

Vitamin D : Source, Metabolism and Effects

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Abstract :- Vitamin D appears today as a vitamin with a multiple potentials. It's involved in many physiological processes. It was for a long time confined for its role in phosphocalcic metabolism. Due to its dual food and endogenous origin, vitamin D constitutes a contributions and needs remain difficult to define and are currently under debate. On the other hand, the metabolism of this vitamin D is better known. Its metabolism involves a first hepatic hydroxylation leading to the formation of 25-hydroxyvitamin D 25OHD as well as a renal hydroxylation resulting in the formation of 1,25(OH)₂ D, the active metabolite of the vitamin D. Vitamin D deficiency is defined by a serum 25OHD concentration below 20 ng/mL. On the other hand, the insufficiency in vitamin D is defined by a concentration between 20 and 30 ng/mL. The deficiency and insufficiency are very frequent situations associated with an increased risk of developing various pathologies. The effects of vitamin D supplementation on reducing the risk of fractures and falls are documented by various intervention studies. The other potential extra osseous effects of vitamin D are mainly documented by observational and experimental studies. Although there is not yet a consensus on the need for vitamin D. All experts agree that the recommended dietary allowance is very insufficient and should be increased.

Keywords:- Vitamin D, Effects, Metabolism, Source.

I. INTRODUCTION

Initially identified for its antirachitic action and then confined for a long time to phosphocalcic metabolism, vitamin D has been the subject of much attention in recent years, which has allowed major advances in the knowledge of its metabolism, its mechanisms of action and by consequent of its many metabolic effects.

II. DOUBLE ORIGIN AND CONTRIBUTION OF VITAMIN D

The blood level of 25-hydroxyvitamin D 25OHD is the best marker of vitamin D status. When the serum level of 25OHD is greater than 30 ng/mL (75 nmol/L), the vitamin D status can be described as optimal. Conversely, the term suboptimal vitamin D status is often used when it's less than 30 ng/mL. This value is in fact considered to be the threshold

below which hyperparathyroidism appears secondary to hypovitaminosis D, involving accelerated bone remodeling and a decrease in bone mineral density, in particular in the cortical bone [1]. A distinction is made between insufficiency, defined by a level of 25OHD between 10 and 30 ng/mL, and deficiency, defined by a level less than 10 ng/mL (25 nmol/L). However, these threshold values are still subject to a wide debate at present. Unlike other vitamins which are provided exclusively through food, vitamin D has a dual origin: exogenous, which corresponds to food intake, but also endogenous, resulting from neosynthesis occurring in the epidermis [2]. Vitamin D is present in our food in two forms: vitamin D₂ or ergocalciferol, produced mainly by plants and fungi, and the form of vitamin D₃ or cholecalciferol (Figure 1) of animal origin. These two forms are liposoluble and relatively stable, in particular to heat.

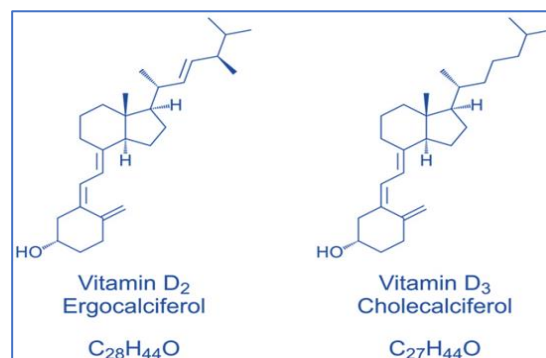


Figure 1 Structure of Vitamin D2 and D3

As well as the objectives in terms of serum values, the means and recommendations to be implemented to reach these threshold values are also the subject of much discussion. In Europe, the recommended daily intakes were set at 5 g/day, which corresponds to a dose making it possible to prevent osteomalacia associated with vitamin D insufficiency. In France, ANSES established intake values in 2001 nutritional advice, for the french adult population [3]. These values range from 5g/day (200 IU/day) for children over 4 years old, adolescents and adults, to 10g/day for children under 3 years, pregnant and breastfeeding women, up to 15g/day for the elderly (Table 1). Other European countries have recently revised their recommendations, such as Germany where the German Nutrition Society advises an intake of 20g/day (800 IU/day) for the majority of population groups [4].

