The Hellenic Endocrine Society Guidelines for the diagnosis and treatment of Vitamin D deficiency

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The Vitamin D team

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2/2017: A brief outline of the problem and a short list of practical guidelines (3 pages) was proposed to the Hellenic Endocrine Society.

11/2017 The Society has approved the idea but decided to expand both the team and the effort to produce a more extensive and valid brochure summarizing the available evidence and adopting other Societies’ suggestions!

Lots of discussions and arguments to arrive to a conclusion that would accommodate both positive attitudes and some ambiguity mostly on extraskeletal outcomes.

The problem

- Greece is part of the “Mediterranean Paradox” as realized by a growing number of clinical studies in several populations.

- 25(OH)D as an index of vitamin D deficiency has several flows.

- There is a lack of a standardized method of measurement.

- Limited clinical studies mostly observational or cross sectional.

- Lack of supplementation studies on extraskeletal outcomes.
HypoVitaminosis D

- **Sufficient Vitamin D**
  - Serum 25(OH)D >30 ng/ml

- **Vitamin D Insufficiency**
  - Serum 25(OH)D 21-29 ng/ml

- **Vitamin D Deficiency**
  - Serum 25(OH)D < 20 ng/ml (<50nmol/L)
  - Mild (10-20ng/ml), severe (<10ng/ml)
<table>
<thead>
<tr>
<th>Vitamin D status (ng/ml)</th>
<th>IOM, WHO, EFSA</th>
<th>The Endocrine Society (USA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe deficiency</td>
<td>&lt; 10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Deficiency</td>
<td>&lt; 10</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>10-20</td>
<td>20-30</td>
</tr>
<tr>
<td>Sufficiency</td>
<td>20-40</td>
<td>30-50</td>
</tr>
<tr>
<td>Toxicity</td>
<td>≥100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
Optimal Level to Prevent Disease?

In a physiological point of view, if 25(OH)D availability falls below cell- or tissue-specific critical concentrations, the cell or tissue enters into vitamin D deficiency state with its local metabolic consequences while the serum 25(OH)D could be still within the ‘so-called’ normal range.

- 30-50 ng/ml?????
- Target higher end????
Vitamin D: minimum, maximum, optimum

The Maasai warriors who live in outdoor most of the time, have an average of 25(OH)D concentrations of approximately 50 ng/mL (125 nmol/L), and appear to be in good health.
Vitamin-D UV dose (kJ/m²)

SCIAMACHY - KNMI/ESA

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Clear-sky
21 June 2007
Known Fact...

• People with darker skin such as African Americans or Hispanics have much lower Vit D levels than those with lighter skin

• Elderly have thinner skin, less 7-Dehydrocholesterol
Likely Benefits of Vit D Supplementation

- Prevention and treatment of bone disease
  - Osteopenia, osteoporosis
  - Hip fracture, nonvertebral fractures
  - > 65 yrs, 800-2000 IU/day (indefinitely)

- Fall Prevention
  - 22% reduction (improved muscle function)
  - > 65 yrs, 800-4000 IU/day (indefinitely)
Tissue VDR localisation

**Immune System**
- T and B cells
- macrophages
- neutrophils

**Cardiovascular**
- endothelium
- smooth muscle cells
- myocardium

**Endocrine**
- parathyroids
- β cell pancreas
- thyroid

**Other Tissues**
- exocrine
- neural
- reproductive

**Kidney**
- podocytes
- mesangial cells
- glomerulli

**Musculoskeletal**
- osteoblasts
- osteocytes
- muscle cells

**Other Systems**
- epidermis
- liver
- gastrointestinal
- respiratory

**Connective tissue**
- fibroblasts
- interstitial cells
Factors Contributing to Low Vitamin D Levels in Diabetes

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary intake</td>
<td>Limited intake of foods high in vitamin D</td>
</tr>
<tr>
<td>Sun Exposure</td>
<td>Lack of outdoor physical activity due to possible fatigue, obesity, and or mobility issues</td>
</tr>
<tr>
<td>Obesity</td>
<td>More vitamin D is stored in the fatty tissues and less is biologically active in the serum</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>Less biologically active vitamin D since conversion to the active form occurs in the kidneys</td>
</tr>
<tr>
<td>Genetic variations</td>
<td>Polymorphisms of vitamin D binding protein Polymorphisms of CYP2R1 gene (which is necessary to catalyze the formation of the main circulating vitamin D metabolite)</td>
</tr>
</tbody>
</table>

*Obesity is associated with inflammation, but low levels of vitamin D are also associated with inflammation. Cytokines and other inflammatory agents have been linked to beta cell damage which then impairs insulin synthesis and secretion.

Penckofer et al. 2008
Unproven Benefits of Vit D Supplementation: Prevention/Treatment

- Cardiovascular disease - hypertension, heart failure
- Endocrine disorders - diabetes, glycemia
- Respiratory Diseases - asthma, COPD
- Infectious Diseases - tuberculosis, URI
- Cancer
- Neurologic diseases
  - Multiple sclerosis, depression, dementia/Alz
Not enough evidence to consider Screening

- Major depression syndrome
- Cardiovascular disease
- Chronic fatigue syndrome
- Diabetes Mellitus
Most studies support vitamin D action

However there have been neutral studies

Again there is need for carefully designed interventional studies!!!!!
So how do we select patients to measure vitD??

