KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Vitamin D Imbalance - Part Three

All of that in mind, let's look at a few case studies. A couple of notes. First, my understanding of vitamin D metabolism, deficiency, and toxicity has evolved a lot over the years and continues to. It's only very recently that I've started to include PTH and 1,25(OH)2D in my lab workup, so I don't have a lot of examples of this. Also, it's only recently that we've begun to understand the ethnic and genetic variations in the conversion of calcidiol to calcitriol, so I don't have examples of specific cases there. However, after looking at a few cases, I will propose an algorithm for diagnosing and treatment vitamin D deficiency and toxicity.

Marker	Value	Functional Range	Lab Range
Glucose	87	75 - 90	65 - 99
Hemoglobin A1c	5.8	4.8 – 5.4	4.8 - 5.6
Uric Acid	4.4	3.2 - 5.5	2.5 - 7.1
BUN	12	13 – 18	6 - 24
Creatinine	0.92	0.85 – 1.1	0.57 - 1
BUN/Creatinine Ratio	13	9 – 23	9 - 23
Sodium	141	134 – 140	134 - 144
Potassium	4.5	4.0 – 4.5	3.5 - 5.2
Chloride	102	100 – 106	97 - 108
C02	23	25 – 30	18 - 29
Calcium	9.5	9.2 – 10.1	8.7 - 10.2
Phosphorus	4.2	3.5 – 4.0	2.5 - 4.5
Magnesium	2.3	2.0 – 2.6	1.6 - 2.3
Protein, total	6.9	6.9 – 7.4	6.0 - 8.5
Albumin	4.3	4.0 – 5.0	3.5 - 5.5
Globulin	2.6	2.4 – 2.8	1.5 - 4.5
A/G ratio	1.7	1.5 – 2.0	1.1 - 2.5
Bilirubin, total	0.6	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	57	42 – 107	39 - 117
LDH	142	140 - 180	119 - 226
AST	15	10 - 30	0 - 40
ALT	11	10 - 22	0 - 32
GGT	15	0 - 28	0 - 60
TIBC	351	250 – 350	250 - 450
UIBC	194	150 - 375	131 - 425
Iron	157	85 – 135	27 - 159
Iron saturation	45	15 – 45	15 - 55
Ferritin	28	15 - 120	15 - 150
Vitamin B-12	222	450 – 2000	211 - 946
Vitamin D, 25-hydroxy	9.7	35 - 60	30.0 - 100.0
Cholesterol, total	157	150 - 250	100 - 199
Triglycerides	59	50 – 100	0 - 149
HDL	54	55 – 85	> 39
LDL	91	0 - 175	0 - 99
T. Chol / HDL Ratio	2.9	< 3	0 - 4.4
Triglycerides / HDL Ratio	1.09	< 2	< 3.8
CRP-hs	0.09	< 1.0	0.00 - 3.00
Homocysteine	18.2	< 7.0	0.0 - 15.0

Marker	Value	Functional Range	Lab Range
TSH	1.790	0.5 – 2.5	0.45 - 4.50
T4, total	6.8	6.0 – 12	4.5 - 12
T3 Uptake	26	28 - 35	24 - 39
T3, Total	104	100 – 180	71 - 180
Copper	92		72 - 166
Zinc	65		56 - 134
Zinc / Copper Ratio	0.71	> 0.85	
Serum Methylmalonic Acid (MMA)	645	0 - 325	0 - 378
WBC	3.6	5.0 – 8.0	3.4 - 10.8
RBC	4.44	4.4 – 4.9	3.77 - 5.28
Hemoglobin	12.5	13.5 - 14.5	11.1 - 15.9
Hematocrit	38.5	37 - 44	34 - 46.6
MCV	87	85 – 92	79 - 97
MCH	28.2	27.7 – 32.0	26.6 - 33.0
MCHC	32.5	32 – 35	31.5 - 35.7
RDW	14.2	11.5 – 15.0	12.3 - 15.4
Platelets	261	150 – 415	150 - 379
Neutrophils	49	40 – 60	
Lymphocytes	34	25 – 40	
Monocytes	9	4.0 – 7.0	
Eosinophils	7	0.0 – 3.0	
Basophils	1	0.0 – 3.0	