Age range	recommended nutritional intake (µg/day)	recommended nutritional intake (UI/day)
Children (1 to 3 years old)	10	400
Children (4 to 12 years old)	5	200
Teenagers (13 to 19 years old)	5	200
Adults	5	200
The elderly	10 à 15	400 à 600
Pregnant and breastfeeding women	10	400

Table 1 Recommended Dietary Intakes

Vitamin D metabolism

Vitamin D is very important for growth and bone health. Besides the classic known effects on phosphocalcic and bone metabolism, vitamin D has increasingly better understood effects on other body functions. Vitamin D3 or cholecalciferol, of human or animal origin, and vitamin D2 or ergocalciferol of plant origin. Although there are a few rare dietary sources of vitamin D3, mainly marine fatty fish, and supplements in the form of vitamin D3 or D2 are available, the skin, from 7- dehydrocholesterol, may synthesize vitamin D3 under the action of UVB radiation and it's the main natural source of vitamin D [5]. It's reduced in the elderly, in subjects with pigmented skin, or in the event of atmospheric pollution or cloud cover. Wearing covering clothing or using sunscreens prevents the synthesis of vitamin D. Vitamin D2 or D3 must be transformed at the hepatic level then at the renal level to become fully active by binding to a receptor present in target tissues that it reaches through the bloodstream. It can therefore be considered more like a "pre-pro-hormone". Vitamin D (D2 or D3) is carried in the blood by the vitamin D binding protein (DBP) and is hydroxylated in the liver to form 25-hydroxyvitamin D 25OHD [5]. This hepatic hydroxylation is very poorly regulated. The half-life of 25OHD is on the order of three weeks and its serum concentration represents an individual's vitamin D status. This 25OHD is again hydroxylated under the action of an enzyme, 1-hydroxylase, to make 1,25 dihydroxy vitamin D 1,25(OH)2D or calcitriol, the active metabolite of vitamin D whose half-life is short (4h). This second hydroxylation is classically done in the cells of the proximal renal tubule, but we now know that it's possible in a great many other tissues. Renal 1-hydroxylase is very tightly regulated by hormones of phosphocalcic metabolism. It's stimulated in particular by PTH and inhibited by FGF23 and calcitriol. It makes it possible to produce 1,25(OH)2D, a hormone which will pass into the blood and act on target tissues where it binds to the vitamin D receptor (VDR) located in the cytosol of these cells. This hormonal mechanism is the basis of the classic

phosphocalcic and bone effects of vitamin D [5]. These are genomic effects where, once it has bound calcitriol, the VDR associates with another protein, the receptor of retinoic acid (RXR) and then binds to DNA at specific sites called vitamin D response elements (VDRE), thereby stimulating or inhibiting protein synthesis. The main target tissues of circulating calcitriol are the intestinal cell where it stimulates the absorption of calcium and phosphate, the osteoblast where it stimulates the synthesis of RANKL, a cytokine whose role in bone resorption is fundamental, the kidney where it controls the expression in the distal tubule of the TRPV5 protein necessary for the reabsorption of calcium, and the parathyroids where it controls the secretion of PTH. There is also a route of inactivation of vitamin D via the formation of hydroxyl compounds on carbon 24 thanks to a 24-hydroxylase [5]. Expression of 24-hydroxylase in the proximal tubule is stimulated by FGF23 and calcitriol. Its importance was recently highlighted with the demonstration that inactivating mutations of the gene encoding this enzyme (CYP24A1) were responsible for "hypersensitivity to vitamin D" with severe neonatal hypercalcemia [6]. Very many tissues express VDR, 1-alpha-hydroxylase and 24-hydroxylase. 25OHD enters these tissues where it's converted to calcitriol which acts locally after binding to VDR, heterodimerization with RXR and binding to VDRE. This locally produced calcitriol does not emerge from the cell and therefore doesn't participate in phosphocalcic metabolism. This peripheral production of calcitriol does not appear to be regulated by calciotropic hormones (PTH, FGF23) But depends on a sufficient concentration of 25OHD in the extracellular fluid of these tissues. This is the basis for the unclassical genomic effects of vitamin D which can be described as intracrine. Circulating calcitriol may also exert non-genomic effects on certain tissues (activation of tyrosine kinases, modification of intracellular calcium flux) after binding to poorly identified membrane proteins, probably VDR variants [7]. (Figure 1) summarizes the main steps in vitamin D metabolism.

