Vitamin D in Allergic and Immune Disorders

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ACAAI Meet the Professor Breakfast (S3)

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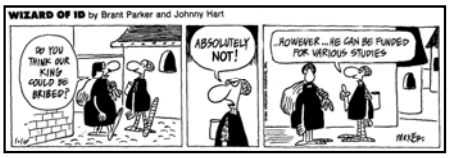
Disclosure

We have no potentially relevant financial interests, conflicts of interest, or other affiliations with any corporate organizations relevant to the subject of my presentation. We do not intend to discuss off label use of medications or devices.



Disclosure

I take 1400 IU of vitamin D q.d.

Hopefully, this topic will interest you enough to read more on your own including some of the references.

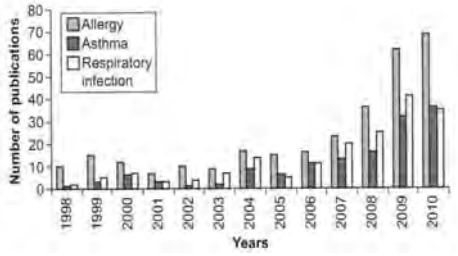
The handout can serve as a framework for our discussion.

Learning Objectives

At the conclusion of this CME activity, the participant will be able to:

1. **Define levels of sufficient, insufficient, and deficient vitamin D.**
2. **Describe associations vitamin D levels and atopic diseases.**
3. **Identify the potential role of vitamin D in immune modulation.**

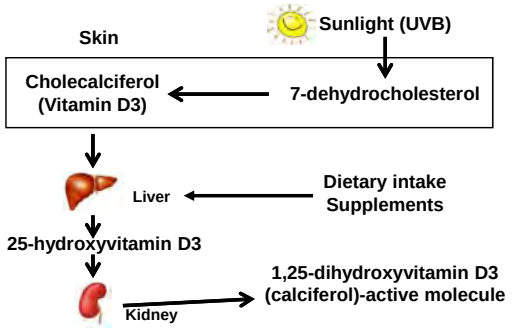
Growth of Publications:
Vitamin D and Allergy, Asthma, and Respiratory Infection



Sales of Vitamin D Supplements in the United States

Nutrition Bus J 2012

Vitamin D Synthesis



RDA for Vitamin D

Age (years)	0-1	1-13	14-18	19-50	51-70	>70
IU/d	400	600	600	600	600	800
Pregnancy and lactation			600	600		

ods.od.nih.gov/factsheets/vitamind-healthprofessional/ (6/24/11)

Sources of Vitamin D

Source	Serving size	IU per serving	% RDV (1-70 yrs.)
Milk, fortified	8 oz.	120	20
Cod liver oil	15 ml.	1360	227
OJ, fortified	8 oz.	137	23
Salmon	3 oz.	447	75
Egg, large	One	41	7
Skin	Up to 30’	20,000	3333

ods.od.nih.gov/factsheets/vitamind-healthprofessional/ (6/24/11)
NEJM. 2011;364:248-54., and others.

Food sources of Vitamin D

Food	IUs per serving
Cod liver oil, 1 tablespoon	**1,360**
Salmon (sockeye), cooked, 3 ounces	794
Mushrooms that have been exposed to ultraviolet light to increase vitamin D, 3 ounces (not commonly available)	400
Mackerel, cooked, 3 ounces	388
Tuna fish, canned in water, drained, 3 ounces	154
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	115-124
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	100
Yogurt, fortified, 6 ounces	80
Liver, beef, cooked, 3.5 ounces	46
Egg, 1 whole (vitamin D is found in yolk)	25

US Department of Agriculture. USDA Nutrient Database for Standard Reference, Release 22; 2009.