Let's start with a really straightforward, easy case. This is a vitamin D 25(OH)D level of 9.7, which is one of the lowest I've seen. I believe 7 is the record for me. There is really no need to test for parathyroid hormone or calcitriol levels here. This is just plain-old, frank vitamin D deficiency. It's a 41-year-old female from India with dark skin who used sunscreen every time she stepped out the door. She was also a vegetarian, so she had very low vitamin D intake and didn't take vitamin D supplements, so this is someone who you could feel very comfortable giving a prescription for vitamin D supplementation and increased sun exposure.

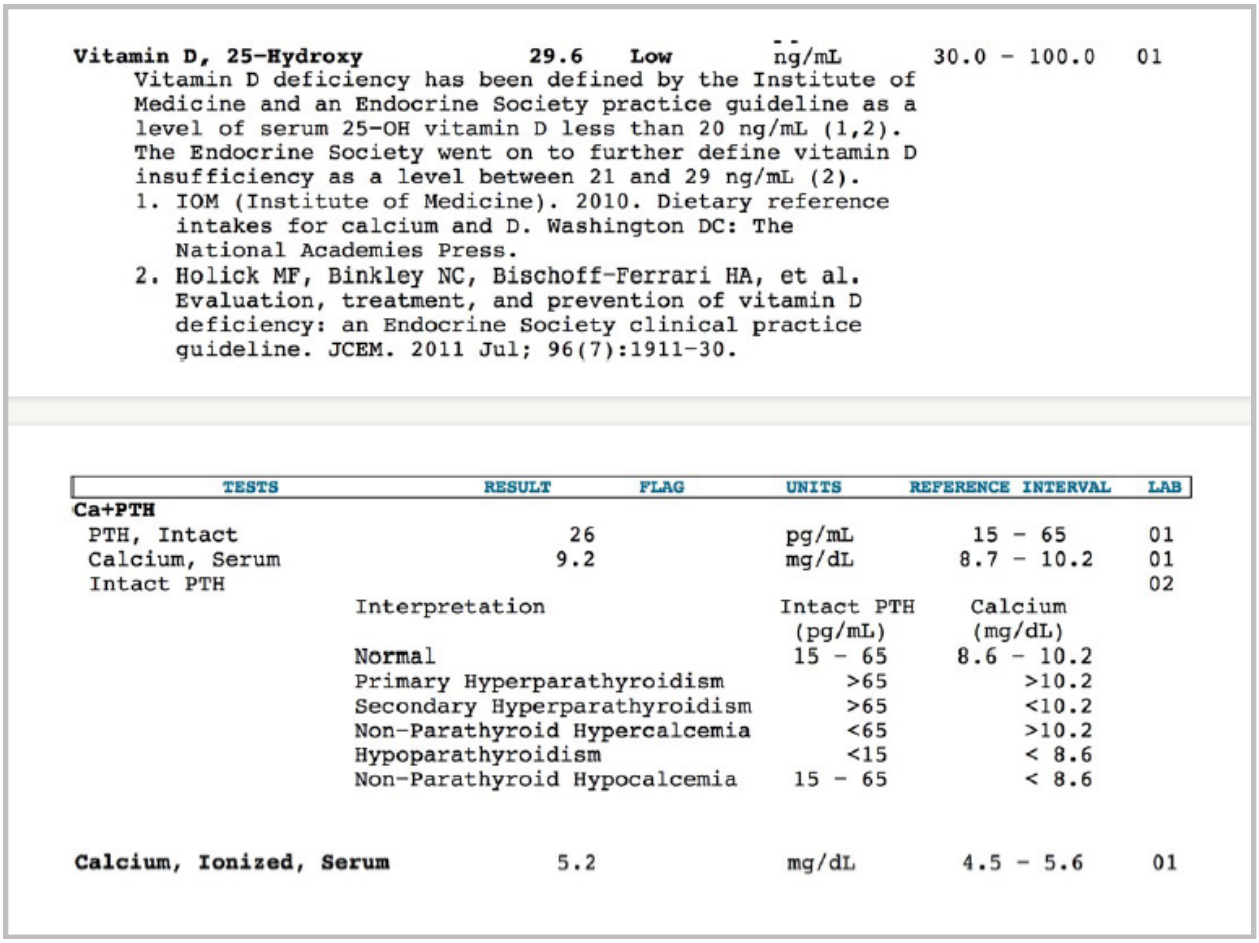
TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Vitamin D, 25-Hydroxy	**16.6**	**Low**	ng/mL	30.0 - 100.0	01

