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Specific function of vitamin D in bone

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Abstract

There are two sources of vitamin D, namely from food and sun exposure. The content of vitamin D is given beneficial in bone and mineral metabolism. Vitamin D helps absorption of calcium in the intestines, thereby accelerating bone mineralization. Bone metabolism is a complex process that occurs throughout life. Very high doses of vitamin D can stimulate an increased rate of bone loss. Vitamin D deficiency causes bone demineralization. Which can cause a decrease in calcium absorption. The functions of these metabolites vary widely in vital metabolic pathways. This review aims to determine the specific function of vitamin D in bone. The search for the data base was carried out by the analytical method. Vitamin D which is absorbed from food or comes from the skin turns into an active form in the form of 1,25- (OH) 2-D3 which will enter the bloodstream, playing an important role in bone and extra-skeletal health.

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INTRODUCTION

Vitamin D plays a role in bone metabolism and is an agent in several extra-skeletal diseases (outside the relationship with bone) such as malabsorption, cardiovascular, metabolic, cancer, autoimmune, and neurological disorders (Bouillon, *et. al*, 2018). Bone metabolism is a complex process that occurs throughout life. Bones are constantly changing through two processes: modelling and renovation (Wu-Wong, 2006). Bone modelling is the process of forming new bone of bone which changes the shape of the bone to adapt to the forces in the environment. Bone remodelling is the process of removing old bone tissue that is being replaced with new tissue, which is important for bone mineral homeostasis.

At present, most humans already know that sunlight can fulfill human vitamin D needs through synthesis in the skin (80-90%) although there is a lot of sunlight in various countries, vitamin D deficiency has now undeniably become a problem (Wacker, 2013). It is a very common condition, and has been considered a widespread public health problem affecting more than 90%, but this depends on the population studied at that time. The need for vitamin D intake in humans also varies according to age. Starting from children, adolescents of childbearing age, adults, post menopause, and the elderly (Nimitphong & Holick, 2013).

There are several factors that influence the skin's vitamin D production, such as winter time, distance from the equator, high levels of melanin, and aging. Major changes that have occurred in

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lifestyle habits over the past few decades can also affect vitamin D synthesis. These include low sun exposure or exposure when there are lower levels of radiation intensity (Nimitphong & Holick, 2013). Sources of vitamin D derived from food are divided into several types, including those from original sources, namely vitamin D from breast milk, fortified foods and supplements. Source of vitamin D derived from foods include fish. oils such as salmon, mackerel, sardines, cod liver oil, liver and egg yolks (Nimitphong & Holick, 2013).

Vitamin D metabolites have many effects on the systemic calcium homeostatic mechanisms impacting bone. Vitamin D deficiency causes hypocalcemia and hypophosphatemia which can lead to rickets (Anderson, et.al, 2011). Vitamin D deficiency can also lead to impaired bone mineralization due to inefficient absorption of calcium and phosphorus and is associated with increased levels of parathyroid hormone (PTH). Vitamin D metabolism can also alter bone response to growth hormone and gene expression and secretion of growth factors which can have an effect. on bones and modulates the action of vitamin D metabolites on bones. Bone strength is determined by a combination of bone mass, morphology, and microarchitecture (Anderson, 2017).

METHOD

This research was carried out using a leading scientific database. To find relevant keywords, we focused on the metabolic pathways of Vitamin D and its role in bone health. The articles included in this study series were published up to 2024. We examined the metabolism of Vitamin D through a narrative review, original research articles, and other pertinent sources.

RESULTS AND DISCUSSION

Metabolism of Vitamin D

Bone metabolism is a complex process that occurs throughout life. Bones are constantly changing through two processes: modeling and renovation. Bone modeling is the process of forming new bone which changes the shape of the bone to adapt to the forces in the environment. Bone remodeling is the process of removing old bone tissue that is being replaced with new tissue, which is important for bone mineral homeostasis. Osteoblasts and osteocytes play two important roles in these two processes (Blomberg, 2010). Vitamin D delivered to the liver by vitamin D-binding protein (DBP) that is responsible for the transport of all vitamin D metabolites and transported therefore mainly protein bound. In the liver, there is vitamin D hydroxylated by 25-hydroxylase into the main circulating form of the hormone 25-hydroxyvitamin D. Excess non-hydroxylated vitamin D is stored in the liver, adipose, tissue and muscles. 25 [OH] D, bound to DBP, is transported to the proximal tubular cells of the kidney. DBP is degraded and 25 [OH] D3 is hydroxylated by 1α-hydroxylase [CYP27B1] to the biologically active form of the hormone, 1,25 di-hydroxyvitamin D3 [1,25 [OH] 2D3] [calcitriol] [25]. But the kidneys are not the only source of CYP27B1: it has also been detected in tissues such as the colon, brain, and pancreas to show different autocrine hormone functions (Demster, 2006). The regulation of CYP27B1 in the renal tubules is controlled by fibroblast growth factor [FGF-23] and by parathyroid hormone [PTH]. PTH is stimulated while FGF-23 inhibits renal production of 1α-hydroxylase through a series of feedbacks. After the hormone is metabolized, it is converted into calcitroic acid and excreted (Bouillon, 2001). The main effect of vitamin D is to increase the absorption of calcium in the small intestine. With hypocalcemia, increased PTH secretion stimulates renal production of 1,25 [OH] 2 D3. The hormone interacts with vitamin D receptors [VDR] in intestinal cells and complexes with retinoic acid x receptor [RXR] in the nucleus. Increased differentiation of osteoblasts and overexpression of VDR (Vitamin D Receptor) in mature osteoblasts leads to increased bone density which can block the mineralization pathway to trigger hypersteoidosis resulting in abnormal maturation of osteoblasts (Wronski et al, 1986; Hock et al, 1986). Apart from its role in promoting bone formation, Vitamin D also promotes bone resorption by increasing the number and activity of osteoclasts (Suda et al, 1992).