2 Teaspoons (10 mL)
Number of Servings:50

Vitamin D 920 IU
Vitamin A 2000 IU
DHA 1058 mg
EPA 690 mg
Lemon Flavoring

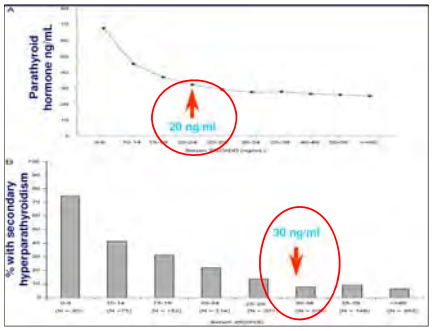
25-OH-D3 Levels and Health

ng/mL	nmol/L**	Health status
<12	<30	DEFICIENT: Associated rickets in infants and children and osteomalacia in adults.
12–19	30–49	INSUFFICIENT: Generally considered inadequate for bone and overall health in healthy individuals
≥20	≥50	SUFFICIENT: Generally considered adequate for bone and overall health in healthy individuals
20-29 30-50	50-75 ≥75	INSUFFICIENT SUFFICIENT
>50	>125	Emerging evidence links potential adverse effects to such high levels, particularly >60 ng/mL (>150 nmol/L)

ods.od.nih.gov/factsheets/Vitamind-healthprofessional/ (6/24/11)
NEJM. 2011;364:248-54.
Allergy Asthma Proc. 2011;32:438-44.

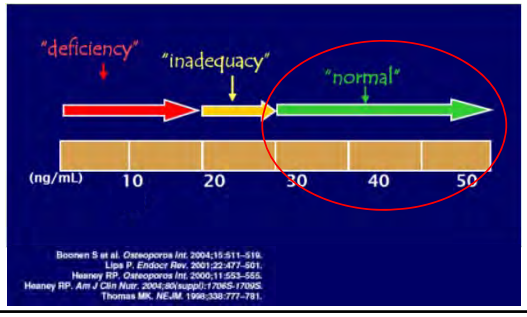
**** Conversion: 1 ng/ml=2.496 nmol/L**

Serum PTH and [25(OH)D]



Hollick, MF et al. J Clin Endocrinol Metab. 2005;90:3215-3224.

Definitions of Vitamin D Status



Who is at Risk of Vitamin D Deficiency?

- Dark complexion.
- Older children/teenagers.
- Girls.
- Obesity.
- More screen time.
- More time indoors
- Extremes of latitude.
- Low milk consumption.
- Breast fed babies.
- Malabsorption.

Vitamin D Deficiency is More Common than You Think

Estimates of 30-80% deficiency reported.

NHANES (2001-2004) study of 6000 1-21 year olds:

- **9% vitamin D deficient (<15 ng/ml).**
- **61% vitamin D insufficient (<30 ng/ml).**
- **Lower in older children, female, African and Mexican Americans, drank milk < once/week, >4 hours per day in front of screens.**

Adolescents (72% Black or Hispanic):

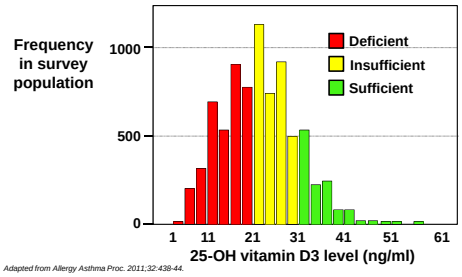
- **24% vitamin D ≤ 15 ng/ml.**
- **42% vitamin D ≤ 20 ng/ml.**

Infants and toddlers 8-24 months (90% Black or Hispanic):

- **12% vitamin D ≤ 20 ng/ml.**
- **40% vitamin D ≤ 30 ng/ml.**

Pediatrics. 2009;124:e362-70.
Arch Pediatr Adolesc Med. 2004;158:531-7.
Arch Pediatr Adolesc Med. 2008;162:505-12.

Vitamin D Levels in a Random Population (NHANES 2005-06)



Adapted from Allergy Asthma Proc. 2011;32:438-44.

Non-Calcemic Roles of Vitamin D

Vitamin D receptor (VDR) and α-1-hydroxylase have been found on and in most cell types and tissues of the body.

