


## Vitamin D: The Versatile Vitamin

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## Outline



- **Skeletal**
  - 15% of vitamin D endocrine function
  - Osteoporosis, osteopenia, osteomalacia
- **Non-skeletal**
  - 85% of vitamin D autocrine/paracrine function
  - Actions of vitamin D in cells
 

<ul style="list-style-type: none"> <li>• Immune functions</li> <li>• Cancer</li> <li>• Cardiac, Stroke</li> <li>• Multiple Sclerosis</li> </ul>	<ul style="list-style-type: none"> <li>• Autoimmune</li> <li>• Type 1 DM</li> <li>• Depression</li> <li>• Ethnic differences</li> </ul>
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## Risk Factors for Vitamin D Deficiency

- **Not in sun for past 50 years**
  - 1950, 1960s: air conditioning and TV
  - 1970s, 1980s: children in school
- **Not found in foods, except fortified foods**
  - Milk, cereal
- **Dark skin**

## Exposure to Sun

- **A single dose of UVB radiation**
  - Light-skinned
  - 10-15 min
  - 20,000 IU vitamin D2 in 24 hours
- **Dark skin can make D**
  - But takes longer
  - Up to 10X as long

## Sunshine


1<sup>st</sup> conversion in skin  
 $D_3$

↓


2<sup>nd</sup> conversion by liver  
 $25D_3$  - Calcidiol

↓



<p>3<sup>rd</sup> conversion in kidney <math>1,25D_3</math> Calcitriol</p> <p>↓</p> <p>Absorb Calcium Strengthen Bones</p>	<p>3<sup>rd</sup> conversion in cells <math>1,25D_3</math> Calcitriol</p> <p>↓</p> <p>Cell VDR – Immune/ Resistance to Disease</p>
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## Sources of Vitamin D




Supplements

Fortified Foods

Pool together



### Vitamin D Iceberg

15% calcium economy  
*endocrine*

85% cell cycle regulation,  
gene control  
*autocrine*

### Rickets + Osteomalacia

- Rickets**
  - Failure to mineralize; skull, rib, leg
  - Cod liver oil
- Osteomalacia**
  - Hard shell, soft inside
  - Lack of D
  - Fast weight loss

Khokhar JS, Brett AS, Desai A. Radionuclide imaging. Am J Med Sci 2009;337(4):245-247  
Pfeifer et al. Osteoporos Int, July 16, 2008.

### Osteoporosis + Osteopenia

Normal bone matrix      Osteoporosis

Osteoporosis in the vertebrae

Normal Bone Mineral Density ( $> -1.0$ )  
Osteopenia ( $-1.0$  to  $-2.5$ )  
Osteoporosis ( $< -2.5$ )

### Vitamin D Action – Skeletal

- Structure
  - Assist with calcium absorption
- Skeletal – Calcium Balance
  - When blood levels Vit D - 32 ng/mL (80 nmol/L)

### Vitamin D Action –Skeletal

Vitamin D Threshold

Minimal/optimal, serum Vit D level is about 32 ng/mL for best calcium absorption. Calcium absorption rises as 25(OH)D rises.

Heaney RP. Vitamin D endocrine physiology. J Bone Miner Res. 2007 Dec;22 Suppl 2:V25-7

### Vitamin D Deficiency : Non-Skeletal

- Started accumulating for 7-10 years ago (after the last RDAs were printed)
- Epidemiological relationships
- Then discover “if” and “how”
- Expand research to larger groups
- Then determine levels needed

<http://www.medicalnewstoday.com/articles/161618.php>

## Vitamin D Actions

**Tight vs Disjunction**

- DNA errors or epigenetic events
- Rapidly dividing, aggressive, compete, penetrate membrane
- Vit D activates cell adhesion
  - E-cadherins, catenins, laminin
- Low vitamin D – disjunction

## Cadherins

(Calcium dependent adhesion molecules)

