VITAMIN D: THE ALL-ROUNDER

Dr. Wolfgang Bayer, Laboratory Dr. Bayer GmbH, Stuttgart/Germany

Vitamin D is a collective name assigned historically to a group of seco steroids with the biological activity of vitamin D. These are lipid-soluble substances structurally closely related to cholesterol and hence cholecalciferol (Vitamin D_3), calcidiol (25-hydroxyvitamin D_3) and calcitriol (1,25-dihydroxyvitamin D_3) are important.

Vitamin D does not meet the classical criteria for a vitamin as it can be fully synthesized by the organism from cholesterol. It can also be counted as a hormone by virtue of its physiological effects. One of vitamin D's central biological functions is its effect on calcium metabolism, phosphate metabolism, and hence bone metabolism. The peptide hormones calcitonin and parathormone are also involved in these activities. It has recently been shown that the functional importance of vitamin D extends far beyond bone metabolism, as vitamin D receptors occur in a number of organs and tissues such as the brain, muscles, pancreas, and cells of the immune system. Vitamin D or its active metabolites are involved in regulation of cell differentiation, insulin metabolism, immune defence and other vital body functions (reviews in Bischoff-Ferrari, 2006; Holick, 2007; Zittermann, 2003). The extra-skeletal effects of vitamin D (in immunomodulation, for instance) were known about in the early 20th century, as the following excerpt from Simplicissimus dated 15th March 1926 shows (Fig. 1). This seems to have been partly forgotten, and vitamin D was long researched thereafter only in terms of its activity in bone metabolism. A rethink has come about only in the course of the past two decades.

Excerpt from Simplicissimus, March 15th, 1926

Es ist Elternpflicht

jeden Säugling in seinem ersten Lebensjahr vorbeugend mit der Hanauer Quarzlampe bestrahlen zu lassen, da auch die Entstehung der Rachitis durch vorbeugende Bestrahlung sicher verhindert werden kann. „Rachitis bekämpfen heißt auch den Keuchhusten, den Keuchhusten und banalen Erkrankungen ihre Gefährlichkeit nehmen." (Hueter.)

Fig. 1: Translation of excerpt.
It is the parent's obligation to irradiate preventative their baby in his first year of life with the Hanau-quartz iodine lamp. Rickets is avoidable by prophylactic irradiation. To fight the rickets also means to stop dangerous diseases like measles, pertussis or other trivial sickness.

Metabolism

Vitamin D_3 can be produced in the skin from the precursor 7-dehydrocholesterol in response to exposure to UV light (Fig. 2). Vitamin D is also taken up with the diet. Resorption is enhanced by dietary fat and biliary acids. Natural sources of vitamin D in human nutrition are very low and almost all of them are in animal products. Fruit and vegetables contain almost no vitamin D. As a result, self-synthesis of vitamin D in the skin usually far surpasses dietary intake as a source. Vitamin D is metabolised in the liver to the metabolite 25-hydroxyvitamin D_3 through the effects of 25-hydroxylase. This metabolite mainly circulates in the blood, is subject to very little regulatory influence, and is used to determine a person's individual level of vitamin D. A second hydroxylation process to 1,25-dihydroxyvitamin D_3 takes place in the kidneys. The latter is the metabolite with the highest biological activity in terms of calcium metabolism. Although it was long believed that only the kidney has the 1α-hydroxylase enzyme needed for the second hydroxylation, it has been shown during the past two decades that numerous other cells and tissues are able to synthesise this vitamin D metabolite, which is one of the determinants of vitamin D's extra-skeletal activity.

Diagnostic procedures

25-hydroxyvitamin D_3 constitutes the main pool of vitamin D metabolites in plasma and is a suitable marker to detect deficiency states due to inadequate intake and/or low UV exposure, and to identify toxicity. Deficiency in the metabolite 1,25-dihydroxyvitamin D_3 primarily occurs in subjects with advanced renal failure as a result of a lack of 1α-hydroxylase in the kidney. Elevated levels can be detected in the presence of increased extra-renal formation of this vitamin D metabolite, as is the case in conditions such as sarcoidosis (rare inflammatory connective tissue disease) and various granulomatous disorders.