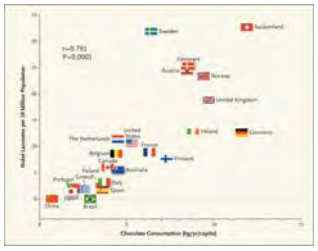
Numerous conditions have been associated with vitamin D deficiency:

- **Atherosclerosis.**
- **Cardiac contractility.**
- **Autoimmunity.**
- **Neoplasm**
  - **Breast**
  - **Colon**
  - **Prostate**
- **Impaired insulin synthesis.**
- **In the PICU:**
  - **More critical illness**
  - **Longer admission.**
  - **Pressor need.**
  - **Risk of septic shock**

Associations of Vitamin D Status with Things We Do for a Living

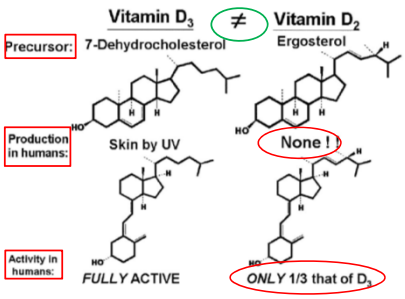
- Atopic diseases
  - Total and specific IgE
  - Asthma
  - Atopic dermatitis
- Anaphylaxis
- Food Allergy
- Chronic urticaria?
- Infections
  - Atopic dermatitis
  - Influenza, resp. viruses
  - Tuberculosis, HIV
- Autoimmunity
  - Type 1 diabetes mellitus
  - Multiple sclerosis
  - Rheumatoid arthritis

An Association Does not Imply Cause and Effect. It is Merely a Place to Start Your Research.



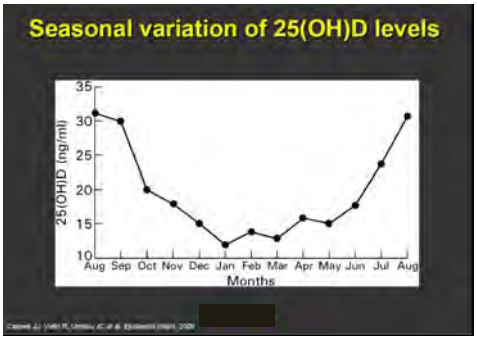
N Engl J Med 2012;367:1562-1564.

Isomers of Vitamin D_2 & D_3



Bioequivalence

- **Higher affinities of D3 for:**
  - **Hepatic 25-hydroxylase**
  - **Vitamin D-BP (VDBP)**
  - **Vitamin D receptor (VDR)**



Vitamin D Production in the Skin Is Related to Skin Type: (The Darker the Skin the More Sunlight Exposure Required to Make Enough Vitamin D)

Skin Type	Color	Sensitivity
Type 1	Pale, Never Tans	Usually burns, red and Painful
Type 2	Very light tan, May freckle	Usually burns, tans gradually
Type 3	Light tan, Brown, Olive	Usually tans, rarely burns.
Types 4-6	Brown, Dark Brown, Black	Always tans fast, almost no burns

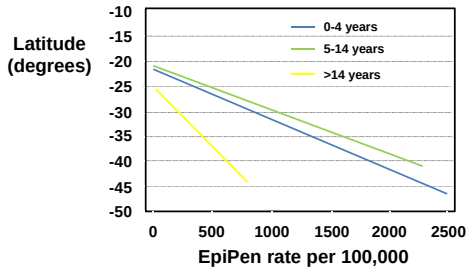
Skin Type: Melanin Content

- Type I skin always burns, never tans, and is extremely fair.
- Type II skin always burns, occasionally tans, and is considered fair.
- Type III skin occasionally burns, gradually tans, and is considered medium.
- Type IV skin rarely burns, always tense, and is considered Olive.
- Type V skin seldom burdens, always tense, and is considered medium to dark.
- Type VI skin never burns, always tends darkly, and is considered dark

Latitude and Epinephrine Prescriptions

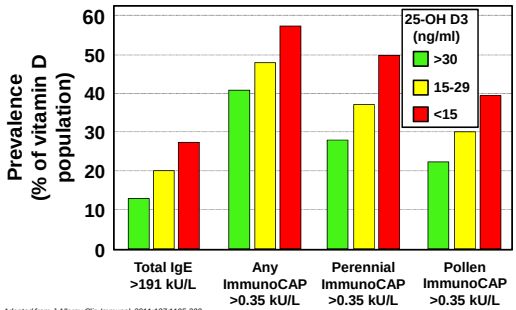
J Allergy Clin Immunol. 2007;120:131-6.