The complex binds to the vitamin D responsive element [VDRE] from the calcium channel [TRPV6] which increases calcium uptake into cells and increases calcium absorption. Second, in osteoblasts, vitamin D interacts with VDR and increases plasma membrane expression of RANKL [Receptor Activator for Nuclear Factor κ B Ligand]. RANK on preosteoclasts binds to RANKL on osteoblasts which in turn converts preosteoclasts into osteoclasts. This conversion releases

chemicals such as hydrochloric acid to metabolize calcium deposits from the bones into the circulation to maintain an optimal physiological range (Frost, 1990).

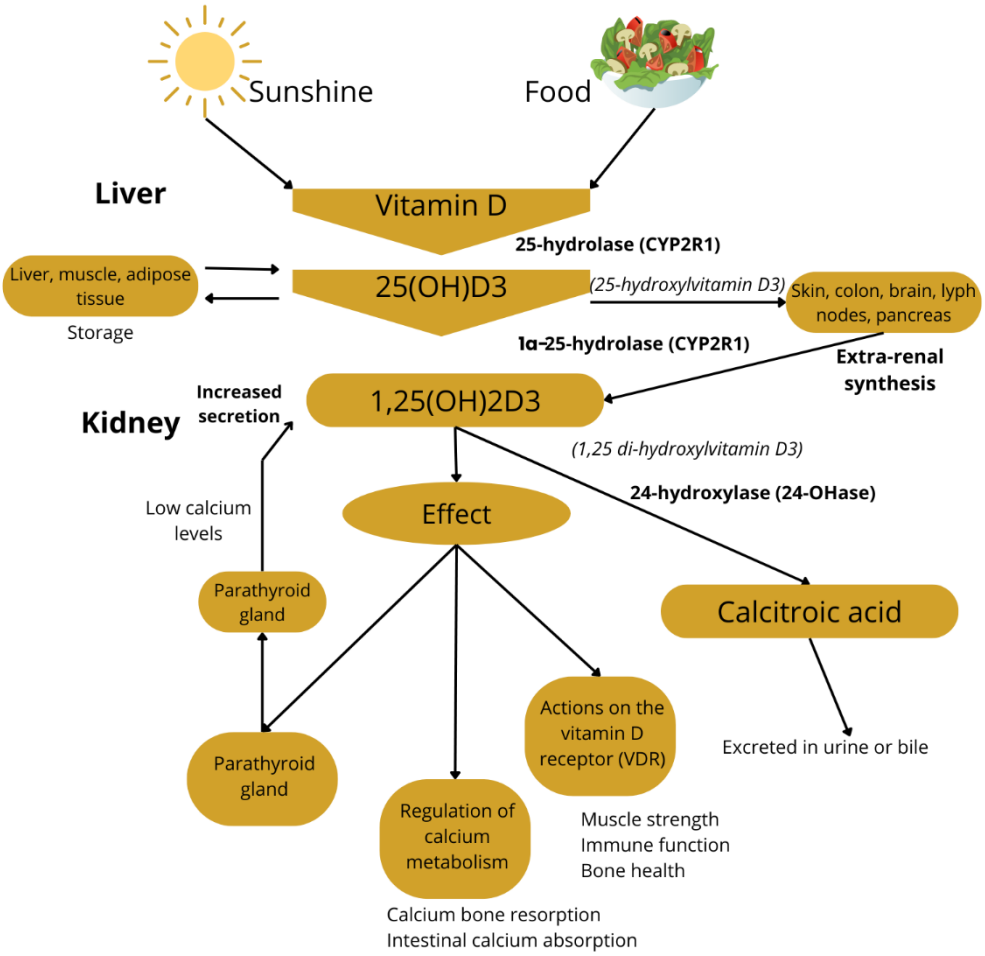

Figure 1. Metabolism of Vitamin D in Human (Modified from Anderson, 2011)

Effect of Vitamin D

Vitamin D is a steroid hormone which is important for calcium absorption and bone mineralization which is positively related to bone mineral density. The main effect of vitamin D is to increase the absorption of calcium in the small intestine specifically in the ileum and jejunum (Bouillon et al, 2001; Holick, 2006; Khosla, 2001; Laird et al, 2010; Holick, 2007). Research has been conducted using specific vitamin D, namely serum 25 (OH) vitamin D3 (Carbonare et al, 2018). In early childhood, vitamin D will induce the cessation of pre-adipocyte growth. Vitamin D in adult adipocytes has a smaller effect than pre-adipocytes in children (Felicidade, 2018). The inhibition of adipocyte differentiation depends on the concentration of vitamin D present in the body. In particular, vitamin D inhibits adipogenesis by reducing the expression of genes encoding CCAAT-enhancer-binding proteins (C / EBPs), PPARγ, lipoprotein lipase (LPL), and adipocyte protein 2 (aP2). All of these proteins are involved in the early and late phases of adipocyte differentiation (Kong & Li, 2006).

