemonovichc, T. L., & Salatac, R. A. (2011). The Role of Vitamin D Deficiency in Sepsis and Potential Therapeutic Implications. *Journal of Infection*, 63 (5), 321-326. doi:10.1016/j.jinf.2011.07.002

Wittkamp, M., Tangpricha, V., Brown, L. A., & Hebbar, K. (2012). Prevalence of Vitamin D Deficiency in Critically Ill Pediatric Patients. *Critical Care Medicine*, 40(12). doi:10.1097/01.ccm.0000424539.41200.ac

World Health Organization Scientific Group on the Prevention and Management of Osteoporosis (2003). Prevention and Management

of Osteoporosis: Report of a WHO Scientific group. Geneva: World Health Organization.

Yu, W., Ma, Y., Flynn, G., Muindi, J. R., Kong, R., Trump, D. L., & Johnson, C. S. (2010). Calcitriol enhances gemcitabine antitumor activity in vitro and in vivo by promoting apoptosis in a human pancreatic carcinoma model system. Cell Cycle, 9(15), 3094 - 3101. doi:10.4161/cc.9.15.12381