When should we measure vitamin D in clinical practice?

Jean-Claude Souberbielle
Necker hospital, Paris, France
few significant dietary sources

UVB (290-315 nm)

skin → 7-dehydrocholesterol

Pre-vitamin D3

Vitamin D3 (cholecalciferol) → Vitamin D2 (ergocalciferol)

Liver

25OHD

Non classical genomic effects

1 alpha hydroxylase

1,25OH2D

DNA

VDR

FGF23

1,25OH2D

24,25OH2D

Calcitroic acid

VDR-MMARS

Activation tyrosine kinases

Intracellular Ca++

Several tissues including muscle; β cells

Classical endocrine genomic effects

Non genomic effects

Numerous tissues including immune cells (monocytes, macrophages, T-cells…), cardiomyocytes, endothelial cells, breast, prostate, colon (normal and tumoral), brain, …and much more
« classical » effects
- stimulates absorption of calcium and phosphorus by the gut
  - direct effects on bone
  - effects on kidney
  - control of PTH secretion

Favours bone mineralisation

700-800UI /day (+calcium)
reduce RR of « non vertebral » fractures in the elderly

« non classical » effects

Muscle
700-800UI /J (+calcium)
reduce RR of falls in the elderly

Immune System
- stimulation of « innate » immunity
- inhibition of « adaptative » immunity
  (favours Th2 and TReg versus Th1, Th17)

Vasculature
- direct effects
- indirect effects
  (insulin, inflammation, calcifications, PTH, blood pressure…)

Cancers

Other
  (cognition (?); renoprotection; Preeclampsia;…all-cause mortality)

Importance of « genetic »:
SNP of VDR, CYP27B1, CYP24, DBP…
What is the « level of evidence »?
(Evidence-based Medicine)

- « ecologic » studies
- « observation » studies
- « exprimental » studies
- « intervention » studies (RCTs)

*Meta-analyses*
“The panel on calcium and related nutrients quickly reached consensus that serum 25OHD was the correct functional indicator of vitamin D status.... Hence, on this point at least, there is consensus (notably, that was not the case as recently as 5-10 years ago).”

Heaney R. *Editorial*  
Vitamin D: how much do we need, and how much is too much. Osteoporosis Int (2000) 11: 553-555
Millions Euros reimbursed in France for 25OHD measurements
Measure 25OHD
1) in patients for whom we have a « reasonably evidence-based » target

In this case, « reasonably evidence-based » means based on RCTs (as much as possible) with « hard » end-points (corroborated by observational, experimental studies)
Two groups released recently different recommendations on the use of vitamin D. Both groups acknowledged that their recommendations were based on « musculoskeletal health »

**IOM (JCEM 2011)**
A 25OHD serum level of 50 nmol/L is largely sufficient and « covers the requirements of at least 97.5% of the population »

**Endocrine Society (Holick JCEM 2011)**
Vitamin D deficiency ⇔ 25OHD<50 nmol/L
Vitamin D insufficiency ⇔ 25OHD = 50-75 nmol/L

Surprisingly, the two groups reached these different conclusions after the (extensive) analysis of virtually the same data

*Public health recommendations versus (individual) Patient care ?*
My (current) opinion/clinical practice is:
For our patients with (or suspect of...) bone and mineral
diseases/anomalies, our target 25OHD range is
75-150 nmol/L

Caution !!! : we acknowledge that the 75 nmol/L cut-off is based
on studies that used – mostly – the « historic » DiaSorin RIA.
Will need to be re-validated after the
(very important) standardization of 25OHD assays !!

Based on what?
Variation of fracture prevention by dose and achieved 25(OH)D

- Pooled relative risk (RR):
  0.86 (95% CI, 0.77-0.96) for non-vertebral fractures

Anti-fracture efficacy (non-vertebral) increased significantly with higher received dose and higher achieved 25(OH)D level

-25OHD level above which there is no clinical/radiological/biological signs of rickets/osteomalacia (15-25 nmoL/L ?)

-25OHD level above which there is no histological signs of mineralization defect (75 nmol/L Priemel et al JBMR 2010; 25: 305-12 - von Domarus et al Clin Orthop Relat Res 2011 - see also Need et al JBMR 2007; 22: 757-61)

-relationship between PTH/25OHD:
25OHD threshold below which PTH may increase (many studies 40 to 110nmol/L)

-basal 25OHD levels below which PTH decreases after vitamin D supplementation Malabanan Lancet 1998 (50 nmol/L); Okazaki JBMM 2011 (70 nmol/L)

-Minimal 25OHD concentration for optimal effect of bisphosphonates 82 nmol/L : Carmel ES et al Osteoporos Int online 12 Jan 2012

-intestinal absorption of calcium = f([25OHD]
80 nmol/L Heaney J Am Coll Nutr 2003 (but…controversial)
This target 25OHD range (75-150 nmol/L) may be considered as being too high by some persons (and too conservative by others!!)

... But ...