Waist circumference reflects visceral adiposity which is directly related to cardiovascular disease and metabolic disorders, and shows clearly that vitamin D depends on body mass as explained by the concept of vitamin D storage in adipose tissue (Gallagher, 2013). Research shows that waist circumference is highly correlated with vitamin D absorption and fat mass. Adipocyte damage which is considered to influence waist circumference can trigger MSC differentiation into osteoblasts. Transcription factors PPARγ and RUNX2 affect the differentiation of mesenchymal stem cells into adipocytes or osteoblasts (Carbonare et al, 2018; Ge et al, 2016). However, the reduction in

waist circumference in patients on vitamin D therapy can be explained by a direct effect on the pre-adipocyte pathway (Carbonare et al, 2018).

Bone mineral density or (BMD) is a useful measure for predicting fracture risk (Duppe et al, 1997; Marshall et al, 1996). This increase in vitamin D and PTH status did not benefit bone mass and bone turnover parameters (Andersen et al, 2008). Total BMD increased significantly in the hip and spine, not in the femoral neck, in both arms. Meanwhile, subtotal BMD increased only at high doses (Rahme et al, 2017). In the elderly, vitamin D deficiency can lead to low levels of bone density, poor muscle function, and the risk of fractures and osteoporosis. Adequate and inadequate supplementation of calcium and vitamin D has been shown to reduce the risk of bone loss and fracture (Arabi et al, 2006; Dawson-Hughes et al, 1997; Holick, 2007; Chapuy et al, 2002; Murad, 2011; Reid, 2015; Bolland, 2014).

Bone strength is determined by a combination of bone mass, morphology, and microarchitecture (Samelson et al, 2019). Vitamin D supplementation at doses of 700-800 IU reduces the risk of hip and nonvertebral fractures in the elderly. But the dose of vitamin D at a dose of 400 IU is not sufficient for prevention of fractures (Jennings et al, 2018). High doses of vitamin D can suppress PTH (Parathyroid Hormone) directly on parathyroid cells or indirectly by increasing intestinal calcium absorption. This may reduce PTH-mediated bone formation. However, if high doses of vitamin D did stimulate increased rate of bone loss, this could be of greater clinical significance in the elderly with osteoporosis (Burt et al, 2019). There is also evidence that very high doses of vitamin D (monthly or yearly) can be dangerous, with an increased risk of falls or fractures (Sanders et al, 2010; Sanders et al, 2013). Other studies have shown that vitamin D supplements only increase bone density in adults with adequate calcium intake and according to dosage (Macdonald et al, 2018). Vitamin D therapy in osteomalacia, results in a 50% increase in BMD within 12 months (El-Desouki et al, 2004).

Vitamin D is essential for bone health. The correlation is also tied to muscle strength, minimizing the risk of inflammation in the bones (Laird, 2010) (Figure 1). Vitamin D plays a role in bone metabolism and agents in several extra-skeletal diseases (outside the relationship with bone) such as malabsorption, cardiovascular, metabolic, cancer, autoimmune, and neurological disorders (Cashman, 2018; Carbonare et al, 2017; Ebeling et al, 2018). Vitamin D promotes the maturation of osteoblasts from MSC (Mesenchymal stem cells) and promotes osteogenic differentiation (Posa et al, 2018; Posa et al, 2016; Liu et al, 1999). During pregnancy, vitamin D is an important component for the development of fetal organs (Javaid, 2006; Hart, 2015; Hewison & Adams, 2010). Vitamin D deficiency in early pregnancy will affect birth weight and organ completeness in the neonatal body (Eggemoen et al, 2017). During menopause, vitamin D maintains muscle function (Hensen et al, 2016; Bouillon, 2017). Many children and adults who are obese, when checked for low levels of vitamin D in their blood (Kamei et al, 1993). Adipose tissue is formed from the maturation of pre-adipocyte cells, these cells are found in more than normal numbers in obese individuals (Chawla et al, 2011; Moreno-Navarrete & Fernandez-Real, 2012).

Vitamin D deficiency causes impaired bone mineralization due to inefficient absorption of calcium and phosphorus and is associated with increased levels of parathyroid hormone (Lerchbaum, 2019). Vitamin D is very important for bones, preventing bone rickets, especially in the postnatal period after weaning. Rickets is a bone growth disorder caused by a lack of vitamin D which causes soft and brittle bones, so they break easily. Vitamin D metabolites have many effects on the systemic calcium homeostatic mechanisms impacting bone. Vitamin D deficiency causes hypocalcemia and hypophosphatemia which can trigger rickets (Bikle, 2012). Lack of vitamin D for a long time causes bone demineralization. That initially causes a decrease in calcium absorption and finally the release of calcium from the bones to maintain calcium concentration. Continuous bone remodeling and resorption weakens bone structure and increases the risk of fracture through secondary hyperparathyroidism which ultimately leads to the development of osteomalacia and osteoporosis (Lips, 2001; WHO, 1994; Binkley et al, 2002). Vitamin D metabolites can also change bone response to growth hormone and gene expression and growth factor secretion which can have an effect on bones and modulate the work of vitamin D metabolites on bones (Bikle, 2010).

