

# **Vitamin D and Asthma: What is the Connection?**

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# Disclosure

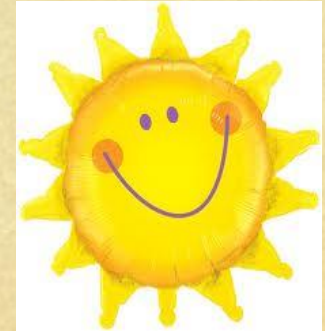
- ◆ Monaghan Medical Corporation – speaker
- ◆ Novartis – speaker
- ◆ Genetech – speaker

Thank you Monaghan!

# Learning Objectives

- ◆ Discuss basic physiology of vitamin D and the potential consequences of vitamin D deficiency.
- ◆ Describe the potential impact of vitamin D and asthma.
- ◆ Evaluate the emerging role of vitamin D as an adjunctive therapy in asthma management.

# Vitamin D- The Facts



- Vitamin D deficiency is public health problem for adults and children worldwide.
- Many epidemiological studies have shown that vitamin D deficiency increases the risk of asthma and allergies.
- Low levels of vitamin D have been associated with asthma severity, poor control with recurrent exacerbations.

# Rochester Epidemiology Project

National Institutes of Health-funded

Mayo Clinic 2002 – 2011

Geographic population identifying health trends

N = 20,308

8% of subjects vitamin D levels > 50 ng/mL

**16,246 people were vitamin D deficient**

Mayo Clinic, 2015

# What is vitamin D deficiency?

**Deficiency < 20 ng/ml 25(OH)D concentration**

- ◆ Insufficiency: 20-30 ng/ml
- ◆ Sufficiency: 30-50 ng/ml
- ◆ Toxic: > 150 ng/ml

Endocrine Society Clinical Practice Guideline

# Vitamin D Deficiency Increase Risk

Osteoporosis

Osteoporotic fracture

Osteomalacia

Rickets

Heart disease

Autoimmune disease

Multiple sclerosis

Alzheimers

Type 1 Diabetes

Some cancers

Depression

Cardiovascular disease

# Vitamin D Deficiency Increase Risk

Asthma

Cystic fibrosis

Chronic Obstructive Pulmonary Disease  
(COPD)