...
Luxwolda M et al
Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/L.
British Journal of Nutrition 2012; in press

Maasai
Mean 25OHD : 119 nmol/L (range 58-167)

Skin type VI; moderate degree of clothing; spend the major part of the day outdoor, but avoid direct exposure to sunlight when possible.

Hadzabe
Mean 25OHD : 109 nmol/L (range 71-171)
So...measure 25OHD in which patients?
Patients with osteoporosis
(with and without fracture)
1) Measure 25OHD with other biological parameters
(serum calcium, phosphate, PTH…calciumuria?…) aiming to exclude
a secondary cause of low bone mass/fracture

2) If 25OHD<75 nmol/L prescribe vitamin D according to
protocols used locally to reach and sustain a 25OHD >75 nmol/L
(which depend on what is available in a given country)

3) Measure again 25OHD after 6 (?) months, check observance,
and adapt posology if needed
Patients at risk of osteoporosis because

- They receive treatments that are potentially deleterious for bone (i.e. glucocorticoids; anti-aromatase; analogs of GnRH…)

- They have a malabsorption syndrome (celiac disease, Crohn’s disease, cystic fibrosis…)

- After bariatric Surgery (specially gastric bypass)
3.1.3 In patients with CKD stages 3-5D, we suggest that 25OHD levels might be measured, and repeating testing determined by baseline values and therapeutic intervention (2C).

We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).
Patients with Primary Hyperparathyroidism (PHPT)
Question 5: conclusion:

“Vitamin D deficiency is common in patients with PHPT, and measurement of serum 25-OHD levels is recommended routinely. Vitamin D deficiency should be treated before making any medical or surgical management decisions. …

…It is also recommended that further research be conducted to determine the optimal vitamin D levels for individual with PHPT, including randomized clinical trials data with vitamin D supplementation”

Most studies have concluded that PHPT patients with vitamin D deficiency have a more severe (biological and skeletal) phenotype than those with a «normal» vitamin D status. (higher PTH and larger tumours, lower BMD and/or higher bone turnover [bone markers or bone biopsy], higher risk of fracture)


21 PHPT patients (serum calcium <3 mmol/L and 25OHD<20 ng/mL) received 50 000 IUD3/w for one month and 50 000 IU/mo thereafter for 12 mo => increase in 25OHD (11 ± 5 ng/mL to 31 ± 6 ng/mL at 12 mo), no increase in serum calcium (or phosphate); 26 % decrease in serum PTH (PTH decrease correlated with 25OHD increase), decrease in TAP, no modification in 24 h urine calcium as a group but 2 became hypercalciureic

- PHPT patients with vitamin D deficiency have worse post-parathyroidectomy outcomes => Be sure that post parathyroidectomy vitamin D (and calcium) status is optimal.
An exception:
Patients with granulomatous diseases, especially sarcoidosis

Due to the capacity of non-controlled 1-alpha hydroxylation of circulating 25OHD, these patients may become (severely) hypercalcemic/hypercalciuric. They are thus usually not supplemented with vitamin D and often asked to avoid sunlight. They are consequently often severely vitamin D deficient.

Recommendation by the Endocrine Society group (Holick JCEM) is to measure 25OHD serum concentration and maintain close to 50 nmol/L in order to avoid both severe vitamin D deficiency and hypercalcemia.
Measure also 25OHD

2) in patients with (possible) symptoms of severe vitamin D deficiency (without other explanation) such as diffuse muscle and bone pain, or in elderly persons who fall frequently, or in patients with symptoms of vitamin D « intoxication » such as kidney stone, nephrocalcinosis

3) In patients with treatments that (possibly) modify vitamin D metabolism such enzymatic inductors or inhibitors (ketokonazole; anti-seizure drugs; some medications used in AIDS…)

In these patients, there are no special target 25OHD level (although 50-150 nmol/L seems reasonable), the question being to eliminate a severe vitamin D deficiency or vitamin D intoxication
...and more generally in patients for whom an evaluation of calcium/phosphorus metabolism is prescribed (including measurement of serum calcium, phosphate, PTH at least) to diagnose/eliminate a « calcium/phosphate » disease

i.e. patients with
- rickets/osteomalacia
  - osteoporosis
- renal stone, nephrocalcinosis
  - chondrocalcinosis
- symptoms of either hypo- or hypercalcemia (without explanation)
Mrs B. 66 yrs
Low-trauma vertebral fracture (T11)
BMD : -3.2 T-score lumbar spine;
  -3.0 T-score Total hip

Calcemia : 2.49 mmol/L (2.20-2.60)
Phosphatemia : 1.01 mmol/L (0.80-1.40)
  25OHD : 17 nmol/L (75-150)
  PTH : 112 pg/mL (10-46)

eGFR (MDRD) : 71 mL/mn/1.73 m²
  Calcium intake : 765 mg/day
Conclusion

Although many persons/patients do not need to have their 25OHD measured, there are still groups of patients who may benefit from this measure.

This is my current opinion.

My list of patients in whom I propose to measure 25OHD may change with new published data (in particular RCTs showing beneficial – or deleterious – non classical clinical effects of vitamin D)
Thank you for attention