25 (OH) vitamin D Function

Vitamin D has been recognized as one of the key hormones in the process of bone metabolism. Vitamin D is an important key in the maintenance of calcium companion bone (McCollum, 1957). Vitamin D was identified from the results of the isolation of 7-dehydrocholesterol from pork rinds and yeast, which were called D2 and D3, respectively (Holick, 2006). Vitamin D deficiency has been agreed as a circulating concentration of 25 (OH) vitamin D <20 ng / ml because it has an optimal circulating concentration of <32 ng / ml based on the optimization of the PTH concentration. With a specification of 21-29 ng / ml indicating relative deficiency and 30 ng / ml or more as adequacy indicated as optimal work (Lips, 2001)

1,25 Dihydroxyl can increase bone mineralization by stimulating the supply of calcium and phosphate from digested food in the intestine. The efficiency is 30-40% for calcium and 80% for phosphorus. (Holick, 2006). From a study by Bischoff-Ferrari et al (2006) showed that levels of 25 (OH) vitamin D were associated with bone mineral density of Mexican-American women with the result that levels of 40 ng / ml or more indicated maximum bone density. The level of 25-hydroxy vitamin D is estimated from the bone mineral density present in it.

Until after weaning, mice with VDR removal targets, namely VDR - / - mice (which exhibit vitamin D resistance), and with 1α (OH)ase removal targets, namely, 1α (OH) ase - / - mice (which are vitamin D deficient real), normal length and morphology and mineral content of growth plates and normal long bones. However, after weaning, long bone growth and rickets features such as expansion of the epiphyseal growth plate are observed, due to dilation and disorganization of the hypertrophic zone with apoptotic disorders of hypertrophic chondrocytes. Low serum phosphate levels due to resistance or vitamin D deficiency appear to decrease apoptosis of hypertrophic chondrocytes via the caspase-9-mediated mitochondrial pathway (Donohue and Demay 2002; Sabbagh et al. 2005).

Vitamin D Receptor (VDR)

From the experiments conducted by Donuhue and Demay (2002), mice whose VDR metabolic pathway was removed showed growth characteristics of rachitis such as expansion of the epiphytic growth plate due to disruption in the apoptosition of hypertrophic chondrocytes.

Decreased activity of the 1,25 (OH) 2 D / VDR system may have an effect on changes in the cartilage growth plate model that was initially caused by reduced removal of hypertrophic chondrocytes (Lin et al., 2002).

Hormonal regulation of serum calcium (Ca) and phosphorus (P). Low serum calcium (↓ Ca), conversion by the kidneys can convert 25 (OH) D to 1,25 (OH) 2D, and can stimulate the release of PTH from the parathyroid glands. The increase in PTH (↑ PTH) can then stimulate the conversion of 25OHD to 1.25 (OH) 2 D so that urine phosphorus increases (↑ Pu), and then serum phosphate decreases (↓ P). PTH and 1,25 (OH) 2D can also produce bone resorption to increase serum calcium (↑ Ca). The increase in 1,25 (OH) 2D can increase the release of FGF23 from bone (Goltzman, 2018). This regulation demonstrates the importance of vitamin D for bone growth.

Reduction of (↓) 1,25 (OH) 2 D may result in reduced extracellular fluid phosphorus which may decrease apoptosis of hypertrophic chondrocytes through decreased caspase-mediated mitochondrial pathway activity. This activity can reduce the availability of calcium and reduce cartilage calcification. This decrease also results in a decrease in VEGF and a decrease in vascular invasion as well as a decrease in RANKL which results in a reduced number and activity of chondroclasts / osteoclasts (Figure 2).. This mechanism causes rachitic or 1,25 (OH) 2 D resistance (Goltzman, 2018).

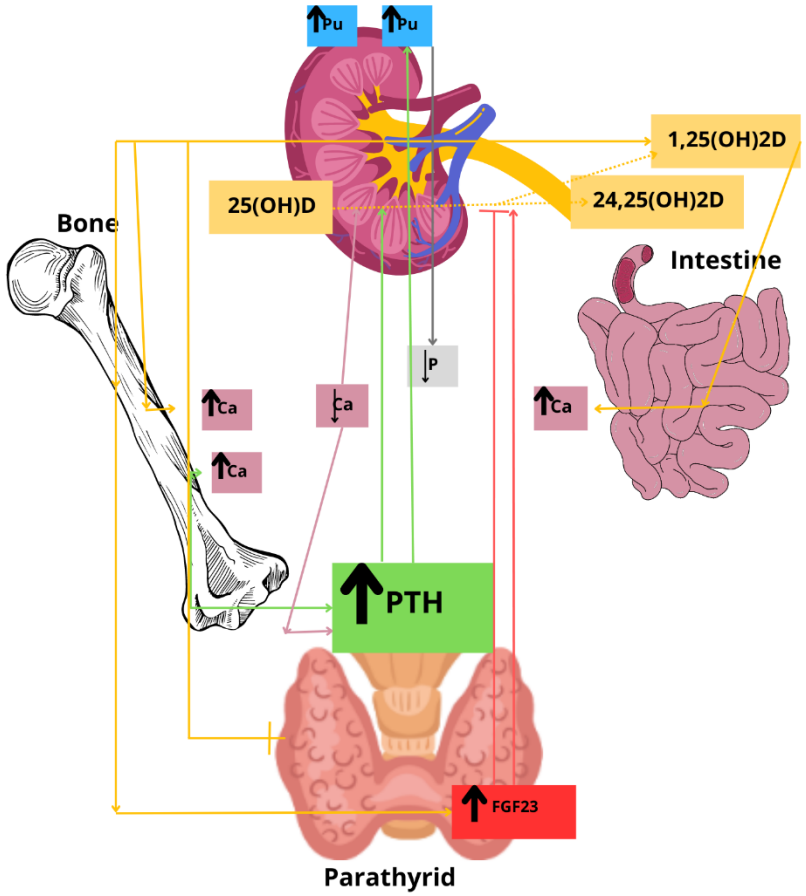

Figure 2. Regulation Metabolic Pathway of Vitamin D (Modified from Goldzman, 2018)