Latitude and Epinephrine (Southern Hemisphere)



Adapted from Ann Allergy Asthma Immunol. 2009;103:488-95.

Vitamin D Levels and Atopy



Adapted from J Allergy Clin Immunol. 2011;127:1195-202.

Vitamin D and Asthma Control

- Vitamin D levels are correlated with FEV_1, FVC, asthma control, and steroid responsiveness.
- Vitamin D level is inversely correlated with asthma symptoms, bronchial hyperreactivity, asthma exacerbations, steroid requirement, and bronchial smooth muscle mass.
- Vitamin D deficiency is a risk for asthma hospitalization and airway remodeling, and is associated with steroid resistant asthma.

Allergy Asthma Proc. 2011;32:438-44.
J Allergy Clin Immunol. 2007;120:1031-5.
Am J Clin Nutr. 2007. 85:788-95.
Br J Nutr. 2010;104:1051-7.
Ann Allergy Asthma Immunol. 2010;105:191-99.
J Allergy Clin Immunol. 2007;120:1031-5.
J Allergy Clin Immunol. 2010;125:995-1000.
J Allergy Clin Immunol. 2010;126:52-8.
Am J Resp Crit Care Med. 2011;184:1342-9.
Eur Resp J. 2011;38:1320-7.

Asthma and Vitamin D Supplementation

- **Vitamin D enhances T cell steroid responsiveness *in vitro*.**
- **Supplementation at 1 (cod liver oil) decreases risk of allergies and asthma at 31 years.**
- **In established and newly diagnosed asthma, vitamin D supplementation leads to better asthma control.**

J Allergy Clin Immunol. 2010;125:995-1000.
J Allergy Clin Immunol. 2007;120:1031-5.
J Allergy Clin Immunol. 2011;1294-6.
Ann Allergy Asthma Immunol. 2012;108:281-2.

Vitamin D Levels, Lung Function, and Steroid Response in Adult Asthma

E. Rand Sutherland[1,2], Elena Goleva[3,4], Leisa P. Jackson[3], Allen D. Stevens[1], and Donald Y. M. Leung[3,4]

[1]Department of Medicine, and [2]Department of Pediatrics, National Jewish Health, Denver, Colorado; and [3]Department of Medicine, and [4]Department of Pediatrics, University of Colorado, Denver, Colorado

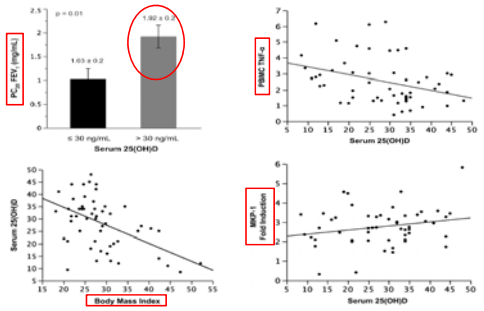
Sutherland, ER et al. Am J Respir Crit Care Med. 2010;181:699-704.

Sutherland

- 54 adult asthmatics
- **Objective:** Determine whether there is correlation between vit D, asthma severity, & treatment response
- Low vit D levels were associated with increased production of pro-inflammatory protein in blood
- Subjects with higher vit D levels had:
  - Better lung function measures *(≈23 mL increase in FEV_1 for every 1 ng/mL increase in serum vit D)*
  - Improved AHR
  - Better response to corticosteroid *in vitro*

[Sutherland, ER et al. Am J Respir Crit Care Med. 2010;181:699-704].

Sutherland



Pre-, Peri, and Neonatal Vitamin D and Risks for Atopy

- VDR polymorphisms.
- Low maternal vitamin D intake and levels and low cord levels of 25-OH-D3 are associated with increased risk of atopic dermatitis in infancy and for wheeze and/or asthma at 3, 5, and 9 years old.
- Breast fed babies at risk.