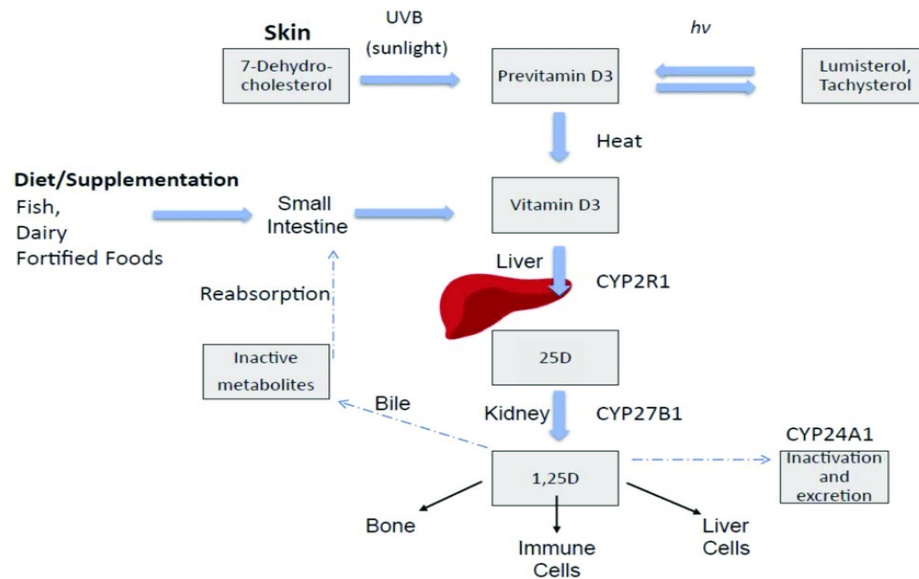


Figure 1 Vitamin D metabolism

Classics effects of vitamin D

The various endocrine effects of vitamin D are necessary for bone mineralization. Profound vitamin D deficiency can cause conditions characterized by defective bone mineralization, rickets in children and osteomalacia in adults. A shallower deficit can promote osteoporosis, especially in the cortical bone. In observational studies, vitamin D deficiency is associated with low bone mineral densities and an increased relative risk of osteoporotic fractures [8]. Vitamin D supplementation, most often combined with calcium, reduces the risk of non-vertebral fractures in people over 65 years of age as long as vitamin D doses are at least 800 IU/day [9]. For all of these situations, correcting a vitamin-calcium deficiency is a prerequisite for initiating disease-modifying osteoporosis [10].