VDR has a role in the continuous replacement or remodelling of bone throughout life, with osteoblast bone formation building bone (anabolic effect) and osteoclastic bone resorption eliminating bone (catabolic effect). These actions are generally paired, although not always balanced. Cells from the osteo-blast lineage originate from mesenchymal stem cells in the bone marrow and differentiate through osteoblasts to osteoblasts and osteocytes to maturity. Osteoclasts are derived from hematogenous precursors and result from the fusion of mononuclear cells from the monocyte / macrophage lineage. (Goldzman, 2018). Studies of conditional removal of VDR from osteo-blast lineages suggest that early osteoblasts can mediate increased bone resorption induced by 1,25 (OH) 2D (Yamamoto et al. 2013)

CONCLUSION

Vitamin D which is absorbed from food or comes from the skin turns into an active form in the form of 1,25- (OH) 2-D3 which will enter the bloodstream, playing an important role in bone and extra-skeletal health. Vitamin D helps absorption of calcium in the intestines, thereby accelerating bone mineralization. Vitamin D promotes the maturation of osteoblasts from MSC (Mesenchymal stem cells) and promotes osteogenic differentiation. In the other cases, elevated vitamin D levels can inhibit parathyroid hormone (PTH) activity either by directly affecting parathyroid cells or by enhancing calcium absorption in the intestines. This action may decrease PTH-induced bone formation. With a metabolic-appropriate level of vitamin D, this vitamin will work optimally in bone formation and increase bone density in adults.

In further research, the maximum concentration of vitamin D can be investigated. The research needs to be conducted to determine the correct dose that can be accepted by the human body. It is very important to determine the optimal Vitamin D dosage that the body should receive according to age and health conditions.

AUTHOR CONTRIBUTIONS

Each author of this article played an important role in the process of method conceptualization, simulation, and article writing.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

Andersen R, Molgaard C, Skovgaard LT, Brot C, Cashman KD, Jakobsen J, Lamberg-Allardt C,Ovesen L. (2008). Effect of vitamin D supplementation on bone and vitamin D status among Pakistani immigrants in Denmark: a randomised double-blinded placebo-controlled intervention study. *British Journal of Nutrition*, 100(1):197–207. https://doi.org/10.1017/S000711450789430X

Anderson, P. H., Atkins, G. J., Turner, A. G., Kogawa, M., Findlay, D. M., & Morris, H. A. (2011). Vitamin D metabolism within bone cells: effects on bone structure and strength. *Molecular and cellular endocrinology*, 347(1-2), 42-47. https://doi.org/10.1016/j.mce.2011.05.024

Anderson, P. H. (2017). Vitamin D activity and metabolism in bone. *Current Osteoporosis Reports*, 15, 443-449. https://doi.org/10.1007/s11914-017-0394-8

Arabi A, Baddoura R, Awada H, Salamoun M, Ayoub G, & El-Hajj Fuleihan G. (2006). Hypovitaminosis D osteopathy: is it mediated through PTH, lean mass, or is it a direct effect?. *Bone*, 39(2), 268-75. https://doi.org/10.1016/j.bone.2006.01.140

Bikle DD. (2010). Vitamin D: an ancient hormone. *Experimental Dermatology*, 20(1), 7–13. https://doi.org/10.1111/j.1600-0625.2010.01202.x

Bikle DD. (2012). Vitamin D and bone. *Skeletal Regulations*, 10(2), 151-159. https://doi.org/10.1007/s11914-012-0098-z

Binkley, N.C., Schmeer, P., Wasnich, R.D., & Lenchik, L. (2002). What are the criteria by which a densitometric diagnosis of osteoporosis can be made in males and non-Caucasians?. *Journal of Clinical Densitom*, 5, 219-227. https://doi.org/10.1385/jcd:5:3s:s19

Bischoff- Ferrari A. H., Giovannucci, E., Willett, W. C., Dietrich, T., & Dawson-Hughes, B. (2006). Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *The American Journal of Clinical Nutrion*, 84, 18–28. https://doi.org/10.1093/ajcn/84.1.18

Jensen M. B., Nielsen J. E., Jorgensen A., Meyts E. R., Kristensen, D. M., Jorgensen, N., Skakkebaek, N. E., Juul, A., & Leffers, H. (2010). Vitamin D receptor and vitamin D metabolizing enzymes are expressed in the human male reproductive tract. *Human Reproduction*, 25(5), 1303–1311. https://doi.org/10.1093/humrep/deq024

Bouillon, R., Marcocci, C., Carmeliet, G., Bikle, D., White, J. H., Dawson-Hughes, B., Lips, P., Munns, C. F., Lazaretti-Castro, M., Giustina, A., & Bilezikian, J. (2019). Skeletal and extra-skeletal actions of vitamin D: Current evidence and outstanding questions. *Endocrine Reviews,* 40(4), 1109-1151. https://doi.org/10.1210/er.2018-00126

Bouillon, R. (2017). Comparative analysis of nutritional guidelines for vitamin D. *Nature Reviews Endocrinology*, 13(8), 466–479. https://doi.org/10.1038/nrendo.2017.31

Bolland, M. J., Grey, A., Gamble, G. D., & Reid, I. R. (2014). The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes--authors' reply. *Lancet Diabetes Endocrinol*, 2(5):364-5. https://doi.org/10.1016/S2213-8587(13)70212-2

Bouillon, R. (2001). *Vitamin D: from photosynthesis, metabolism, and action to clinical applications*. In: Degroot, L., Jameson, J.L. and Burger, H.G., Eds., Endocrinology, 3rd Edition, WB Saunders, Philadelphia, 1009-1028.

