Lack of Standardization: Clinical Impact

Nov 14, 2013

Neil Binkley, M.D.
University of Wisconsin School of Medicine and Public Health
Madison, WI, USA
Disclosures: None

Note: Orange Font = My Opinion
The Clinical Impact = Confusion

Vitamin D prevents heart disease
Can Vitamin D Replace Flu Shots?

Vitamin D increases skin cancer risk
New Study Warns Against Excessive Vitamin D Intake

<table>
<thead>
<tr>
<th>Component</th>
<th>Result</th>
<th>Flag</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D3, 25-Hydroxy</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D2, 25-Hydroxy</td>
<td>&lt;5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D, 25-Hydroxy</td>
<td>28</td>
<td>L</td>
<td>30 - 80</td>
</tr>
</tbody>
</table>

Comment
Vitamin D status in a patient is judged by Total 25-OH Vitamin D.
Total 25-OH Vitamin D clinical reference values:
- < 10 ng/mL Severe deficiency
- 10-29 ng/mL Mild to moderate deficiency
- 30-50 ng/mL Optimum levels
- > 50 ng/mL Toxicity possible
The Clinical Impact = Confusion
The IOM report …makes a positive contribution by grounding its recommendations on the available evidence base…. (we are) generally in agreement with these conclusions.”

"The IOM recommendations for vitamin D fail in a major way on logic, on science and on effective public health guidance….our recommendation to the American public is that the IOM report should be taken with a grain of salt…”

Reid IR & Avenell A, JBMR, 26;452-454, 2011

Ross, et. al., J Clin Endocrinol Metab, 96; 53-58, 2011

Heaney RP & Holick MF, JBMR, 26;455-457, 2011
Respected Groups Have Differing Daily Intake Recommendations

- Nutrient Reference Values for Australia and New Zealand: 200-600 IU
- CPME (Comité Permanent des Médecins Européens): 600-800 IU
- Food and Nutrition Board: 600-800 IU
- International Osteoporosis Foundation: 800-1,000 IU
- The Endocrine Society: 1,500-2,000 IU
Respected Groups Have Recommendations That Directly Conflict

- The USPSTF recommends exercise or physical therapy and vitamin D supplementation to prevent falls in community-dwelling adults aged 65 years or older who are at increased risk for falls.
- The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D<sub>3</sub> and 1,000 mg or less of calcium for the primary prevention of fractures in non-institutionalized postmenopausal women.

http://www.uspreventiveservicestaskforce.org/uspstf/uspsfalls.htm
http://www.uspreventiveservicestaskforce.org/uspstf/uspsvitd.htm
How Can Patients and Clinicians NOT be Confused?
What’s a Clinician to Do?
Recognize That Diagnostic Cutpoints Are Used in Clinical Care, but Human Physiology is Rarely Black and White

Consider Osteoporosis….

65 yo female, BMI 25 with no other clinical risk factors

- T-score = -2.4: Dx = Osteopenia, 10 yr Fx risk = 13%
- T-score = -2.6: Dx = Osteoporosis, 10 yr Fx risk = 14%

A 25(OH)D of 29 ng/mL is Not Different than 31 ng/mL
Remember the Obvious: We Are Not All The Same....
We Are Not All The Same.....
Dramatic Differences in 25(OH)D Response to Oral Vitamin D

Postmenopausal women receiving cholecalciferol 2300-2500 IU daily for 4-6 months

Unpublished data; Binkley, et al.
Recognize Assay Variability and Ask...
25(OH)D is Being Measured in a Sea of Other Vitamin D Metabolites

It is not surprising that “25(OH)D” assays measure some of these other metabolites.

Known examples include 3-epi 25(OH)D and 24, 25(OH)_2D.
One Confounder is 3-Epi-25(OH)D

- Given the identical structure (and therefore identical MW) seems likely that epimers of 25(OH)D might lead to higher 25(OH)D values
  - Reports exist that the C-3 epimer may confound 25(OH)D measurement by some liquid chromatography-tandem mass spectrometry methods
- Historically felt to occur only in infants
  - Present at generally low levels in virtually all human sera
- Source, and physiologic importance (if any) remain to be clarified
Another Confounder is 24, 25(OH)$_2$D$_3$

- Often considered to be simply an inactivating step of 25(OH)D; i.e., a degradation product ultimately leading to calcitroic acid
  - Not surprising that some have found no rationale for 24, 25(OH)$_2$D$_3$ measurement
- Some work finds 24, 25(OH)$_2$D$_3$ to possess physiologic effects on cartilage and bone
  - 24, 25(OH)$_2$D$_3$ supplementation reduces PTH in humans with X-linked hypophosphatemic rickets
Despite Standardization Efforts; 25(OH)D Variability Persists
Mean 25(OH)D Values for Various Methods

Data from DEQAS April 2013 distribution
Example of Potential Effect of Confounders on Total 25(OH)D Measurement

It is my bias that we need to standardize measurement of at least 25(OH)D, 3-epi 25(OH)D and 24, 25(OH)\(_2\)D AND understand the physiologic role(s) if any.
Yet Another Confounder May be The Presence of Metabolites of Both Ergocalciferol and Cholecalciferol

Cholecalciferol (Vitamin D₃)

Ergocalciferol (Vitamin D₂)

Differ only in side chain structure (C22-23 double bond and C24 methyl group)
Vitamin D$_2$ and D$_3$ Appear to be Equally Effective in Treating Rickets

“More than forty studies have been made in order to determine whether the two forms of vitamin D are equally effective....”