Vitamin D deficiency has been defined by the Institute of Medicine and an Endocrine Society practice guideline as a level of serum 25-OH vitamin D less than 20 ng/mL (1,2). The Endocrine Society went on to further define vitamin D insufficiency as a level between 21 and 29 ng/mL (2).

1. IOM (Institute of Medicine). 2010. Dietary reference intakes for calcium and D. Washington DC: The National Academies Press.
2. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. JCEM. 2011 Jul; 96(7):1911-30.

PTH, Intact	**68**	**High**	pg/mL	15 - 65	01

This is a 45-year-old female patient of Asian descent. Her 25(OH)D is 16.6. Again, this is deficient by pretty much any standard, including the Institute of Medicine, so it's probably unnecessary to run PTH, but I did it anyway as just a learning experience. As you can see, PTH is well above the cutoff of 30 that I suggested earlier, and it is, in fact, out of the lab range at 68, so this confirms biological vitamin D deficiency.



Vitamin D, 25-Hydroxy 29.6 Low -- ng/mL 30.0 - 100.0 01

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TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Ca+PTH					
PTH, Intact	26		pg/mL	15 - 65	01
Calcium, Serum	9.2		mg/dL	8.7 - 10.2	01
Intact PTH					02

Interpretation	Intact PTH (pg/mL)	Calcium (mg/dL)
Normal	15 - 65	8.6 - 10.2
Primary Hyperparathyroidism	>65	>10.2
Secondary Hyperparathyroidism	>65	<10.2
Non-Parathyroid Hypercalcemia	<65	>10.2
Hypoparathyroidism	<15	< 8.6
Non-Parathyroid Hypocalcemia	15 - 65	< 8.6

Calcium, Ionized, Serum	5.2		mg/dL	4.5 - 5.6	01

Here is a 46-year-old black female. 25(OH)D is marked low according to the standard lab range at 29.6, although just barely. However, when we tested her parathyroid hormone, it was below 30. It was 26, which is optimal, and then we also tested her serum calcium and ionized calcium, and those were normal as well. Despite being flagged as having a low 25(OH)D level, supplementation for her is not necessary because PTH is optimally suppressed, and calcium levels are normal.