Burt, L. A., Billington, E. O., Rose, M. S., Raymond, D. A., Hanley, D. A., & Boyd, S. K. (2019). Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial. *American Medical Association*, 322(8), 736-745. https://doi.org/10.1001/jama.2019.11889

Carbonare, D. L., Valenti, M. T., Del Forno, F., Caneva, E., & Pietrobelli, A. (2017). Vitamin D: daily vs. monthly use in children and elderly-what is going on?. *Nutrients*, 9(7),652. https://doi.org/10.3390/nu9070652

Cashman, K. D. (2018). Vitamin D requirements for the future-lessons learned and charting a path forward. *Nutrients*, 10(5), 533. https://doi.org/10.3390/nu10050533

Chapuy, M. C., Pamphile, R., Paris, E., Kempf, C., Schlichting, M., Arnaud, S., Garnero, P., & Meunier, P. J. (2002). Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. *Osteoporos International*, 13(3):257-64. https://doi.org/10.1007/s001980200023

Chawla, A., Nguyen K. D., &Goh Y. P. (2011). Macrophage-mediated inflammation in metabolic disease. *Nature Reviews Immunology*, 11(11), 738–749. https://doi.org/10.1038/nri3071

Dawson-Hughes B., Harris S. S., Krall, E. A., & Dallal, G. E. (1997). Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *The New England Journal of Medicine*, 337(10), 670-6. https://doi.org/10.1056/NEJM199709043371003

Dempster D. W. (2006). *Anatomy and function of the adult skeleton. In: Favus MJ,editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. 6th ed*. Washington, DC: The American Society for Bone and Mineral Research.

Donohue, M. M. & Demay, M. B. (2002). Rickets in VDR null mice is secondary to decreased apoptosis of hypertrophic chondrocytes. *Endocrinology*, 143(9), 3691–3694. https://doi.org/10.1210/en.2002-220454

Duppe, H., Gardsell, P., & Johnell, O. (1997). A single bone density measurement can predict fractures over 25 years. *Calcified Tissue International*, 60(2), 171–174. https://doi.org/10.1007/s002239900209

Ebeling, P., Adler, R., Jones, G., Liberman, U. A., Mazziotti, G., Minisola, S., Munns, C., Napoli, N., Pittas, A., Giustina, A., Bilezikian, J. P., & Rizzoli, R. (2018) Management of endocrine disease: Therapeutics of vitamin D. *European Journal of Endocrinology*, 179(5), R239–R259. https://doi.org/10.1530/EJE-18-0151

Eggemoen, A. R., Jenum, A. K., Mdala, I., Knutsen, K. V., Lagerlov, P., & Sletner, L. (2017). Vitamin D levels during pregnancy and association with birth weight and body composition of the newborn: A longitudinal multiethnic population-based study. *British Journal of Nutrition*, 117(07):985–993. https://doi.org/10.1017/S000711451700068X

Ekwaru, J. P., Zwicker, J. D., Holick, M. F., Giovannucci, E., & Veugelers, P. J. (2014). The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25 hydroxyvitamin D in healthy volunteers. *PLoS ONE*, 9(11): e111265. https://doi.org/10.1371/journal.pone.0111265

El-Desouki, M. I., Othman, S. M., & Fouda, M. A. (2004). Bone mineral density and bone scintigraphy in adult Saudi female patients with osteomalacia. *Saudi Medical Journal*, 25(3), 355-358. https://doi.org/

Felicidade, I., Sartori, D., Coort, S. L. M., Semprebon, S. C., Niwa, A. M., D'Epiro, G. F. R., Biazi, B. I., Marques, L. A., Evelo, C. T., Mantovani, M. S., & Ribeiro, L. R. (2018). Role of 1α,25 Dihydroxyvitamin D3 in adipogenesis of SGBS cells: New insights into human preadipocyte proliferation. *Cellular Physiology and Biochemistry*, 48(1), 397–408. https://doi.org/10.1159/000491770

Frost, H. M. (1990). Skeletal structural adaptations to mechanical usage (SATMU): 2. Redefining Wolff's law: the remodeling problem. *The Anatomical Record,* 226(4), 414–22. https://doi.org/10.1002/ar.1092260403

Goltzman, D. (2018). Function of vitamin D in bond. *Hitochemistry and Cell Biology*, 149(4), 305–312. https://doi.org/10.1007/s00418-018-1648-y

Gallagher, J. C., Yalamanchili, V., & Smith, L. M. (2013). The effect of vitamin D supplementation on serum 25OHD in thin and obese women, *The Journal of Steroid Biochemistry and Molecular Biology*. 136, 195–200. https://doi.org/10.1016/j.jsbmb.2012.12.003

Ge, C., Cawthorn, W. P., Li, Y., Zhao, G., Macdougald, O. A., & Franceschi, R. T. (2016). Reciprocal control of osteogenic and adipogenic differentiation by ERK/MAP kinase phosphorylation of Runx2 and PPARγ transcription factors. *Journal of Cellular Physiology*, 231(3), 587–596. https://doi.org/10.1002/jcp.25102

Holick, M. (2006). Resurrection of vitamin D deficiency and ricket. *The Journal Clinical Investigation*, 116, 2062–72. https://doi.org/10.1172/JCI29449

