biomnis
SPECIALISED MEDICAL PATHOLOGY
Focus
issue 33

Updates: Vitamin D

The most well known role of vitamin D is its involvement in Calcium, phosphate and bone metabolism. However, over the last several years, a large number of potentially beneficial effects of vitamin D have been highlighted, starting an extraordinary interest in this vitamin, as confirmed by the number of publications on this subject going from over 5000 to over 15 000 per year from 1993 to 2005.

Vitamin D in general

From April to September in Europe, exposure to UVB is the main source of vitamin D3. Circulating vitamin D3 undergoes hydroxylation in the liver to form vitamin D3 25(OH). It is then converted into its active form, vitamin 1.25$(OH)_2$ or calcitriol by 1α-hydroxylase in the proximal tubules in the kidney.
The serum levels of vitamin D2+D3 25(OH) reflect the organism's vitamin D reserves. The quantification of 1.25$(OH)_2$ vitamin D is only requested in 2nd or 3rd line testing with restricted indications: hypercalcemia and/or hypercalciuria with decreased levels of PTH, differential diagnosis of vitamin resistant rickets, primary phosphate diabetes and kidney failure.

Vitamin D deficiency on a worldwide scale

According to studies, 40 - 100% of patients in the world have a deficiency in 25-hydroxyvitamin D [25(OH)D] (Holick M.F. *N Engl J Med* 2007) caused by the nutritional intake of vitamins D2 and D3 being insufficient and the restricted sun exposure in city dwellers. The variability factors are numerous: age, skin pigmentation (black skinned individuals have a lower serum concentration of vitamin D than white skinned individuals), sun cream, atmospheric pollution, cloud coverage, urban life, clothing, obesity, alcohol consumption, smoking, disease (malabsorptions, kidney failure and liver failure) and treatments. This is where the problem of establishing reference ranges arises.
This is why, in practice, the experts have defined "advised (or recommended) values" for 25-hydroxyvitamin D [25(OH)D] = 30 - 70 ng/ml.

	Serum levels of 25-hydroxy-vitamin D [25(OH)D]	
	ng/ml	nmol/ml
Vitamin D deficiency	< 10	< 25
Vitamin D insufficiency	10 - < 30	10 - < 75
Recommended ranges	30 - 70	75 - 175
Possible intoxication	> 150	> 375

The action mechanisms of vitamin D

- It has endocrine actions (skeletal effects), which compete to maintain the calcium and phosphate homeostasis by increasing the intestinal absorption of calcium and phosphorus and by negative feedback control of PTH secretion.
- It also has intracrine effects (non-skeletal). Indeed, the cells of certain tissues (muscles, colon, prostate, breast and pancreas etc.) express vitamin D receptors (VDR) and 1-alpha hydroxylase, which lead to a local production of 1.25$(OH)_2$D which in turn interacts with 300 - 1000 genes not involved in calcium and phosphate metabolism.

The extraskeletal effects of vitamin D

- **Cancer:** Cancer: several observational studies found a decrease in the risk of colon, breast, prostate or pancreatic cancer in subjects with a concentration of 25-hydroxyvitamin D [25(OH)D] in the recommended values compared to control subjects. One interventional study showed a reduction in the risk of breast cancer in women who received 1100 IU/day of vitamin D for 4 years versus a placebo group.
- **Cardiovascular mortality:** a deficit in vitamin D is associated with a relatively raised risk of disease and cardiovascular mortality. Several interventional studies have shown a beneficial effect of vitamin D *versus* a placebo on the occurrence of major cardiovascular or cardiovascular mortality; other studies are in progress searching for a significant reduction of these events.
- **Immune system:** vitamin D may play an immunomodulatory role in autoimmune disease (multiple sclerosis and type 1 diabetes) and during infections.

- **Autres :** a deficit in 25-hydroxyvitamin D [25(OH)D] is associated with an increase in falls caused by muscle weakness in elderly subjects, as well as mental disorders (dementias and depression), allergies and asthma. Nevertheless, we only have a very few interventional studies available, except for those on muscle weakness in the elderly which is included in the indications for vitamin D supplementation.