Marker	Value	Functional Range	Lab Range
Glucose	97	75 - 90	65 - 99
Hemoglobin A1c	5.4	4.4 – 5.4	4.8 - 5.6
Uric Acid	8.4	3.7 – 6.0	3.7 - 8.6
BUN	20	13 – 18	6 - 20
Creatinine	1.24	0.85 – 1.1	0.76 - 1.27
BUN/Creatinine Ratio	16	8 – 19	8 - 19
Sodium	145	135 – 140	134 - 144
Potassium	5.2	4.0 – 4.5	3.5 - 5.2
Chloride	101	100 – 106	97 - 108
C02	26	25 – 30	18 - 29
Calcium	10.6	9.2 – 10.1	8.7 - 10.2
Phosphorus	4.2	3.0 – 4.0	2.5 - 4.5
Magnesium	2.2	2.0 – 2.6	1.6 - 2.3
Protein, total	7.5	6.9 – 7.4	6.0 - 8.5
Albumin	5.1	4.0 – 5.0	3.5 - 5.5
Globulin	2.4	2.4 – 2.8	1.5 - 4.5
A/G ratio	2.1	1.5 – 2.0	1.1 - 2.5
Bilirubin, total	0.5	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	70	42 – 107	39 - 117
LDH	161	140 - 180	121 - 224
AST	30	10 - 25	0 - 40
ALT	25	10 - 26	0 - 44
GGT	14	5 - 29	0 - 65
TIBC	314	275 – 425	250 - 450
UIBC	185	175 - 350	150 - 375
Iron	129	40 – 135	40 - 155
Iron saturation	41	17 – 45	15 - 55
Ferritin	342	30 - 100	30 - 400
Vitamin B-12	802	450 – 2000	211 - 946
Vitamin D, 25-hydroxy	30.4	35 - 60	30.0 - 100.0
Cholesterol, total	217	150 - 240	100 - 199
Triglycerides	73	50 – 100	0 - 149
HDL	97	55 – 85	> 39
LDL	105	0 - 175	0 - 99
T. Chol / HDL Ratio	2.2	< 3	0 - 5.0
Triglycerides / HDL Ratio	0.75	< 2	< 3.8

Marker	Value	Functional Range	Lab Range
CRP-hs	1.08	< 1.0	0.00 - 3.00
Homocysteine	15.0	< 7.0	0.0 - 15.0
TSH	0.839	0.5 – 2.5	0.45 - 4.50
T4, total	10.1	6.0 – 12	4.5 - 12
T3 Uptake	26	30 - 38	24 - 39
T3, Total	123	100 – 180	71 - 180
Copper	90		72 - 166
Zinc	183		56 - 134
Zinc / Copper Ratio	2.03	> 0.85	
Serum Methylmalonic Acid (MMA)	162	< 300	0 - 378
WBC	5.9	5.0 – 8.0	3.4 - 10.8
RBC	5.23	4.4 – 4.9	4.14 - 5.8
Hemoglobin	16.1	14 - 15	12.6 - 17.7
Hematocrit	47.4	40 - 48	37.5 - 51.0
MCV	91	85 – 92	79 - 97
MCH	30.8	27.7 – 32.0	26.6 - 33.0
MCHC	34	32 – 35	31.5 - 35.7
RDW	12.9	11.5 – 15.0	12.3 - 15.4
Platelets	252	150 – 415	150 - 379
Neutrophils	49	40 – 60	
Lymphocytes	38	25 – 40	
Monocytes	8	4.0 – 7.0	
Eosinophils	4	0.0 – 3.0	
Basophils	1	0.0 – 3.0	

Next patient is a 31-year-old male. Chief complaint is digestive distress, fatigue, anxiety, poor concentration, and poor exercise tolerance. His vitamin D is almost below the lab range at 30.4. However, serum calcium is high at 10.6.

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Renal Panel (10)					
Glucose, Serum	78		mg/dL	65 - 99	01
BUN	10		mg/dL	6 - 20	01
Creatinine, Serum	0.95		mg/dL	0.76 - 1.27	01
eGFR If NonAfricn Am	107		mL/min/1.73	>59	
eGFR If Africn Am	124		mL/min/1.73	>59	
BUN/Creatinine Ratio	11			8 - 19	
Sodium, Serum	141		mmol/L	134 - 144	01
Potassium, Serum	4.6		mmol/L	3.5 - 5.2	01
Chloride, Serum	98		mmol/L	97 - 108	01
Carbon Dioxide, Total	23		mmol/L	18 - 29	01
Calcium, Serum	**10.3**	**High**	mg/dL	8.7 - 10.2	01
Verified by repeat analysis					
Phosphorus, Serum	4.2		mg/dL	2.5 - 4.5	01
Albumin, Serum	5.0		g/dL	3.5 - 5.5	01

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
PTH, Intact	16		pg/mL	15 - 65	01

Additional testing found that PTH was well below 30, so he is not suffering from biological vitamin D deficiency, and you definitely don't need to supplement here. Also, serum calcium was again

high, and this is another reason why it is probably not a good idea to supplement with vitamin D in this case. He was already supplementing with calcium because he thought it might be helpful for joint pain, and that was what was increasing his serum calcium levels.