Hart, P. H., Lucas, R. M., Walsh, J. P., Zosky, G. R., Whitehouse, A. J. O., Zhu, K., Allen, K. L., Kusel, M. M., Anderson, D., & Mountain, J. (2015). Vitamin D in fetal development: Findings from a birth cohort study. *Pediatrics*, 135(1):e167-73. https://doi.org/10.1542/peds.2014-1860

Hensen, K. E. & Johnson, M. G. (2016). An update on vitamin D for clinicians. *Current Opinion in Endocrinology & Diabetes and Obesity*, 23(6), 440–444. https://doi.org/10.1097/MED.0000000000000288

Hewison, M. & Adams, J. S. (2010). Vitamin insufficiency and skeletal development in utero. *Journal of Bone and Mineral Research*, 25(1), 11–13. https://doi.org/10.1002/jbmr.2

Hock, J. M., Gunness-Hey, M., Poser, J., Olson, H., Bell, N. H., & Raisz, L. G. (1986). Stimulation of undermineralized matrix formation by 1,25 dihydroxyvitamin D3 in long bones of rats. *Calcified Tissue International*, 38(2),79–86. https://doi.org/10.1007/BF02556834

Holick, M.F. (2006). "Resurrection of vitamin D deficiency and rickets". Journal Clinical Invest; 116(8):2062-2072. https://doi.org/

Holick, M. F. (2007). Vitamin D deficiency. *The New England Journal of Medicine,* 357(3), 266–281. https://doi.org/10.1056/NEJMra070553

Javaid M. K., Crozier, S. R., Harvey, N. C., Gale, C. R., Dennison, E. M., Boucher, B. J., Arden, N. K., Godfrey, K. M., & Cooper, C. (2006). Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: A longitudinal study. *The Lancet*, 367(9504), 36-43. https://doi.org/10.1016/S0140-6736(06)67922-1

Jennings A, Cashman KD, Gillings R, Cassidy, Tang J, Fraser W, Dowling KG, Hull GLJ, Berendsen AAM, Groot LCPGM, Pietruszka B, Wierzbicka, Ostan R, Bazzocchi A, Battista G, Caumon E, Meunier N, Malpuech-Brugere C, Franceschi C, Santoro A, & Fairweather-Tait SJ. (2018). A mediterranean-like dietary pattern with vitamin D3 (10 μg/d) supplements reduced the rate of bone loss in older Europeans with osteoporosis at baseline: results of a 1-y randomized controlled trial. *The American Journal of Clinical Nutrition*, 108(3), 633–640. https://doi.org/10.1093/ajcn/nqy122

Kamei Y, Kawada T, Kazuki R, Ono T, Kato S, & Sugimoto E. (1993). Vitamin D receptor gene expression is upregulated by 1,25-dihydroxyvitamin D3 in 3T3 L1preadipocytes. *Biochemical and Biophysical Research Communications*, 193(3), 948–955. https://doi.org/10.1006/bbrc.1993.1717

Khosla, S. (2001). The OPG/RANKL/RANK system. *Endocrinology*, 142(12), 5050-5055. https://doi.org/10.1210/endo.142.12.8536

Kong J & Li YC. (2006). Molecular mechanism of 1,25-dihydroxyvitamin D3 inhibition of adipogenesis in 3T3-L1 cells. *American Journal of Physiology-Endocrinology and Metabolism*, 290(5), E916–E924. https://doi.org/10.1152/ajpendo.00410.2005

Laird E, Ward M, McSorley E, Strain JJ, & Wallace J. (2010). Vitamin D and bone health: potential mechanisms. *Nutrients*, 2(7), 693-724. https://doi.org/10.3390/nu2070693

Lerchbaum E, Trummer C, Theiler-Schwetz V, Kollmann M, Wolfler M, Pilz S, & Obermayer-Pietsch B. (2019). Effects of Vitamin D supplementation on bone turnover and bone mineral density in healthy men: A post-hoc analysis of a randomized controlled trial. *Nutrients*, 11(4), 731. https://doi.org/10.3390/nu11040731

Lips, P. (2001). Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocrinology*, 22(4), 477-501. https://doi.org/10.1210/edrv.22.4.0437

Liu P, Oyajobi BO, Russell RG, & Scutt A. (1999). Regulation of osteogenic differentiation of human bone marrow stromal cells: Interaction between transforming growth factor-beta and 1,25(OH)(2) vitamin D(3) in vitro. *Calcified Tissue International*, 65(2), 173–180. https://doi.org/10.1007/s002239900678

Lin R, Amizuka N, Sasaki T, Aarts MM, Ozawa H, Goltzman D, Henderson JE, & White JH (2002) 1Alpha,25-dihydroxyvitamin D3 promotes vascularization of the chondro-osseous junction by stimulating expression of vascular endothelial growth factor and matrix metalloproteinase 9. *Journal of Bone and Mineral Research,* 17(9), 1604–1612. https://doi.org/10.1359/jbmr.2002.17.9.1604

Macdonald HM, Reid IR, Gamble GD, Fraser WD, Tang JC, & Wood AD. (2018). 25-Hydroxyvitamin D Threshold for the Effects of Vitamin D Supplements on Bone Density: Secondary Analysis of a

Randomized Controlled Trial. *Journal of Bone and Mineral Research*, 33(8), 1464-1469. https://doi.org/10.1002/jbmr.3442

Marshall D, Johnell O, & Wedel H. (1996). Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *British medical journal,* 312(7041), 1254–1259. https://doi.org/10.1136/bmj.312.7041.1254

McCollum, E. (1957). *A History of Nutrition 1957*. Boston: Houghton Mifflin Co.