Allergy Asthma Proc. 2011;32:438-44.
J Allergy Clin Immunol. 2007;120:1031-5.
Am J Clin Nutr. 2007; 85:788-95.
Am J Resp Crit Care Med. 2011;184:1342-9.
J Allergy Clin Immunol. 2007;120:1031-5.
J Allergy Clin Immunol. 2010;125:995-1000.
J Allergy Clin Immunol. 2010;126:52-8.
Ann Allergy Asthma Immunol. 2010;105:191-99.
Pediatrics. 2012 ;130(5):1128-35.
Eur Resp J. 2011;38:1320-7.
Br J Nutr. 2010;104:1051-7.

Vitamin D and Infections

- Vitamin D supplementation maintains epithelial barrier and improves control of atopic dermatitis.
- Deficiency is associated with increased risk of sinusitis and increased rate of viral respiratory illnesses.
- Supplementation decreases rate of URIs and influenza (dose dependent).
- Vitamin D enhances immunity to M. tuberculosis.

Br J Dermatol. 2008;159:245-7.
J Allergy Clin Immunol. 2008;122:415-7.
Pediatrics. 2011;127:180-7.
J Epidemiol Infect. 2007;135:1095-8.
Clin Exp Med. 0012;8 (epub ahead of print)
Clin Devel Immunol. 2012;430972. epub 7/5/12.
PLoS One. 2012;7(7):e40692

National Jewish Hospital for Consumptives



How Can We Make Sense of All That?

It's easy…..

VDR and α-1-hydroxylase are everywhere!

They have to be there for a reason, not by accident.

VDR and α-1-hydroxylase are everywhere

- **APCs (Dendritic cells, monos, macros, etc.):**
  - **Exposure to lipopolysaccharide up-regulates VDR and α-1-hydroxylase.**
  - **Vitamin D3 up-regulates toll-like receptors (TLR) for better response to microbes.**
  - **Vitamin D3 up-regulates antimicrobial proteins, maintains epithelial barrier integrity in AD.**
  - **Vitamin D3 enhances tolerance in adaptive immunity by up-regulating IL-10, IL-19, and TGF-β (enhances Treg [FoxP3+] cell development).**
  - **Vitamin D3 down-regulates co-stimulatory molecules CD40 and CD80/86.**

VDR and α-1-hydroxylase are everywhere

- **Lymphocytes:**
  - **Decreased proliferation.**
  - **Inhibition of Th1 and Th2 cytokines by naïve (cord) T cells with enhanced Treg phenotype.**
  - **Vitamin D3 enhances IL-2 production.**
  - **Enhances steroid responsiveness and immunosuppressive effects.**
  - **Decreased IL-6, decreased IL-12 induced IFN-γ synthesis.**
  - **Decreased CD40 and CD80/86 on B cells→ Decreased T cell activation.**
  - **Better response to SCIT.**

VDR and α-1-hydroxylase are everywhere

Other cells we think about everyday:

- **Mast Cells**
  - **Inhibition of maturation.**
  - **Apoptosis.**
- **Decreased eosinophil recruitment.**
- **Respiratory epithelium and smooth muscle.**
  - **Inhibits smooth muscle proliferation.**
  - **Decreased RANTES (CCL5) production.**
  - **Decreases matrix metalloproteinase production.**
  - **Helps fetal lung growth (mice).**

Reversing the defective induction of IL-10–secreting regulatory T cells in glucocorticoid-resistant asthma patients

Emmanuel Xystrakis,[1] Siddharth Kusumakar,[1] Sandra Boswell,[1] Emma Peek,[1] Zoë Urry,[1] David F. Richards,[1] Tonye Adikibi,[1] Carol Pridgeon,[2] Margaret Dallman,[2] Tuck-Kay Loke,[1] Douglas S. Robinson,[2,3] Franck J. Barrat,[4] Anne O'Garra,[5] Paul Lavender,[1] Tak H. Lee,[1] Christopher Corrigan,[1] and Catherine M. Hawrylowicz[1]

[1]Medical Research Council and Asthma-UK Centre in Allergic Mechanisms of Asthma at King's College London, Strand, London, United Kingdom. [2]Life Sciences and [3]Medical Research Council and Asthma-UK Centre in Allergic Mechanisms of Asthma at Imperial College, Imperial College, London, United Kingdom. [4]Dynavax Technologies Corp., Berkeley, California, USA. [5]Laboratory of Immunoregulation, National Institute for Medical Research, Mill Hill, London, United Kingdom.

