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Review

Developing vitamin D dietary guidelines and the lack of 25-hydroxyvitamin D assay standardization: The ever-present past

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ABSTRACT

Unstandardized laboratory measurement of 25-hydroxyvitamin D (25(OH)D) confounds efforts to develop clinical and public health vitamin D guidelines. The Vitamin D Standardization Program (VDSP), an international collaborative effort, was founded in 2010 to correct this problem. Nearly all published vitamin D research is based on unstandardized laboratory 25(OH)D measurements. While it is impossible to standardize all old data, it may be possible to identify a small subset of prior studies critical to guidelines development. Once identified it may be possible to calibrate their 25(OH)D values to the NIST and Ghent University reference measurement procedures using VDSP methods thereby permitting future guidelines to be based on standardized results. We simulated the calibration of a small set of ten clinical trials of vitamin D supplementation on achieved 25(OH)D under minimal sun exposure. These studies were selected because they played a prominent role in setting the 2010 vitamin D dietary reference intakes (DRI). Using random-effects meta-regression analysis, Vitamin D External Quality Assessment (DEQAS) data on assay bias was used to simulate the potential bias due to the lack of assay standardization by calibrating the achieved 25(OH)D levels from those 10 studies to: (1) the largest negative, and (2) the largest positive bias from the DEQAS all laboratory trimmed mean (ALTM) for the appropriate assay and year of analysis. For a usual vitamin D intake of 600 IU/day the difference in mean achieved 25(OH)D values for those two options was 20 nmol/L. However, without re-calibration of 25 (OH)D values it is impossible to know the degree to which any of the current guidelines may have been biased. This approach may help stimulate the search for and standardization of that small subset of key studies and, in the cases where standardization is impossible, to identify areas of urgently needed vitamin D research.

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Abbreviations: 25(OH)D, 25-Hydroxyvitamn D; VDSP, Vitamin D Standardization Program; RMP, reference measurement procedure; IOM, Institute of Medicine; DRI, dietary reference intakes; DEQAS, Danish External Quality Assessment Scheme; NIST, National Institute of Standards and Technology; CLBA, competitive ligand binding assay; CDC, Centers for Disease Control; NIH, National Institutes of Health; PT/EQA, proficiency testing/external quality assurance; CAP, College of American Pathologists; ALTM, all laboratory trimmed mean.

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1. Introduction

Lack of vitamin D assay standardization continues to thwart efforts to develop consensus on clinical and public health guidelines that define optimal vitamin D status [1,2]. Currently, following introduction of the Vitamin D Standardization Program (VDSP) [3,4] in 2010, progress is being made in standardizing both commercially- and laboratory-developed 25-hydroxyvitamin D (25(OH)D) assays to the NIST and Ghent University reference measurement procedures [5–7]. However, the decades-long period prior to development of a reference measurement procedure (RMP) has left a large amount of unstandardized (25(OH)D) research data which is the only source of data that can be used in developing vitamin D guidelines. For example, in developing the 2010 Institute of Medicine (IOM) Calcium and Vitamin D Dietary Reference Intakes (DRI), a small set of ten clinical trials evaluating the impact of supplemented vitamin D_3 on achieved 25(OH)D concentration under minimal sun exposure played a prominent role in setting the vitamin D DRI [8]. Although the DRI Committee [8] acknowledged the 25(OH)D assay limitations, published data were not available to quantify the effect that assay differences in the ten contributing studies might have had on the outcome of their deliberations. Therefore, the default inference was that the guidelines were universally applicable, irrespective of the bias and performance of the 25(OH)D assays used in the clinical setting or in monitoring current levels and trends through national health surveys, e.g., the US National Health and Nutrition Examination Surveys (NHANES).

Although it was not possible for the IOM Committee at that time to assess accuracy and performance of the 25(OH)D assays used in each of the ten studies, past data from proficiency testing schemes might offer insight into the general performance of the assays used in these prior studies. Accordingly, we have used data from the vitamin D External Quality Assessment Scheme (DEQAS) to demonstrate the potential impact that lack of 25(OH)D standardization may have had on predicting the achieved 25(OH)D concentrations in the ten published studies used for setting the DRI. Furthermore, it is our contention that among the thousands of vitamin D research papers that have been published there exists a small subset of past studies which, if identified and standardized may allow use of these prior data to develop clinical and public health guidelines based on standardized 25(OH)D concentrations. The hope is that our suggested approach will help stimulate the search for and standardization of that small subset of key studies and in the cases where standardization of old data is now impossible to identify areas of urgently needed vitamin D research.

Table 1
Study characteristics of randomized control trials conducted at latitude > 49.5° N and Antarctica. Used in IOM DRI Report, Fig. 5-4 (p. 384). A hypothetical re-analysis of Fig. 5-4: IOM Vitamin D and Calcium DRI Report, 2010 [8].

Study no.	Source	Country	Latitude	Total vitamin D	Baseline 25(OH)D		Achieved 25(OH)D	
				Intake (IU/D)	Mean	SD	Mean	SD
1	Ala-Houhala	Finland	61	600	49.3	19	71.3	23.8
	Ala-Houhala	Finland	61	200	46	15.5	43.3	19.5
2	Cashman	Ireland	51–55	792	55.1	22.8	73.8	20
	Cashman	Ireland	51–55	568	54.3	21.8	69.5	17
	Cashman	Ireland	51–55	364	51.8	22.1	53.2	17
	Cashman	Ireland	51–55	188	58.8	25.9	58.8	17.1
3	Cashman	Ireland	51–55	744	75.9	24.8	69	18.6
	Cashman	Ireland	51–55	540	72.2	26.8	60	13.4
	Cashman	Ireland	51–55	372	60	29.4	49.7	11.4
	Cashman	Ireland	51–55	136	65.7	26.5	37.4	12.2
4	Larsen	Denmark	56	136	33	19	34	19
	Larsen	Denmark	56	536	37	19	46	17
5	Schou	Denmark	55	96			33.7	3.3
	Schou	Denmark	55	96			32.3	4.1
	Schou	Denmark	55	696			50.2	4.5
	Schou	Denmark	55	696			43.4	2.9
6	Smith	Antarctica	78	2305	45	14	71	23
	Smith	Antarctica	78	1342	44	19	63	25
	Smith	Antarctica	78	659	44	18	57	15
7	Van Der Klis	Netherlands	53.2	64	61.2	2.4	61.2	2.4
	Van Der Klis	Netherlands	53.2	464	61.2	2.4	87.9	26.9
	Van Der Klis	Netherlands	53.2	864	61.2	2.4	87.9	26.9
8	Viljakainen	Finland	61	200	47.8	18.2	42.8	18.2
	Viljakainen	Finland	61	388	46.3	17.4	51.7	17.4
	Viljakainen	Finland	61	596	46.7	16.2	58.8	15.2
9	Viljakainen	Finland	61	1104	62.3	13.6	90.1	13.6
	Viljakainen	Finland	61	716	60.3	11.6	75.4	11.6
	Viljakainen	Finland	61	264	64.7	18.5	52.2	18.5
10	Viljakainen	Finland	61	1188	44.1	13.5	67.8	13.5
	Viljakainen	Finland	61	824	46.5	10.2	60.9	10.2
	Viljakainen	Finland	61	588	46	14.3	56.9	14.3
	Viljakainen	Finland	61	436	52.2	19.9	43.9	19.9

Studies conducted under those conditions to rule out vitamin D produced in skin from ultraviolet light.