Calcitriol(1,25 di-OH Vit D)	56.7		pg/mL	19.9 - 79.3	03
Vitamin D, 25-Hydroxy	**27.2**	**Low**	ng/mL	30.0 - 100.0	01

Vitamin D deficiency has been defined by the Institute of Medicine and an Endocrine Society practice guideline as a level of serum 25-OH vitamin D less than 20 ng/mL (1,2). The Endocrine Society went on to further define vitamin D insufficiency as a level between 21 and 29 ng/mL (2).

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Estradiol, Sensitive	12.7		pg/mL		03
	Female:				
	Follicular:			30.0 - 100.0	
	Luteal:			70.0 - 300.0	
	Postmenopausal:			< 15.0	

Verified by repeat analysis
This test was developed and its performance characteristics determined by LabCorp. It has not been cleared by the Food and Drug Administration.
Methodology: Liquid chromatography tandem mass spectrometry(LC/MS/MS)

PTH, Intact	48		pg/mL	15 - 65	01

Here is a 60-year-old Caucasian female with extreme fatigue, brain fog, neuropathic pain, and a history of Lyme. Her 25(OH)D is low. Her calcitriol, or 1,25(OH)2D is high-normal, and this might suggest vitamin D sufficiency if you used the measurement where you combine the two that I suggested before in the presentation. Look at PTH. It's well above 30, so that does confirm biological vitamin D deficiency, and this patient would definitely need either increased UV light exposure or supplementation and increased intake of foods that are rich in vitamin D.

Immunoassay					01
Vitamin D, 25-Hydroxy	**170.8**	**High**	ng/mL	30.0 - 100.0	01

Results verified by repeat testing
Vitamin D deficiency has been defined by the Institute of Medicine and an Endocrine Society practice guideline as a level of serum 25-OH vitamin D less than 20 ng/mL (1,2). The Endocrine Society went on to further define vitamin D insufficiency as a level between 21 and 29 ng/mL (2).

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This patient is a 47-year-old male supplementing with 20,000 IU of vitamin D for several months. His chief complaints were IBS, muscle soreness, decreased stamina, leg twitching and pain,

frequent urination and thirst, and all of those are in line with vitamin D toxicity symptoms. You can see his level is 171 ng/mL, so that's in the toxic range by anyone's account. This isn't common, but it's not that rare either. I probably see at least three to four people a year, if not more, with vitamin D levels well above 100 ng/mL.