Non-classicals effects

The studies have reported an association between vitamin D deficiency and diseases:

- vitamin D deficiency is associated with sarcopenia in the elderly. It has a demonstrated action on muscle and treatment with vitamin D (800 IU/day) combined with calcium reduces the relative risk of falls in elderly subjects, which may explain the reduced risk of peripheral fractures [11];
- vitamin D deficiency is associated with an increased relative risk of developing various colorectal [12] and breast [13] cancers;
- Vitamin D deficiency is associated with an increased risk of cardiovascular events as well as cardiovascular mortality [14]. The mechanisms are complex and relate to direct effects of vitamin D on vascular endothelial cells, but also indirect effects because vitamin D controls insulin secretion and insulin sensitivity, decreases inflammation, controls proteins involved in the formation of vascular calcifications, reduces the secretion of parathyroid hormone and controls the renin gene which gives it antihypertensive properties;
- vitamin D is an immunomodulator. Numerous experimental studies have shown inhibition of acquired immunity and stimulation of innate immunity by vitamin D. This inhibition of acquired immunity by 1,25OH₂D appears to be beneficial

in a number of cases. autoimmune pathologies such as multiple sclerosis, type 1 diabetes, rheumatoid arthritis, lupus [15].

- vitamin D deficiency in early pregnancy has been associated with an increased risk of preeclampsia [16] and gestational diabetes [17];
- in patients with renal failure not on dialysis, vitamin D deficiency is associated with a more rapid progression of kidney disease [18];
- Vitamin D deficiency is associated with earlier mortality in various prospective observational studies [19], but also interventional [20].

These classic and unclassical effects of vitamin D depend in part on the genetic specificities of individuals. There are indeed different polymorphisms of VDR and 1-alpha hydroxylase potentially having consequences on the actions of calcitriol, or the ability to synthesize this metabolite.

III. DISCUSSION

Several positive intervention studies conducted through meta-analysis, observational studies and experimental studies, showing decreased risk of falls and non-vertebral fractures, recent controlled trials showing administration of vitamin D which decreases PTH and/or biological markers of bone remodeling, which have also shown beneficial effects on the relative risk of cancer [21], on intermediate parameters associated with cardiovascular health by reducing the concentration of pro-inflammatory cytokines [22], biological parameters testifying to insulin resistance in glucose-intolerant patients [23], arterial pressure in hypertensive patients [24] or on certain infectious pathologies [25]. However, the results of these studies are not necessarily transposable to the general population and large intervention trials are therefore still necessary. In addition, a study where a very high dose (500,000 IU of vitamin D₃) was administered annually for three years to osteoporotic women of about 80 years, reported worse results in the group treated with vitamin

D than in the placebo group with a transient excess, during the three months following administration, of falls and fractures [26]. An excellent example illustrating these points perfectly is the large WHI study where more than 36 000 postmenopausal american women were randomized to receive either a placebo or 1000 mg of calcium and 400 IU of vitamin D3 per day [27]. The main objective was to assess the effect of this intervention on the relative risk of osteoporotic fractures. No decrease in fracture risk was observed over the six year period. In this study, compliance was 50% which greatly reduced the statistical power. Two recent placebo controlled studies where the same dose of vitamin D3 (20000 IU/week) was given for the same duration (one year) to patients with multiple sclerosis living in Finland. In the first study [28], the intervention did not modify the clinical and imaging parameters of the patients, while in the second, the T1 lesions on MRI and the progression score (EDSS) were significantly improved [29]. The number of patients in the two studies was the same and the only thing that differed was the annualized relapse rate which was 0.1 in the first study (one relapse every ten years) and 0.5 in the second (one outbreak every two years).

IV. CONCLUSION

At present, many significant advances have been made in the knowledge of the metabolism and genomic and non-genomic effects of vitamin D. Among these major advances, the demonstration of the extra-renal synthesis of 1,25(OH)2D which calls into question the central role of the kidney in the synthesis of the active form of vitamin D. Vitamin D insufficiency is a very common situation which is associated with an increased risk of developing many diseases, not only bone and the occurrence of numerous physiopathological disorders. Vitamin D supplementation reduces the relative risk of non-vertebral fractures in people over 60 years of age and of falls in older people. The other potential effects are mostly documented by observational and experimental studies.