Interstitial pneumonia



# Factors Influencing Vitamin D

Age

Body fat

Level of skin melanin

Latitude

Amount of sun exposures

Use of sunscreen

Health status

# Latitude and vitamin D production in the skin



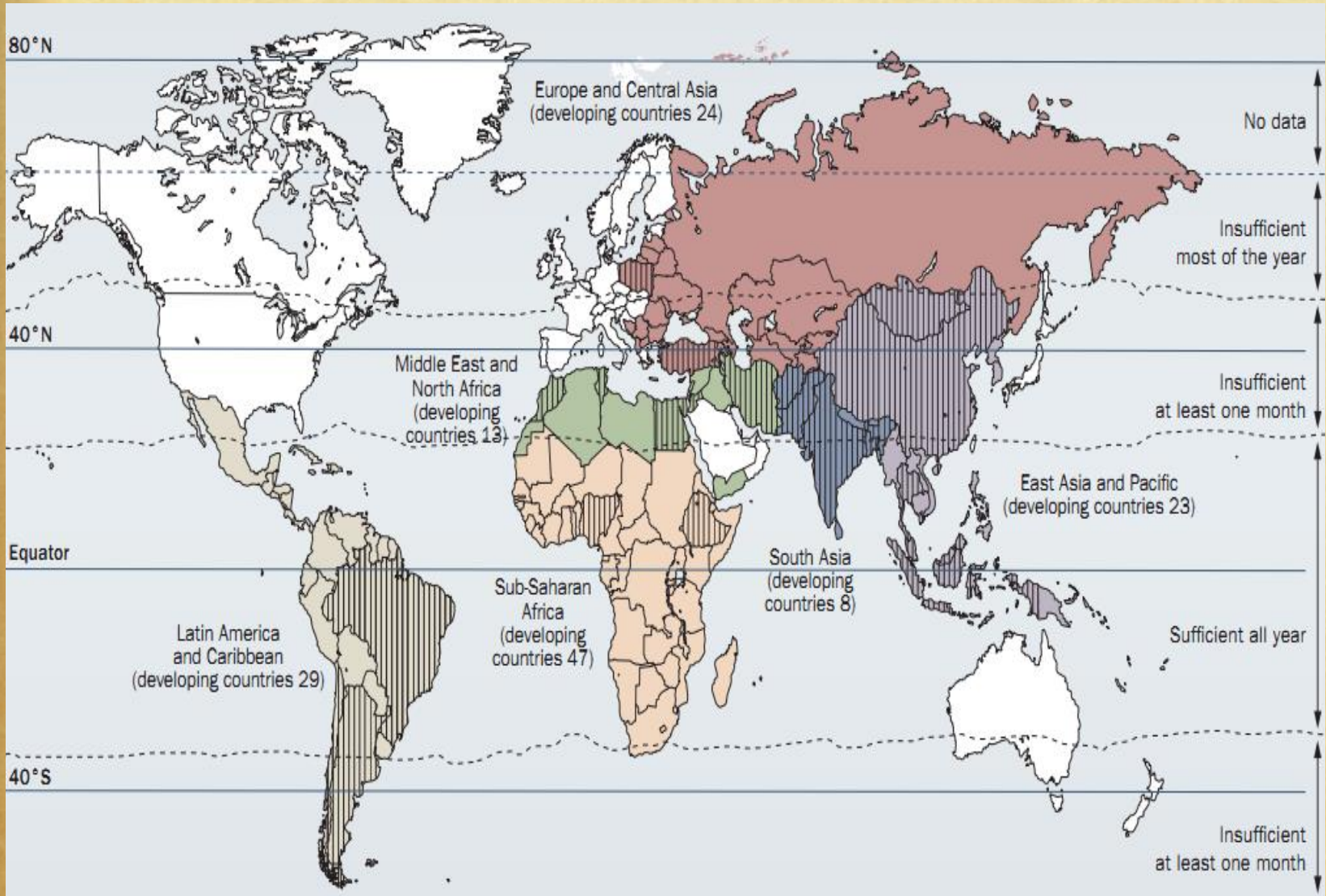
Except during the summer months, the skin makes little if any vitamin D from the sun at latitudes above 37 degrees north (in the United States, the shaded region in the map) or below 37 degrees south of the equator.

People who live in these areas are at relatively greater risk for vitamin D deficiency.

# Cleveland

41.4822° N      81.6697° W





# Vitamin D Influences Cellular Response



Vitamin D impacts the function of inflammatory and structural cells, including dendritic cells, lymphocytes, monocytes, and epithelial cells.

# **Vitamin D deficiency and viral infection-induced exacerbations**

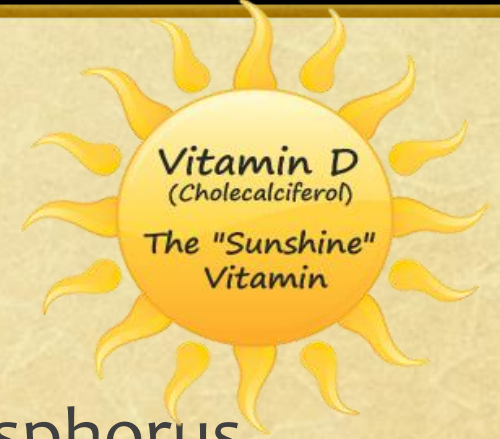
- ◆ Lower levels associated with increase markers of allergy and asthma severity.
- ◆ Insufficient levels associated with risk of severe exacerbation, particularly in the absence of inhaled corticosteroids.

# What is Vitamin D?

- ◆ Vitamin D is a secosteroid hormone synthesized by the skin following exposure to ultraviolet B light.
- ◆ A fat-soluble vitamin.
- ◆ Significant immunomodulatory effects and anti-inflammatory properties.
- ◆ Important role in immune regulation and bone metabolism.



# Vitamin D



- ◆ Absorbs dietary calcium and phosphorus from the intestines.
- ◆ Suppresses the release of parathyroid hormone, a hormone that causes bone reabsorption.
- ◆ Maintains normal calcium and phosphate levels → promoting bone health.



# Vitamin D

- ◆ Vitamin D Receptors are found on every tissue in the body.
- ◆ Vitamin D is the primary regulator of at least 600 crucial genes.