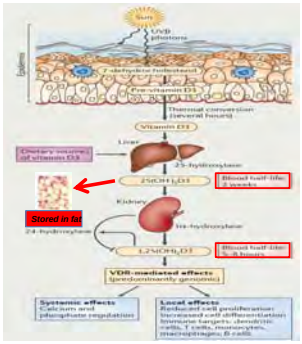
Xystrakis, E et al. J Clin Invest. 2006;116(1):146-155.

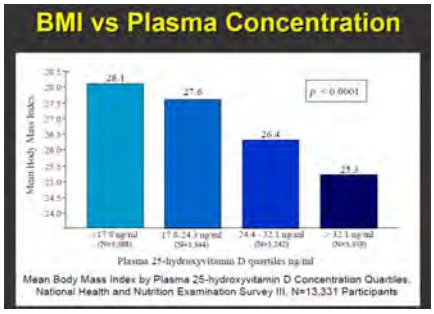
Response to Glucocorticoids in SR Asthmatics?

- Human CD4⁺ Treg secrete high levels of IL-10 when stimulated in presence of dexamethasone (dexa) & vit D_3.
- **Dexa** does not enhance secretion of IL-10 by CD4⁺ T cells of SR asthmatics.
- **Vit D_3** overcame inhibition of GC-receptor (GC-R) expression by dexa while IL-10 upregulated GC-R expression by CD4⁺ T cells.
- **Conclusion:** Vit D_3 treatment may overcome poor GC responsiveness in SR asthmatics.

Xystrakis, E et al. J Clin Invest. 2006;116(1):146-155.

UV Radiation & Vitamin D Synthesis



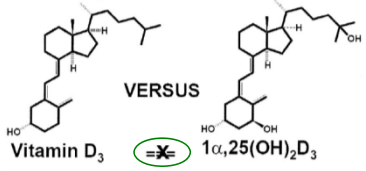


Causes of Vitamin D Deficiency

- **Indoor/Sedentary Lifestyle**
- Above **37 degrees North Latitude (Atlanta) little or no vit D3 can be produced between November and February**.
- Aging reduces 7-dehydrocholesterol in skin
  - **By age 70 by 75%**
- **Sunscreen Use:** absorbs UVB rays
  SPF 8 decreases synthesis by 92.5%
  SPF 15 decreases synthesis by 99%
- **Skin Pigment-Melanin:** absorbs UVB rays by up to **99%**

Vitamin D_3 vs 1^{α},25(OH)$_2$-Vitamin D_3

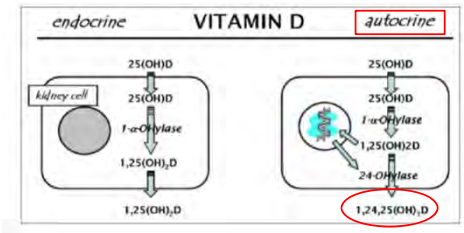
Are they the same or different?



Properties:

Biologically Inactive Itself	Steroid Hormone
Does not bind to VDR	Acts through VDR
Nutritional Substance	

Two Faces of Vitamin D Function

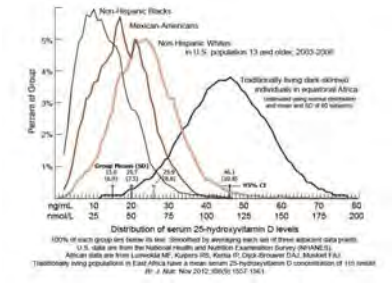


Lappe, JM. J Evidence-Based Compl Alt Med. 2011;16(1):58-72.

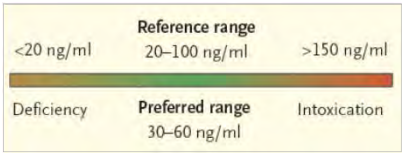
Reverse Causation?