“Only generalizations of an uncertain nature can be drawn from the conflicting and confusing data obtained. For practical purposes the vitamin D in viosterol may be regarded as being equal to the vitamin D of cod liver oil.”
Progress in 25(OH)D measurement has been made

Well-organized international standardization efforts are in place and moving forward

Issues persist regarding potential confounders and other analytes including, but potentially not limited to:

- 3-epi 25(OH)D
- 24, 25 (OH)\(_2\)D
- Need to measure both D\(_2\) and D\(_3\) metabolites
- D binding protein
- Free/bioavailable 25(OH)D
- Etc, etc……
Is Vitamin D Status Assessment Where Lipid Measurement Was Many Years Ago??

ANGINA PECTORIS IN HEREDITARY XANTHOMATOSIS

CARL MÜLLER, M.D.

Arch Intern Med. 1939;64(4):675-700.

The Role of Lipids and Lipoproteins in Atherosclerosis

John W. Gofman, Frank Lindgren, Harold Elliott, William Mantz, John Hewitt, Beverly Strisower, and Virgil Herring

Gofman, J, et. al., Science, 111: 166-171, 1950
The “What Are We Measuring?” Question Substantially Flaws Systematic Reviews/Meta-Analyses

Additionally, but Importantly…..
Need to Link Outcome to Blood Level Achieved

“An identical nutrient intake (i.e., prescribed dose) may or may not produce a measurable response.”

Heaney, RP, NEJM, 2012, 367, 77-78

Until we link outcomes to blood levels achieved, and understand what analytes to measure, meta-analyses will not answer the “how much is enough” question.
We Can’t Meta-Analyze Our Way Out of This, But Need to Care for Patients Today…

What Do I Do Clinically??
“I suggest that the 25(OH)D levels in the lifeguards are normal.”

Hollis, J Nutr, 135:317-325, 2005

IF we use highly sun exposed people to define a goal 25(OH)D concentration what is our target?
“We studied two traditional tribes. Both live 2-4° south of the equator in Tanzania, have skin type VI and neither uses sunscreen.”

“Maasi spend most of their days in the sun wearing clothes that cover mainly their upper body and upper legs. Whenever possible they avoid direct exposure to the sun and prefer a shady place…”

Hadzabe are traditional hunter-gatherers. They live in small bands of 10-30 in arid bush lands. They have no personal belongings… shelters are only used during the rain or night. Similar to the Maasai, they avoid direct exposure to the sun whenever possible… spending the middle part of the day sleeping, eating or talking in a cooler place under a tree or rock.”

“Never go to excess, but let moderation be your guide.”

Marcus Cicero
(Roman philosopher and Statesman; 106-43 BC)
Whether You Wish to Aim for 20 ng/mL or 30 ng/mL, Clinical Judgment Needs to Consider Assay Variability
What’s a Clinician to Do? Aim High!

To Maintain Serum 25(OH)D of $\geq 20$ ng/mL or $\geq 30$ ng/mL

<table>
<thead>
<tr>
<th>Measured</th>
<th>“True” Value</th>
<th>Maintain</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D</td>
<td>20 ng/mL</td>
<td>$\sim 10$ to $\sim 35$ ng/mL</td>
<td>$\sim 35$ ng/mL</td>
</tr>
<tr>
<td>25(OH)D</td>
<td>30 ng/mL</td>
<td>$\sim 15$ to $\sim 45$ ng/mL</td>
<td>$\sim 45$ ng/mL</td>
</tr>
</tbody>
</table>

Recognize that the reported value may be low: with this approach, the maximum is likely to be $\sim 50$ to $\sim 60$ ng/mL, below that attainable by UV exposure.
If I Were King…

- Acknowledge That We Don’t Know the “Right” Answer
- Target ≥ 30 ng/mL (Aim High)
The current guideline fails in both respects and therefore is in need of reexamination.
Require Laboratory Traceability of 25(OH)D Measurements to the NIST Standards
Demand Additional Research to Define Which Vitamin D Metabolites Have Physiologic Effect(s) and How Best to Evaluate Vitamin D Status in a Given Individual
Vitamin D inadequacy (however defined) is common
  - Fixing this is cheap and virtually side effect free

Little need to utilize D$_2$ (ergocalciferol); this unnecessarily confounds assay methodologies

Ancestral human 25(OH)D mean is ~ 40 ng/mL

Recognize that our current “25(OH)D” measurements are imperfect, standardization is needed and that improved knowledge and perhaps “D assay panels” are coming
  - Much more work is needed

“We know an insufficient amount about vitamin D insufficiency.”

M. Drezner, M.D., ASBMR 2006
Thank You