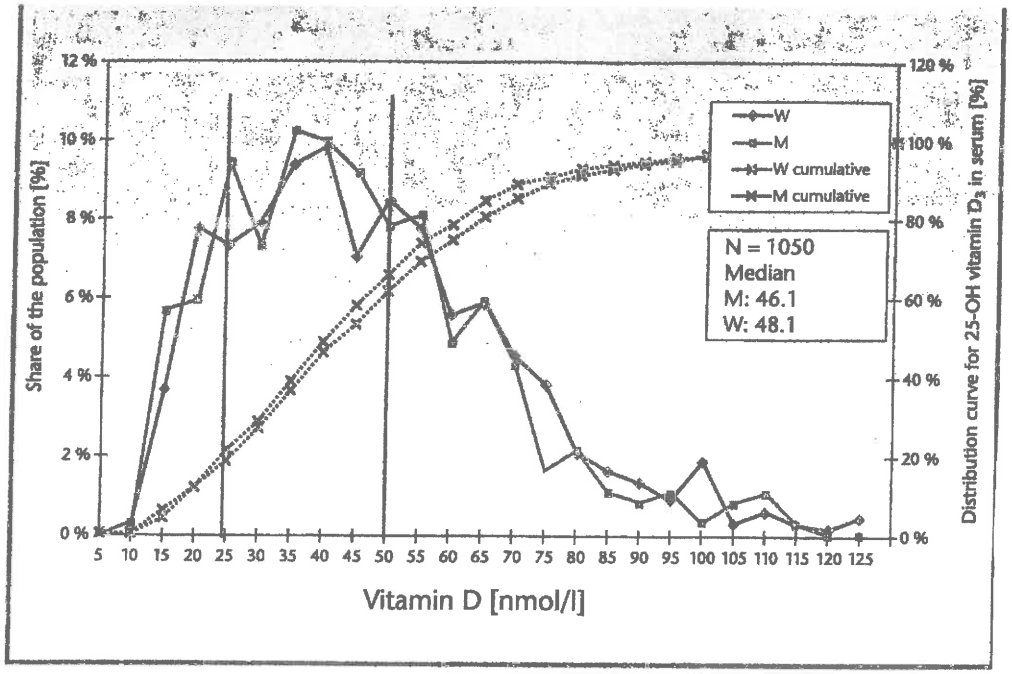

Fig. 3: 25-hydroxyvitamin D_3 in serum, supply situation in Germany.

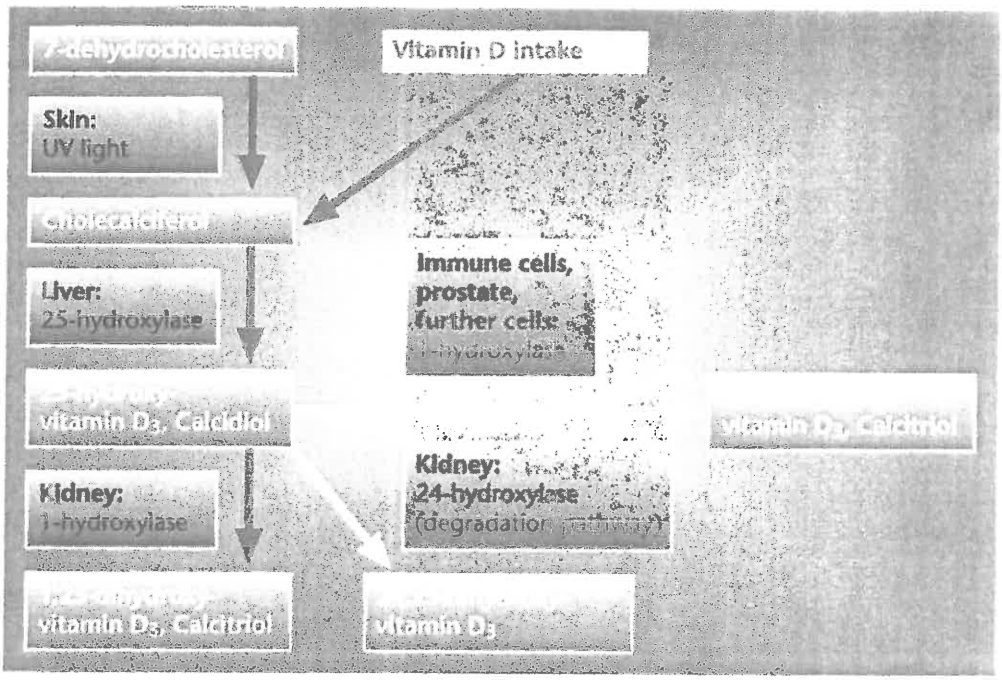

Fig. 2: Simplified illustration of the Vitamin D metabolism.

Vitamin D levels

On the basis of documented data, vitamin D deficiency can be said to be endemic in Central Europe (Bayer and Schmidt, 2004; Hintzpeter et al., 2008), and this could have serious clinical implications.