Marker	Value	Functional Range	Lab Range
Glucose	90	75 - 90	65 - 99
Hemoglobin A1c	5.5	4.4 – 5.4	4.8 - 5.6
Uric Acid	6.4	3.2 - 5.5	2.5 - 7.1
BUN	12	13 – 18	6 - 24
Creatinine	1.13	0.7 – 1.0	0.57 - 1.00
BUN/Creatinine Ratio	11	9 – 23	9 - 23
Sodium	138	135 – 140	134 - 144
Potassium	4.8	4.0 – 4.5	3.5 - 5.2
Chloride	97	100 – 106	97 - 108
C02	24	25 – 30	18 - 29
Calcium	10.5	9.2 – 10.1	8.7 - 10.2
Phosphorus	3.4	3.0 – 4.0	2.5 - 4.5
Magnesium	1.7	2.0 – 2.6	1.6 - 2.6
Protein, total	6.9	6.9 – 7.4	6.0 - 8.5
Albumin	4.9	4.0 – 5.0	3.5 - 5.5
Globulin	2.0	2.4 – 2.8	1.5 - 4.5
A/G ratio	2.5	1.5 – 2.0	1.1 - 2.5
Bilirubin, total	0.4	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	65	42 – 107	39 - 117
LDH	136	140 - 180	119 - 226
AST	21	10 - 23	0 - 40
ALT	15	10 - 20	0 - 32
GGT	15	5 - 21	0 - 60
TIBC	304	275 – 425	250 - 450
UIBC	247	175 - 350	150 - 375
Iron	57	40 – 135	35 - 155
Iron saturation	19	17 – 45	15 - 55
Ferritin	42	30 - 100	15 - 150
Vitamin B-12	1786	450 – 2000	211 - 946
Vitamin D, 25-hydroxy	62.2	35 - 60	30.0 - 100.0
Cholesterol, total	147	150 - 250	100 - 199
Triglycerides	88	50 – 100	0 - 149
HDL	46	55 – 85	> 39
LDL	83	0 - 175	0 - 99
T. Chol / HDL Ratio	3.2	< 3	0 - 4.4
Triglycerides / HDL Ratio	1.91	< 2	< 3.8

Marker	Value	Functional Range	Lab Range
CRP-hs	0.38	< 1.0	0.00 - 3.00
Homocysteine	12.0	< 7.0	0.0 - 15.0
TSH	0.919	0.5 – 2.5	0.45 - 4.500
T4, total	8.4	6.0 – 12	4.5 - 12.0
T3 Uptake	27	28 - 35	24 - 39
T3, Total	84	100 – 180	71 - 180
WBC	6.0	5.0 – 8.0	3.4 - 10.8
RBC	4.44	4.4 – 4.9	3.77 - 5.28
Hemoglobin	13.2	13.5 - 14.5	11.1 - 15.9
Hematocrit	38.3	37 - 44	34 - 46.6
MCV	86	85 – 92	79 - 97
MCH	29.7	27.7 – 32.0	26.6 - 33.0
MCHC	34.5	32 – 35	31.5 - 35.7
RDW	13.1	11.5 – 15.0	12.3 - 15.4
Platelets	253	150 – 415	150 - 379
Neutrophils	58	40 – 60	
Lymphocytes	34	25 – 40	
Monocytes	7	4.0 – 7.0	
Eosinophils	1	0.0 – 3.0	
Basophils	0	0.0 – 3.0	

Here is a 56-year-old Caucasian female. Note that her 25(OH)D levels are borderline high at 62.2, and also note that her calcium level, serum calcium level, is out of the lab range, high at 10.5. When you see high 25(OH)D and high calcium in the absence of vitamin D or calcium supplementation, you need to check parathyroid hormone.

PTH AND IONIZED CALCIUM

PTH, INTACT AND CALCIUM

PTH INTACT		67 H	14-64 pg/mL

Interpretive Guide	Intact PTH	Calcium
Normal Parathyroid	Normal	Normal
Hypoparathyroidism	Low or Low Normal	Low
Hyperparathyroidism		
Primary	Normal or High	High
Secondary	High	Normal or Low
Tertiary	High	High
Non-Parathyroid Hypercalcemia	Low or Low Normal	High

CALCIUM		10.5 H	8.6-10.4 mg/dL
CALCIUM, IONIZED	5.5		4.8-5.6 mg/dL

We did that in this case, and she did have elevated parathyroid hormone levels at 67, which is out of the lab range. She had elevated serum calcium again at 10.5, and she had high-normal ionized calcium, which is thought to be a more accurate marker of calcium levels. This combination of markers would often be indicative of hyperparathyroidism. Note that 25(OH)D is not always out of the lab range in hyperparathyroidism, and, in fact, it can even be normal or low. In those cases,

25(OH)D deficiency or low levels of 25(OH)D can obscure hyperparathyroidism, which doesn't become evident until vitamin D is repleted through sun exposure or supplements. Elevated serum calcium is the most important indicator of hyperparathyroidism, and we'll talk a little bit more about that when we talk about calcium.