REFERENCES

- [1]. Souberbielle JC, Friedlander G, Kahan A, Cormier C. Evaluating vitamin D status. Implications for preventing and managing osteoporosis and other chronic diseases. *Joint Bone Spine* 2006;73(3):249-53
- [2]. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357(3): 266-81
- [3]. Martin A. The “apports nutritionnels conseilles (ANC)” for the French population. *Reprod Nutr Dev* 2001;41(2):119-28
- [4]. GNS. New reference values for vitamin D. *Ann Nutr Metab* 2012;60(4):241-6
- [5]. Holick M, Chen T, Lu Z, et al. Vitamin D and skin physiology: a D-lightful story. *J Bone Miner Res* 2007;22(suppl. 2):V28-33
- [6]. Schlingmann KP, Pirruccello JP, Do R, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. *N Engl J Med* 2011;365:410-21
- [7]. Nemere I, Schwartz Z, Pedroso H, et al. Identification of a membrane receptor for 1,25-dihydroxyvitamin D3 which mediates rapid activation of protein kinase C. *J Bone Miner Res* 1998;13:1353-9
- [8]. Bischoff-Ferrari H, Dietrich T, Orav EJ, et al. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. *Am J Med* 2004;116:634-9
- [9]. Bischoff-Ferrari H, Willett W, Wong J, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency. *Arch Int Med* 2009;169:551-61
- [10]. Benhamou CL, Souberbielle JC, Cortet B, et al. La vitamine D chez l'adulte : recommandations du GRIO. *Presse Med* 2011;7-16
- [11]. Bischoff-Ferrari H, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ* 2009;339:b3692
- [12]. Feskanich D, Ma J, Fuchs CS, et al. Plasma vitamin D metabolites and risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev* 2004;13:1502-8
- [13]. Garland CF, Gorham ED, Mohr SB, et al. Vitamin D and prevention of breast cancer: pooled analysis. *J Steroid Biochem Mol Biol* 2007;103(3—5):708-11
- [14]. Pilz S, Tomaschitz A, Ritz E. Vitamin D status and arterial hypertension: a systematic review. *Nat Rev Cardiol* 2009;6:621-30
- [15]. Aronson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. *Ann Rheum Dis* 2007;66:1137-42
- [16]. Bodnar L, Catov J, Simham H, et al. Maternal vitamin D deficiency increases the risk of preeclampsia. *J Clin Endocrinol Metab* 2007;92:3517-22
- [17]. Poel YHM, Hummel P, Lips P, et al. Vitamin D and gestational diabetes: a systematic review and meta-analysis. *Eur J Intern Med* 2012;23:465-9
- [18]. Bienaime F, Girard D, Anglicheau D, et al., Vitamin D, renal function and outcome in renal transplantation. *J Am Soc Nephrol* 2013 (sous presse)
- [19]. Zitterman A, Iodice S, Pilz S, et al. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. *Am J Clin Nutr* 2012;95:91-100
- [20]. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007;167:1730-7
- [21]. Lappe JM, Travers-Gustafson D, Davies KM, et al. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;85:1586-91
- [22]. Schleithoff SS, Zittermann A, Tenderich G, et al. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr* 2006;83:754-9
- [23]. Mitri J, Dawson-Hughes B, Hu F, et al. Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the calcium and vitamin D for diabetes mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr* 2011;94:486-94

- [24]. Witham MD, Nadir MA, Struthers AD. Effect of vitamin D on blood pressure a systematic review and meta-analysis. *J Hypertens* 2009;27:1948-54
- [25]. Camargo C, Ganmaa D, Frazier L, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics* 2012;130:561-7
- [26]. Sanders KM, Stuart AL, Williamson EJ, et al. Annual highdose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 2010;303:1815-22
- [27]. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin d supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-83
- [28]. Kampman MT, Steffensen LH, Mellgren SI, et al. Effect of vitamin D3 supplementation on relapse, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial. *Mult Scler* 2012;18:1144-51
- [29]. Soilu-Hänninen M, Aivo J, Lindstrom BM, et al. A randomised double-blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon beta-1b in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2012;83: 565-71