The reference range for the metabolite 25-hydroxyvitamin D_3 is 50 to 175 nmol/l (for the over-50s: 63 to 175 nmol/l), based on biochemical criteria such as optimisation of calcium metabolism and prevention of secondary hyperparathyroidism. However numerous new studies show that the lower limit for 25-hydroxyvitamin D_3 should be set at 80 to 100 nmol/l (Bischoff-Ferrari, 2006) for preventive medical purposes. This concerns coronary protection effects, blood pressure lowering, immunomodulatory and antitumor activities. In the over-70s, secondary hyperparathyroidism is absent only in the presence of 25-hydroxyvitamin D_3 levels above 100 nmol/l. Analysis of vitamin D levels in Germany (Bayer and Schmidt, 2004) shows that, on an annual average, about 70 % of patients have 25-hydroxyvitamin D_3 levels below the cut-off of 50 nmol/l. Only about 10 % of patients have levels above 100 nmol/l. Because of the higher exposure to sunlight in summer, vitamin D levels are higher in the summer months than in winter, in which only 20 % of patients achieve the 25-hydroxyvitamin D_3 cut-off of 50 nmol/l. Data from the Robert Koch Institute (Hintzpeter et al., 2008) also show that 57 % of the general adult population in Germany have vitamin D deficiency (Fig. 3). Hence, vitamin D deficiency must be said to be endemic in Central Europe.

Safety of vitamin D dosing

The most important potential side effect of excessive doses of vitamin D is hypercalcemia, which can range from a mild increase in serum calcium concentrations to life-threatening hypercalcemia syndrome. The D.A.CH. working group (DACH, 2000) deems a daily intake of 2000 IU of cholecalciferol (50 µg/day) to be safe. In a well-documented study (Vieth et al., 2001), daily administration of 4000 IU of cholecalciferol for two to five months did not cause hypercalcemia and did not lead to increased urinary excretion of calcium. Serum concentrations of 25-hydroxyvitamin D_3 rose then from 40.7 ± 15.4 nmol/l to 96.4 ± 14.6 nmol/l. It is also important to note that prolonged whole-body exposure to sunlight can result in endogenous production of 250 µg (10,000 IU) of vitamin D (Vieth, 1999). Biesalski et al. (2002) reported a maximum serum concentration of 274 nmol/l 25-hydroxyvitamin D_3 following artificial UV exposure. Only the administration of more than 10,000 IU/day produces a sudden leap in serum concentrations of 25-hydroxyvitamin D_3 (Vieth, 1999). Hypercalcemia cases described to date entailed serum concentrations of 25-hydroxyvitamin D_3 in excess of 220 nmol/l (Mawer et al., 1985). The two vitamin D metabolites 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 should be measured and serum calcium should be monitored in any individuals on high-dose vitamin D therapy.

Physiological effects of vitamin D on calcium and phosphate homeostasis

Vitamin D regulates calcium and phosphate homeostasis by four main mechanisms:

1) Raising intestinal absorption
2) Mobilising calcium and phosphate from bone tissue
3) Raising re-absorption of calcium and phosphate from the glomerular filtrate
4) Inhibiting parathormone biosynthesis so that vitamin D counteracts development of hyperparathyroidism.

The peptide hormones calcitonin and parathormone are also involved in regulating calcium and phosphate metabolism. A deficiency in vitamin D impairs calcium and phosphate metabolism, causes rickets in growing children and osteomalacia in adults (Fig. 4). Osteomalacia is expressed in deficient bone mineralisation, which can cause bone pain and subsequent bone fractures.

Extra-skeletal effects of vitamin D

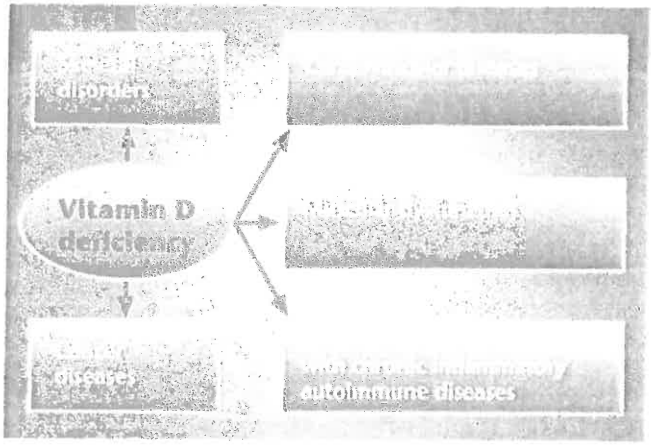

Fig. 4: Effect of vitamin D deficiency.