# Sources of Vitamin D

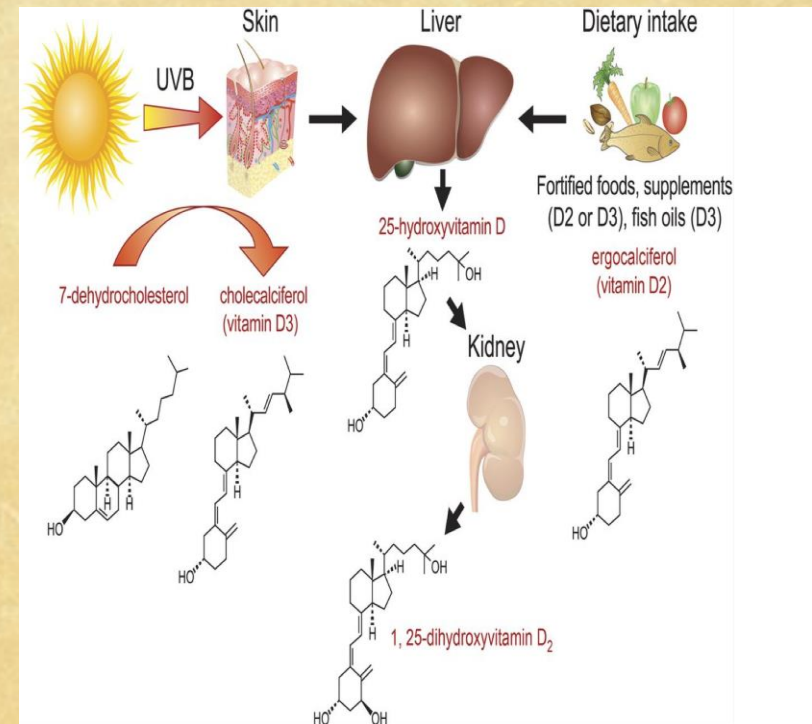


# Biosynthesis of vitamin D

- ◆ Vitamin D<sub>3</sub> is synthesized in the skin under the influence of ultraviolet light of the sun or it is obtained from food.
- ◆ After hydroxylation in the liver into 25-hydroxyvitamin D (25(OH)D) and kidney into 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D)
- ◆ Active metabolite can enter the cell
- ◆ Bind to the vitamin D-receptor and subsequently to a responsive gene (calcium binding protein).

# Biosynthesis of vitamin D

- ◆ After transcription and translation the protein is formed (osteocalcin or calcium binding protein).
- ◆ The calcium binding protein mediates calcium absorption from the gut.
- ◆ The production of **1,25(OH)<sub>2</sub>D** is stimulated by parathyroid hormone (PTH) and decreased by calcium.



**Muscle cells contain vitamin D receptor.  
Several studies have demonstrated that serum  
25(OH)D is related to physical performance.**





## Vitamin D2 ergocalciferol

- ◆ Does not naturally present in the body –less binding capacity to vitamin D receptors
- ◆ Shorter half-life
- ◆ Vitamin D2 is a fungus/yeast-derived product
- ◆ Vitamin D2 is synthetically made from radiating a compound (ergosterol) from the mold ergot

## Vitamin D3 cholecalciferol

- More potent form of vitamin
- More effective than vitamin D2 at serum 25(OH)D concentrations
- Utilized more in clinical trials
- UVB light from the sun strikes the skin, and humans synthesize vitamin D3
- Most healthy fish contain vitamin D3
- Vegetarians/vegans may be opposed to D3

**So what is the connection  
between vitamin D  
deficiency and asthma?**



# Vitamin D

Vitamin D has complex effects on pulmonary cell biology and immunity with impact on inflammation, host defense, wound healing, repair, and other processes.