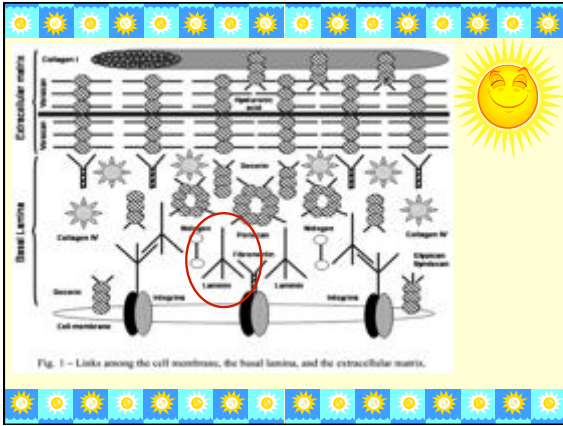
## Cadherins Joining

Phase	Regulation	Protein	Protein
Vitamin D regulates (breast)	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	Right junctions make their cellular communication intact. Cancer cells with functional E-cadherin are not mobile. Metastasis is inhibited.	Lowest 200000 fold of 40-60 right junctions. Functions as 40-60 1:10000 fold disjunction.
Disjunction due to low vitamin D and calcium	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	Left junctions signify. Right junctions and E-cadherin are downregulated. Intracellular communication is reduced in low calcium conditions.	Complexes of cadherins, catenins, and intermediate proteins.
Initiation	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	Cells begin to aggregate under intact support. Cells, which of some nature or developing epithelial cells.	Complexes of cadherins, catenins, and other of epithelial cells to generate stable.
Natural selection	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	Ability of living, most aggressive amongst of these populations, to cell with a 25% growth advantage and 75% three change team in 1000 generations.	Active selection of active cells, leading to natural selection of rapidly dividing cells.
Overgrowth prevention of metastasis	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	Rightly chosen cells compete for resources and their supply, divide and generate resistant population.	Active selection of active cells, leading to natural selection of rapidly dividing cells.

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Metastasis	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	Cells begin to aggregate under intact support. Cells, which of some nature or developing epithelial cells.	Complexes of cadherins, catenins, and other of epithelial cells to generate stable.
Evolution (growth arrest)	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	Ability of living, most aggressive amongst of these populations, to cell with a 25% growth advantage and 75% three change team in 1000 generations.	Active selection of active cells, leading to natural selection of rapidly dividing cells.
Transition	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	Rightly chosen cells compete for resources and their supply, divide and generate resistant population.	Active selection of active cells, leading to natural selection of rapidly dividing cells.

## Cadherins

(Calcium dependent adhesion molecules)



### Vitamin D Actions

- Cell Differentiation
  - Stimulate differentiation
  - Inhibit proliferation

### Vitamin D Actions

- Apoptosis
  - Programmed sequence of events leading to cell death
  - No release of harmful substances

### Vitamin D Deficiency: Reduced Immunity

- The innate immune system
  - Rapid response to bacteria, viruses, parasites, etc.
  - Antimicrobial peptides **defensins** and **cathelicidins**
  - 1,25-dihydroxyvitamin D3 and three of its analogs
    - Cathelicidin antimicrobial peptide (CAMP) gene.
- Antimicrobial peptide and anti-inflammatory

### Vitamin D Actions

- Potent Immune Modulator
  - Enhance innate immunity At same time
  - Inhibit development of autoimmunity

**Cathelicidin + defensins**  
natural anti microbial peptides

### Vitamin D Deficiency: Reduced Immunity

- H1N1 influenza virus outbreak
  - Should be evaluated
- Canada
  - Researchers in PHAC with McMaster University
  - Correlation between severe disease and low vitamin D levels
  - This line of research in seasonal influenza will be adapted to H1N1

PHAC sent e-mail to NutraIngredients-USA.com

### Vitamin D Contradictions, in Terms of Immune Responses

- Does vitamin D help to promote immune reactions, i.e. helps attack foreign antigen ?

Or

**Evidence shows that it does both !**

- Does vitamin D suppress immune attack, and prevent auto-immune disease?

### Vitamin D Deficiency – Autoimmune

- Autoimmune diseases such as
  - Allergies
  - Crohn's
  - Lupus
  - Rheumatoid + Osteo-Arthritis
  - Multiple Sclerosis
  - Fibromyalgia

### Vitamin D Actions

- Anti-inflammatory action
  - Sometimes as COX-2 inhibitor
  - Decreases C-Reactive Protein
  - Infections
- Regulate 200 different genes
  - Responsible biologic processes

### Vitamin D Deficiency: Diabetes & Glucose Control

- 2000 IU/d – Finland
  - 1<sup>st</sup> year of life
  - Reduce risk type 1 diabetes over 30 yr by 80%
- Boston-based Joslin DM Center
  - 75% of young type 1 DM, insufficient Vit D level