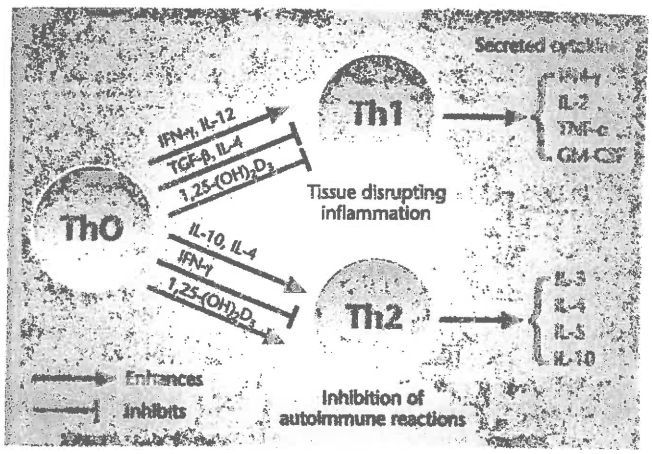

Fig. 5: Th1/Th2 antagonism by autoimmunity.

bone but also in numerous other organs and cells including immune cells, thymus, pancreas, pineal gland, breast gland, testicles, heart muscle, skin, bowels, and kidneys. VDR belongs to a group of nucleic steroid receptors and is a transcription factor with high affinity for 1,25-dihydroxyvitamin D_3. Interactions between 1,25-dihydroxyvitamin D_3 and VDR cause a variety of hormonal effects of this vitamin D metabolite in cells and tissues through the activation or inhibition of transcription of numerous target genes. These are relevant not only to disorders linked with impairment of calcium or phosphate homeostasis but also to autoimmune processes, cancers, cardiovascular disease and much more.

a) Immunological effects and chronic inflammatory disease

With regard to the immunological effects of vitamin D influence on T-helper (Th) cell differentiation is a particular one (Fig. 5). Activation of the Th1 pathway results in increased secretion of cytokines, which are pro-inflammatory, causing tissue destruction and promoting autoimmune disorders. Vitamin D lowers the secretion of cytokines by Th1 cells and also stimulates increased differentiation of Th cells to Th2 cells. In this way, vitamin D can help counteract the development of autoimmune diseases. Epidemiological studies, animal experiments and clinical trials demonstrate a favourable effect of vitamin D in multiple sclerosis (MS), rheumatoid arthritis, chronic inflammatory bowel disease and type 1 diabetes. The Nurses Health Study (Munger et al., 2004) demonstrated inverse relationships between vitamin D levels and onset of MS, and animal studies show an inhibitory effect of vitamin D in experimental autoimmune encephalitis. CRP reduction and regression of disease activity have been demonstrated in rheumatoid arthritis patients receiving the vitamin D metabolite α-Calcidiol as an adjuvant to standard treatment (Andjelkovic, 1999).

b) Cancers

In oncology, numerous epidemiological studies demonstrate inverse relationships between vitamin D intake and the incidence of colorectal, prostate and breast cancers, and experimental studies show antitumor effects of vitamin D. Epidemiological studies on colorectal carcinoma show that a good vitamin D supply with $25OHD_3$ levels > 82 nmol/l is associated with a 50 % risk reduction versus poor intake with levels below 30 nmol/l (Gorham et al., 2007). A similar situation applies for breast cancer (Fig. 6), with epidemiological studies showing a 50 % risk reduction in subjects with 25-hydroxyvitamin D_3 > 130 nmol/l versus subjects with 25-hydroxyvitamin D_3 concentrations below 30 nmol/l (Garland et al., 2007).

c) Hypertension and cardiovascular diseases

Numerous studies demonstrate that low 25-hydroxyvitamin D_3 concentrations are associated with increased risk of cardiovascular diseases, hypertension and metabolic syndrome. In cardiovascular diseases, the effects of vitamin D on the renin-angiotensin system are of special interest, as vitamin D can have a blood pressure-lowering effect.