Given everything we have discussed in this presentation, I've set my functional reference range for vitamin D at 35 to 60 ng/mL. This will undoubtedly catch several people who have so-called low levels of 25(OH)D who are not biologically deficient, but we can use PTH to clarify these situations, and I'd rather err on the side of caution given the association of low 25(OH)D with so many diseases.

How do we advise our patients to keep their 25(OH)D levels in this range, and how do we treat patients with vitamin D deficiency to get their levels back here if they are low? Vitamin D can be obtained from three sources: food; ultraviolet light, either sunlight or UV lamps; and supplements. It's impossible to provide a single guideline for exposure to vitamin D that everyone can follow because there are individual differences, not only in how sunlight affects the production of vitamin D, but also in how vitamin D is absorbed from food and supplements and the rate at which the body stores of vitamin D are mobilized.

In this next section, I'll provide you with a simple, three-step plan for optimizing 25(OH)D levels, but first, let's take a closer look at the three possible sources of vitamin D.

Food sources of vitamin D

Food (3.5 oz. unless otherwise specified)	IUs per serving
High-vitamin cod liver oil (1/2 teaspoon)	2,000
Indo-Pacific Marlin	1,400
Herring	1,100
Fatty bluefin tuna	720
Duck egg	720
Chicken egg (pastured)	480–720
Rainbow trout	600
Eel	200–560
Mackerel	345–440
Standard cod liver oil (1 teaspoon)	400
Sockeye salmon	360
Canned sardines	270
Chicken egg (conventional)	120
Pork liver	50
Beef liver	30
Pork	28

As you can see from the chart on the slide, the only foods that contain significant amounts of vitamin D are cod liver oil, fish, and pastured eggs, which have four to six times the amount of vitamin D as conventional eggs. Now, fortunately, these are all foods I recommend consuming regularly. If you take one-half teaspoon of cod liver oil each day, eat two eggs four times a week, and a total of one pound of cold-water fatty fish a week, that would give you approximately 21,000 IU of vitamin D for the entire week, which is an average of 3,000 IU per day. Now that it a substantial amount, and it may be enough to maintain adequate vitamin D levels for some people.

Vitamin D is unique among vitamins in that it can be produced inside of our own bodies when our skin is exposed to ultraviolet light such as sunlight or a UV lamp. Sunlight has been the primary source of vitamin D, of course, for humans until very recently, since we evolved in equatorial East Africa where we would have been exposed to frequent and intense sunlight throughout much of the year. However, the same can't be said for modern humans. Many of us work indoors, wear clothing that covers most of our bodies, and live at latitudes far from the equator, all of which

reduce the conversion of sunlight to vitamin D. Studies have also shown that stress, inflammation, obesity, and old age can make our bodies less efficient at producing vitamin D from sunlight.

The benefits of sunlight go far beyond vitamin D.

Although this presentation is about vitamin D, we're going to take a detour to explain the most important point that few clinicians or patients are aware of, which is that the benefits of sun or UV exposure go far beyond vitamin D production. Substances that are made from chemical reactions with sunlight are called photoproducts. When human skin is exposed to sunlight, it produces several peptides and hormones that contribute to systemic wellness. These include calcitonin gene-related peptide, or cGRP; neuropeptide substance P; adrenocorticotropic hormone, ACTH; melanocyte-stimulating hormone, MSH; calcitriol; and beta-endorphin.

Sun exposure has been shown to improve hypertension, a wide variety of immune diseases, skin conditions, anxiety and depression, and more, independently of its effect on vitamin D production. In addition, while higher vitamin D levels created by the sun are useful in preventing disease, the research on vitamin D supplementation, as I said before, is mixed. Some studies have shown benefit, but many others have not, and the long-term effects of vitamin D supplementation are understudied. As we've seen, vitamin D toxicity may develop at levels of 25(OH)D that are lower than the upper end of the current laboratory reference range.