### Vitamin D Deficiency: Cancers – 21 Different

Garland C. Vit D and Cancer. Present to IOM, Aug 4, 2009


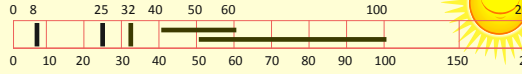
### All Except First Year Cases

### Lab Measurement

- **Deficiency**
  - <8ng/mL
  - (<20 nmol/L)
- **Insufficiency**
  - 8.4-11.6 ng/mL
  - (21-29 nmol/L)
- **Old Lab Values**
  - 12-28 ng/mL
  - (30-70 nmol/L)
- **Current Normal**
  - 25-70 ng/mL
  - (63-175 nmol/L)
  - Need at least 4000 IU per day to support this level
- **Future**
  - 40-60 ng/mL or (50-100)
  - (100-240 nmol/L)
- **Toxic**
  - >200 ng/mL
  - (>500 nmol/L)

### Vitamin D Summary

Level in ng/mL*	Condition
< 8	Rickets and osteomalacia
12 - 28	Osteoporosis and osteopenia
> 32	Necessary for good calcium-PTH homeostasis
40 - 60	Recommended by vit D researchers to Institute of Medicine to become the normal laboratory standard of measure
50 -100	Recommended by Dr. Cedric Garland to be the best normal levels
>200	Beginning of toxic range

### Vitamin D Supplements




RDA+	Today	Future
RDA	= 400 IU	1,000 - 2,000 IU
Upper Level	= 2,000 IU	10,000 IU
Toxic	=	>30,000 IU/day

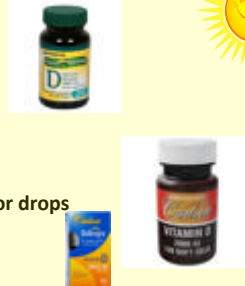
- Individual Vitamin D
  - Softgel or drops
  - Vitamin D3
  - 1000 IU or 2000 IU (50 mcg or 100 mcg)




### Vitamin D Supplements




- Over the counter
  - Walgreens
  - Target
  - CVS
- Internet
  - Be sure it is softgel or drops
  - Amazon.com
  - Vitacost.com
  - Carlson labs



### In Brief - Serum Calcitriol




- ↑ Vit D levels are ↓ (inversely) related to most chronic diseases
- Vitamin D works in multiple systems
- RDA Needs to be higher than current 400 IU




### Summary

#### In Brief - Serum Calcitriol




- Most of us need a supplement
  - 1000 → 2000 IU per day is within current RDA
  - Loading dose of 6000 IU per day for 3 months
- Near Future: 2000 to 10,000 IU
  - We utilize 3500 to 6000 IU per day
- Best to check blood levels
  - 40 to 60 ng/mL or higher
  - Garland suggests 50-100 ng/mL



## Missing vs Addition

- “Dietary omission rather than the addition of chemical carcinogens leads to tumor formation.”
- Nutrients of concern
 

Vitamin D	
– DHA	– Choline
– Vitamin B12	– Soluble fiber
– Calcium	– Iron



## Thank You

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## References

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- Tseng M, Giri V, Bruner DW, Giovannucci E. Prevalence and correlates of vitamin D status in African American men. 2009. *BMC Public Health*, 9:191
- UC San Diego Medical Center. <http://health.ucsd.edu/CoveoSearch?q=vitamin%20D&t=240>



## References on Internet

- Information Gathering Workshop for Dietary Reference Intakes for Vitamin D and Calcium. Researchers present to Food and Nutrition Board of the Institute of Medicine Petitioning them to change the vitamin D recommendations from RDA 400 IU and Upper 2000 IU to RDA of 2000 IU and Upper or 10,000 IU. <http://www.iom.edu/en/Activities/Nutrition/DRIVRD/Calcium/2009-AUG-04.aspx>
- Presentations, either video or power point and audio, of several noted Vitamin D researchers including Garland, Gorham, Giovannucci, Heaney. University of California TV - Vitamin D Deficiency: Treatment and Diagnosis <http://www.ucsv.tv/vitamin/>
- Grassroots - D Action <http://www.grassrootshealth.net/>
- Garland CF, Gorham ED, Mohr SB, Garland FC. [Vitamin D for cancer prevention: global perspective](http://www.ncbi.nlm.nih.gov/pubmed/19523595). *Ann Epidemiol*. 2009 Jul;19(7):468-83. Review. PMID: 19523595 [PubMed - indexed for MEDLINE]
- Snopes is for looking up myths and urban legends to see if accurate, <http://www.snopes.com/>
- Dr. Holick <http://www.uvadventure.org/portals/0/pres/>