Correlations with vitamin D deficiency have also been established for heart failure. Vitamin D is likewise required to maintain muscle function, and skeletal muscles express a vitamin D receptor.
In the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study (Dobnig et al., 2008), 3258 patients aged 62 ± 10 years, who were scheduled for coronary angiography, were screened for the two vitamin D metabolites and a large number of other parameters and observed for 7.7 years. 737 patients (22.6 %) died during this period. Cardiovascular disease was the cause of death in 463 patients. Classification of 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 concentrations into quartiles (QU 4 = highest concentrations, QU 1 = lowest concentrations), low serum concentrations of 25-hydroxyvitamin D_3 and of 1,25-dihydroxyvitamin D_3 are independent of each other and associated with increased all-cause and cardiovascular mortality. Mortality was approximately 10 % in patients with the highest concentrations both of 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 as compared with approximately 40 % in subjects with the lowest concentrations of these two vitamin D metabolites. These correlations apply regardless of BMI, total cholesterol, NYHA (New York Heart Association) classification, and other variables.

Prevention and treatment of vitamin D deficiency

Worldwide vitamin D deficiency is one of the most common vitamin deficiencies, and it can have serious clinical implications. Thus there is an urgent need for preventive and therapeutic measures, and not just in vulnerable high-risk groups. Current recommendations are based on a daily dietary intake of 400 to 1000 IU (10 to 50 µg/day) of cholecalciferol. The target range of 80 to 100 nmol/l of the metabolite 25-hydroxyvitamin D_3 in serum recommended for optimum prevention is achieved however only with a daily intake of at least 2000 IU/day (50 µg/day).

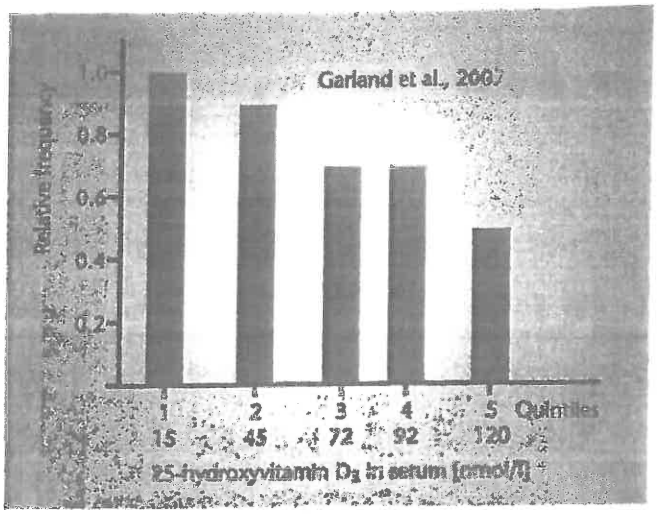

Fig. 6: Vitamin D-status and mamma carcinoma.

References

Andjelkovic Z et al. (1999) Disease modifying and immunomodulatory effects of high dose 1-alpha-(OH)-D3 in rheumatoid arthritis patients. *Clin Exp Rheumatol* **17**: 453–456.

Bayer W und Schmidt K. (2004) Besteht in Mitteleuropa ein endemischer Vitamin D-Mangel? *Erfahrungsheilkunde* **53**: 610–614.

Biesalski HK et al. (2002) Vitamine, Spurenelemente und Mineralstoffe, Thieme Verlag, Stuttgart.

Bischoff-Ferrari HA et al. (2006) Estimation of optimal serum concentrations of 25-hydroxy-vitamin D for multiple health outcomes. *Am J Clin Nutr* **84**: 18–28.

D.A.CH. (2000) Referenzwerte für die Nährstoffzufuhr. Umschau Braus GmbH, Frankfurt.

Dobnig H et al. (2008) Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med* **168**: 1340–1349.

Garland CF et al. (2007) Vitamin D and prevention of breast cancer: pooled analysis. *J Steroid Biochem Mol Biol* **103**: 708–711.

Gorham ED et al. (2007) Optimal vitamin D status for colorectal cancer prevention: a quantitative meta-analysis. *Am J Prev Med* **32**: 210–216.

Hintzpeter B et al. (2008) Vitamin D status and health correlates among German adults. *Eur J Clin Nutr* **62**: 1079–1089.

Holick MF. (2007) Vitamin D deficiency. *N Engl J Med* **357**: 266–281.

Mawer EB et al. (1985) Vitamin D metabolism in patients intoxicated with ergocalciferol. *Clin Sci* **68**: 135–141.

Munger KL et al. (2004) Vitamin D intake and incidence of multiple sclerosis. *Neurology* **62**: 60–65.

Vieth R (1999) Vitamin D supplementation, 25-hydroxyvitamin D concentrations and safety. *Am J Clin Nutr* **69**: 842–856.

Vieth R et al. (2001) Efficacy and safety of vitamin D intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* **73**: 288–294.

Zittermann A. (2003) Vitamin D in preventive medicine. Are we ignoring the evidence? *Br J Nutr* **89**: 552–572.