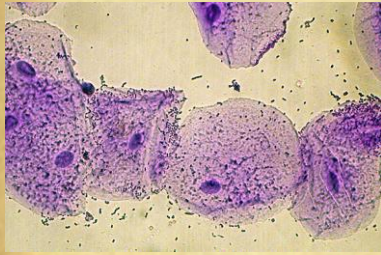


# Association between Vitamin D and Asthma

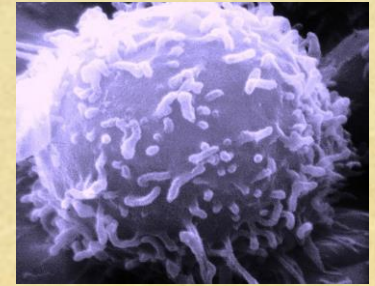
Epidemiological evidence and prospective studies have linked vitamin D deficiency with increased risk of many chronic diseases including:

Diabetes Mellitus, breast cancer, cardiovascular diseases, autoimmune disease, infectious diseases and...

Asthma

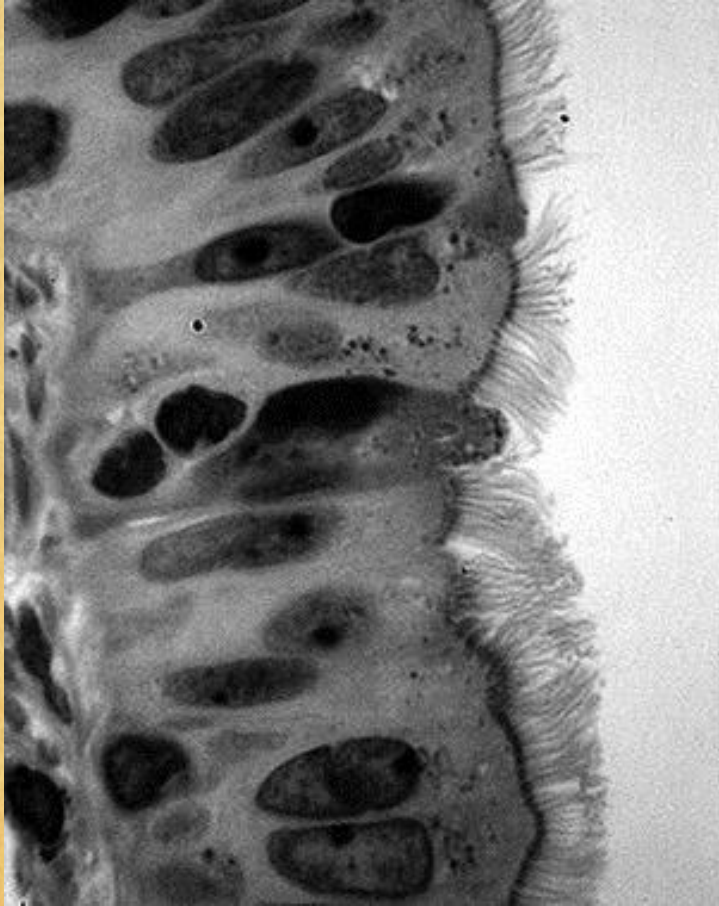


# Vitamin D



- ◆ B lymphocytes:  $1,25\text{-(OH)}_2\text{D}_3$  plays a role in B cell homeostasis – keeping balance
- ◆ T lymphocytes: within the adaptive immune system it can help with proliferation and function of T lymphocytes
- ◆ Airway epithelial cell can express enzymes of the vitamin D metabolism that are capable of converting  $25\text{-(OH)D}_3$  to  $\rightarrow 1,25\text{-(OH)}_2\text{D}_3$

# Epithelial Damage in Asthma



# Airway Epithelial Cells

- ♦ Airway epithelial cells can hydroxylate 25(OH)D to its active form → 1,25(OH)<sub>2</sub>D<sub>3</sub>
- ♦ Resulting in:
  - increased recruitment of macrophages
  - enhanced production of cathelicidin and CD14
  - potentiates host defenses against Mycobacterium tuberculosis and other bacteria, fungi, and viruses

(Holick 2009)



# Impact of Asthma and Vitamin D



- ◆ A role in asthma and atopy has been suggested as many immune cells possess vitamin D receptors.
- ◆ Genetic associations have been demonstrated between receptor variants and asthma.
- ◆ Vitamin D is of particular interest in asthma since vitamin D concentrations decrease with increased time spend indoors, decreased exposure to sunlight, less exercise, obesity, and inadequate calcium intake.