Vitamin D for the treatment and prevention of infectious diseases

Vitamin D and tuberculosis

To date, there have been four clinical studies focusing on vitamin D treatment of patients infected with Mycobacterium tuberculosis; but their results are somewhat contradictory.
We know that a low serum concentration of vitamin D increases the risk of active tuberculosis in exposed subjects, but prospective studies are necessary to confirm this in the population at risk. The question remains to identify the optimal vitamin D serum level to prevent *M. tuberculosis* infection.

Vitamin D and tuberculosis: no recommendations

- **Adjuvant therapy:** the addition of high doses of vitamin D accelerates the recovery of smear-positive patients in relation to the polymorphism of their vitamin D receptor, but there is no significant difference between groups of mixed patients.
- **Preventive treatment (acquaintances and subjects at risk):** in Canada and the USA, the recommendations from the Institute of Medicine specify that an intake of vitamin D cannot be recommended without the dose-response data from control, randomised, asthma, autoimmune diseases and infectious diseases trials.

Vitamin D and HIV

HIV+ patients have the same level of vitamin D deficiency as the general population. These patients, treated over the long-term, are exposed to comorbidities linked to age and vitamin D deficiency, particularly in osteopenia and osteoporosis, where the aetiology is multifactorial: viral course of action, increase in certain osteoporosis risk factors (hypogonadism, difficult living conditions, malnutrition etc.), secondary hyperparathyroidism through alteration of the renal function and decrease in renal hydroxylation of 25-hydroxyvitamin D [25(OH)D] and treatments.

The impact of anti-retroviral treatments on the metabolism of vitamin D

There is a significant decrease in the serum concentration of 25-hydroxyvitamin D [25(OH)D] in patients treated with certain anti-retroviral treatments, such as Efavirenz or Tenofovir.
According to the 2009 guidelines from the *European AIDS Clinical Society*, it is recommended to measure the vitamin D level throughout the follow-up of HIV patients and to give them supplements if they are found to be deficient.

Vitamin D and hepatitis C

In patients suffering from chronic hepatitis C, a low serum level of vitamin D is associated with a higher fibrosis score and a prolonged lower virology response percentage during antiviral therapy.
In those infected by genotype 1 HCV, vitamin D may be used as a non-invasive marker of the severity of hepatic fibrosis (Petta S. et *al. Hepatology 2010*).

Vitamin D supplementation

(According to CL Benhamou et *al*, Presse Med 2011)

Who to treat? Subjects with:

- no or almost no exposure to sunlight
- experiencing repetitive falls
- confirmed osteoporosis (always administer vitamin D, usually in combination with with calcium, before treating osteoporosis)
- a disease inducing osteoporosis or one (or more) osteoporosis inducing medication(s).
- a severe chronic disease (e.g. malabsorption) provoking a vitamin D deficiency or insufficiency.

When to measure 25 OHD?

Before the renewal of vitamin D treatment, and depending on the treatment given:

- In the case of a daily treatment (drops, usually reserved for the elderly): wait for 4 - 6 months between measurements: quantify 25 OHD. Aim:≥ 30 ng/ml. If < 30 ng/ml, increase the dose (double);
- In the case of intermittent treatment (vials of 100 000 units): start with one vial of 100 000 IU every 3 months in subjects with a BMI of < 25 kg/m² or every 2 months if the BMI is > 25 kg/m². Measure 25 OHD just before the 2nd administration of this treatment: if < 30 ng/ml, shorten the interval between administrations (every 1 or 2 month(s)).

Who should be targeted for vitamin D deficiency prevention?

All subjects aged 65 years and over: systematic supplementation, without 25 OHD quantification.

Conclusion

Currently, the majority of the supposed advantages of vitamin D rely on observational or epidemiological studies, which do not establish a causal link.
These studies should be completed via interventional studies aimed at proving that the doses of administered vitamin D are clinically effective.

Carole Emile, following a communication from JY Nizou, CNBH, Angers October 2011 and CME Biomnis, Lyon, November 2011.