- We don’t, we test them all!!!
- We do not test, we just supplement everybody!!!
- We establish risk scores and high risk groups!
Who is at risk ......

- Osteoporosis, Complaints of non-specific musculoskeletal pain
- Hx of inadequate dietary intake of Vitamin D
- Indoors: Homebound/institutionalized, inadequate sun exposure
- Hx of renal or hepatic disease, malabsorption syndromes, bariatric surgery, hyperparathyroidism
- Chronically ill, elderly
- Post-menopausal or pregnant/lactating
- Obese children and adults, granulomatous disease, lymphoma
Consider Screening

Chronic Drug use:

- Anti Epileptic Drug use especially Dilantin and Phenobarb
- Corticosteroids
- Azole antifungals
- Antiretrovirals

These drugs cause catabolism of 25(OH)D and 1,25(OH)2D
Uncertainties.....

- Study design
- Relation between 25(OH)D----1,25 (OH)2D ----- PTH ------???
- Relation between 25(OH)D and other confounders (BMI, exercise)
- Genetic factors (SNPs DBP)
- Tissue 1,25(OH)2D production as opposed to blood concentrations!!
Supplementation
**Terminology-Available supplements**

- **Vitamin D** (Calciferol), **Vitamin D₃** (Cholecalciferol) **Vitamin D₂** (Ergocalciferol)

- **25-hydroxy vitamin D₃**, Calcifediol, 25(OH)- cholecalciferol, 25(OH)Vitamin D₃, Calcidiol, Calciol.

- **25-hydroxy vitamin D₂**, Ercolciol, 25(OH)- ergocalciferol, 25(OH)Vitamin D₂

- **Alfacalcidiol**, 1α-hydroxy vitamin D₃, 1α(OH)Vitamin D₃

- **Calcitriol**, 1,25-dihydroxy vitamin D₃, 1,25-(OH)₂vitamin D₃

- 10μg (micrograms) vitamin D = 400 IU vitamin D

- 2.5 nmol/L serum 25OHD = 1 ng/mL serum25OHD
Treatment Regimens

Consider an initial loading dose over 6-8 weeks and continue with supplementation depending on the amount ingested or synthesized through UV

OR

Start with a daily dose (increased up to 4000 IU) for 8-12 weeks and continue with supplementation depending on the amount ingested or synthesized through UV
<table>
<thead>
<tr>
<th>Scientific Association</th>
<th>Recommended Dietary Allowance D (IU per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 20 yrs</td>
</tr>
<tr>
<td>Recent Guidelines</td>
<td></td>
</tr>
<tr>
<td>Institut Of Medicine / USA (2010)</td>
<td>600</td>
</tr>
<tr>
<td>Australia-New Zealand (2013)</td>
<td>600</td>
</tr>
<tr>
<td>Deutschland (Germany) (2012)</td>
<td>800</td>
</tr>
<tr>
<td>Nordic countries (2012)</td>
<td>400</td>
</tr>
<tr>
<td>UK (Scientific Advisory Committee on Nutrition) (2016)</td>
<td>400</td>
</tr>
<tr>
<td>Netherlands (2012)</td>
<td>400</td>
</tr>
<tr>
<td>Belgium (2009)</td>
<td>400</td>
</tr>
<tr>
<td>France (Société Française de Nutrition) (2012)</td>
<td>200</td>
</tr>
<tr>
<td>European Food Safety Authority (draft version) (2016)</td>
<td>600</td>
</tr>
</tbody>
</table>
Rescreen?

- Consider rescreening in no less than 3 months and then annually when on maintenance dose (best time end of winter)

- Re-test high-risk individuals every 5 years if not on supplementation
Is 25(OH)D the best marker of vitamin D status?

- The best available marker

- Genetic variations (VDBP, CYP24A1) may affect the active vitamin D availability and cannot be diagnosed

- Epimers

- Method of measurement?
  - Competitive protein binding assay, CPBA
  - competitive immunoassays
  - high-performance liquid chromatography- HPLC
  - LC–MS/MS

- Free vs Total?
The role of parathyroid hormone and vitamin D in the metabolism of calcium. 1,25(OH)2D3, 1,25 dihydroxyvitamin D3; P-, phosphate; PTH, parathyroid hormone. (Modified from Boon NA, Colledge NR, Walker BR, Hunter JAA [eds]: Davidson's Principles & Practice of Medicine, 20th ed. Edinburgh, Churchill Livingstone, 2006, p. 772.)
What are the optimal 25-(OH)-D levels?

Defficiency: <10 ng/mL
Insufficiency: ≥10 and <20 ng/mL
Partial Insufficiency: ≥20 to <30 ng/mL
Adequate levels ≥30 ng/mL?????
Toxic levels>100 ng/mL???

Most adults will eventually need vitamin D supplements due to insufficient sun exposure and dietary habits that do not support 25-(OH)-D level ≥30 ng/mL all year through

800 IU/day vitD₃ seems to be adequate to support ADEQUATE levels
Adequate levels are???