Murad, M. H., Elamin, K. B., Abu Elnour, N. O., Elamin, M. B., Alkatib, A. A., Fatourechi, M. M., Almandoz, J. P., Mullan, R. J., Lane, M. A., Liu, H., Erwin, P. J., Hensrud, D. D., & Montori, V. M. (2011). Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis. The *Journal of Clinical Endocrinology & Metabolism*, 96(10), 2997-3006. https://doi.org/10.1210/jc.2011-1193

Moreno-Navarrete JM. & Fernández-Real JM. (2012). *Adipocyte differentiation. In Adipose Tissue Biology; Symonds, M., Ed*. Springer: New York : USA,

Nimitphong, H., & Holick, M. F. (2013). Vitamin D status and sun exposure in southeast Asia. *Dermato-Endocrinology*, 5(1), 34–37. https://doi.org/10.4161/derm.24054

Posa F, Benedetto DA, Cavalcanti-Adam EA, Colaianni G, Porro C, Trotta T, Brunetti G, Muzio LL, Grano M, & Mori G. (2018). Vitamin D promotes MSC osteogenic differentiation stimulating cell adhesion and αVβ3 expression. *Stem Cells International*, 2018(6958713), 1-9. https://doi.org/10.1155/2018/6958713

Posa F, Benedetto DA, Colaianni G, Cavalcanti-Adam EA, Brunetti G, Porro C, Trotta T, Grano M, & Mori G. (2016) Vitamin D effects on osteoblastic differentiation of mesenchymal stem cells from dental tissues. *Stem Cells International*, 2016(9150819):1-9. https://doi.org/10.1155/2016/9150819

Rahme M, Sharara SL, Baddoura R, Habib RH, Halaby G, Arabi A, Singh RJ, Kassem M, Mahfoud Z, Hoteit M, Daher RT, Bassil D, Ferkh KE, & Fuleihan GEH. (2017). Impact of calcium and two doses of vitamin d on bone metabolism in the elderly: A randomized controlled trial. *Journal of Bone and Mineral Research*, 32(7), 1486-1495. https://doi.org/10.1002/jbmr.3122

Reid IR. (2015). Short-term and long-term effects of osteoporosis therapies. *Nature Reviews Endocrinology*, 11(7), 418-28. https://doi.org/10.1038/nrendo.2015.71

Samelson EJ, Broe KE, Xu H, Yang L, Boyd S, Biver E, Szulc P, Adachi J, Amin S, Atkinson E, Berger C, Burt L, Chapurlat R, Chevalley T, Ferrari S, Goltzman D, Hanley DA, Hannan MT, Khosla S, Liu C, Lorentzon M, Mellstrom D, Merle B, Nethander M, Rizzoli R, Sornay-Rendu E, Rietbergen BV, Sundh D, Wong AKO, Ohlsson C, Demissie S, Kiel DP, & Bouxsen ML. (2019). Cortical and trabecular bone microarchitecture as an independent predictor of incident fracture risk in older women and men in the Bone Microarchitecture International Consortium (BoMIC). *Lancet Diabetes Endocrinol*, 7(1), 34-43. https://doi.org/10.1016/S2213-8587(18)30308-5

Sanders KM, Nicholson GC, & Ebeling PR. (2013). Is high dose vitamin D harmful?. *Calcified Tissue International*, 92(2), 191-206. https://doi.org/10.1007/s00223-012-9679-1

Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, & Nicholson, GC. (2010). Annual high-dose oral vitamin D and falls and fractures in older women. *JAMA*, 303(18), 1815-1822. https://doi.org/10.1001/jama.2010.594

Suda T, Takahashi N, & Abe E. (1992). Role of vitamin D in bone resorption. *Journal of Cellular Biochemistry.* 49(1), 53–58. https://doi.org/10.1002/jcb.240490110

Wronski TJ, Halloran BP, Bikle DD, Globus RK, & Morey-Holton ER. (1986). Chronic Administration of 1,25-Dihydroxyvitamin D3: Increased bone but impaired mineralization. *Endocrinology*, 119(6), 2580–2585. https://doi.org/10.1210/endo-119-6-2580

Wacker, M., & Holick, M. F. (2013). Sunlight and Vitamin D: A global perspective for health. *Dermato-endocrinology*, 5(1), 51–108. https://doi.org/10.4161/derm.24494

World Health Organisation. (1994). *Assessment of fracture risk and its application to screening for postmenopausal osteoporosis.* Technical Report Series 843. World Health Organization, Geneva, Switzerland. https://doi.org/

Wu-Wong, J. R., Nakane, M., Ma, J., Ruan, X., & Kroeger, P. E. (2006). Effects of Vitamin D analogs on gene expression profiling in human coronary artery smooth muscle cells. *Atherosclerosis*, 186(1), 20–28. https://doi.org/10.1016/j.atherosclerosis.2005.06.046

Yamamoto Y, Yoshizawa T, Fukuda T, Shirode-Fukuda Y, Yu T, Sekine K, Sato T, Kawano H, Aihara K, Nakamichi Y, Watanabe T, Shindo M, Inoue K, Inoue E, Tsuji N, Hoshino M, Karsenty G, Metzger D, Chambon P, Kato S, & Imai Y (2013) Vitamin D receptor in osteoblasts is a negative regulator of bone mass control. *Endocrinology*, 154, 1008–1020. https://doi.org/10.1210/en.2012-1542