- Some evidence suggests that vit D might increase the risk of allergic disease.
- ***Reverse causation:*** more severe asthmatics spend less time outdoors in which case vit D deficiency is secondary to the disease. *[Wjst, M. Allergy Asthma Clin Immunol. 2009;5:8].*
- Excessive vit D supplementation (cod liver oil) during infancy may increase risk of asthma, food allergy, & allergic rhinitis. *[Hyppönen, E et al. Ann NY Acad Sci. 2004;1037:85-95; Kull, I et al. J Allergy Clin Immunol. 2006;118:1299-1304].*

The Case for Vitamin D



Blood Levels: 25(OH)D Recommendations



- **Literature** (2000-2010): **30-60 ng/mL**
- **IOM** (November 2010): **> 20 ng/mL**

Institutes of Medicine Recommendations (Nov 2010)+

Dietary Reference Intakes for Calcium and Vitamin D

	Calcium			Vitamin D		
Life Stage Group	Estimated Average Requirement (mg/day)	Upper Level Intake (mg/day)	Recommended Dietary Allowance (mg/day)	Estimated Average Requirement (IU/day)	Upper Level Intake (IU/day)	Recommended Dietary Allowance (IU/day)
Infants 0-6 months	*	*	1000	**	**	1000
Infants 6-12 months	*	*	1500	**	**	1500
1-3 years	500	700	2500	400	600	2500
4-8 years	800	1000	2500	400	600	3000
9-13 years	1100	1300	3000	400	600	4000
14-18 years	1100	1300	3000	400	600	4000
19-30 years	800	1000	2500	400	600	4000
31–50 years	800	1000	2500	400	600	4000
51–70 year, males	800	1000	2000	400	600	4000
51–70 year, females	1,000	1200	2000	400	600	4000
>70 years	1,000	1200	2000	400	800	4000
14–18 years, pregnant/lactating	1,100	1300	3000	400	600	4000
19–50 years, pregnant/lactating	800	1000	2500	400	600	4000

*For infants, Adequate Intake is 200 mg/day for 0 to 6 months of age and 260 mg/day for 6 to 12 months of age.

**For infants, Adequate Intake is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age.

Institutes of Medicine Recommendations (Nov 2010)

Dietary Reference Intakes for Calcium and Vitamin D

	Calcium			Vitamin D		
Life Stage Group	Estimated Average Requirement (mg/day)	Upper Level Intake (mg/day)	Recommended Dietary Allowance (mg/day)	Estimated Average Requirement (IU/day)	Upper Level Intake (IU/day)	Recommended Dietary Allowance (IU/day)
Infants 0-6 months	*	*	1000	**	**	1000
Infants 6-12 months	*	*	1500	**	**	1500
1-3 years	500	700	2500	400	600	2500
4-8 years	800	1000	2500	400	600	3000
9-13 years	1100	1300	3000	400	600	4000
14-18 years	1100	1300	3000	400	600	4000
19-30 years	800	1000	2500	400	600	4000
31–50 years	800	1000	2500	400	600	4000
51–70 year, males	800	1000	2000	400	600	4000
51–70 year, females	1,000	1200	2000	400	600	4000
>70 years	1,000	1200	2000	400	800	4000
14–18 years, pregnant/lactating	1,100	1300	3000	400	600	4000
19–50 years, pregnant/lactating	800	1000	2500	400	600	4000

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**For infants, Adequate Intake is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age.

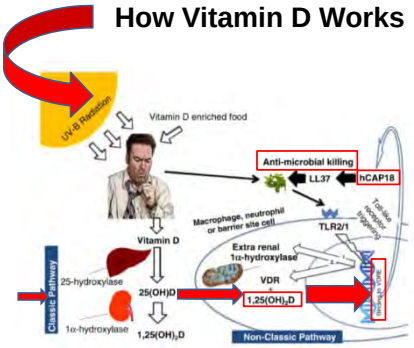
Knowledge Gaps

- What are the differences between naïve T cell responses to vit D & mature T cell responses to vit D?
- What dose of supplemental vit D is optimal for prevention or control of asthma (allergy)?
- Can excessive vit D intake potentiate Th2 responses in asthmatics?

Knowledge Gaps

- Does the host's vit D status modify the effect of the intestinal microbiota on the immune system?
- Does vit D deficiency affect the composition of the intestinal microbiota?

How Vitamin D Works



Complex Problem. Simple Solution?

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