# Vitamin D & Asthma



- ◆ Vitamin D deficiency is found to be linked to increased airway reactivity, lower lung functions, and worse asthma control.
- ◆ Risk factors for vitamin D deficiency include obesity, African-American, and living in Westernized countries.
  - These are also populations known to be at higher risk for developing asthma.

# Vitamin D & Asthma



- ◆ Vitamin D deficiency may predispose to asthma or increase asthma morbidity by altering lung development in early life.
- ◆ Vitamin D may influence asthma by regulating the expression of disease-susceptibility genes.

# Vitamin D & Asthma



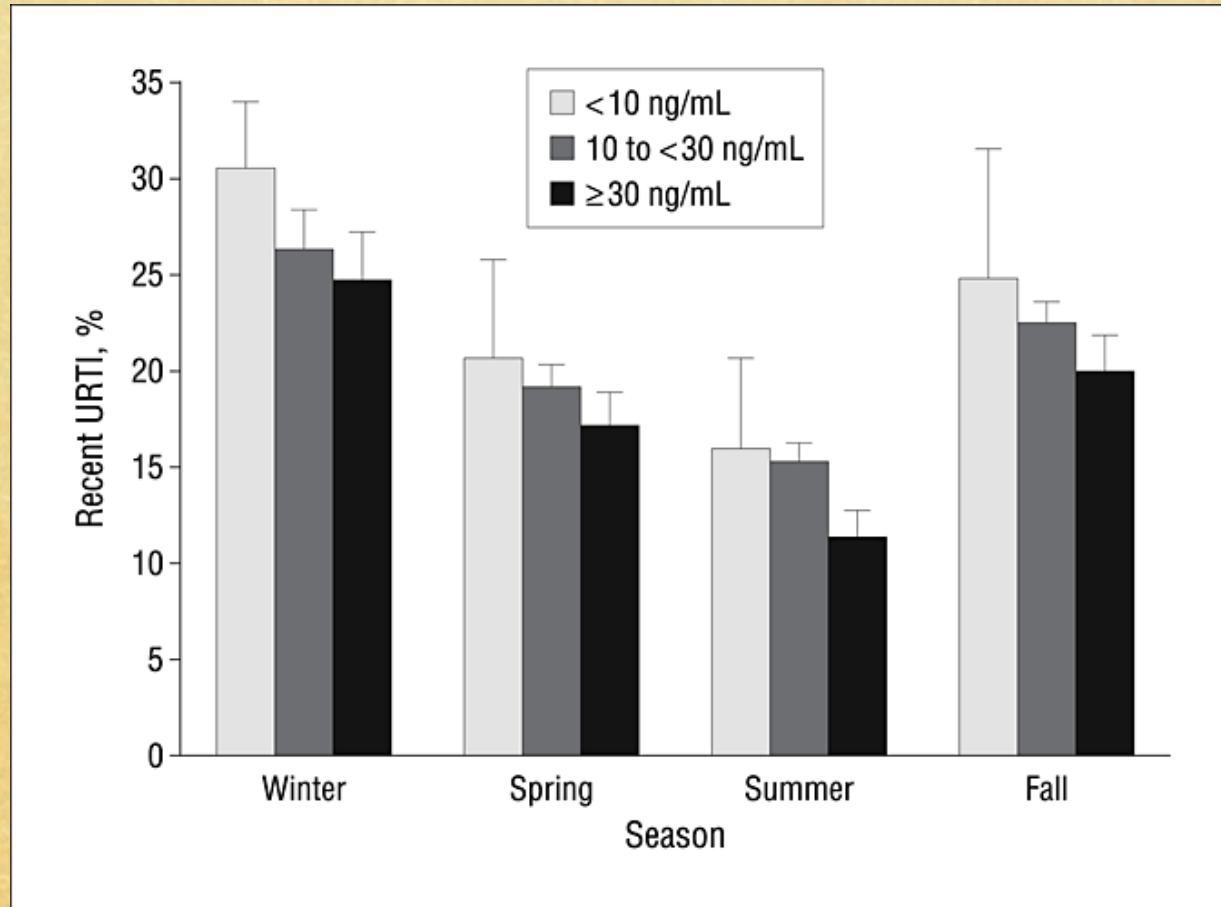
- ◆ Glucocorticoid responses are seen with 25(OH)D levels > 30 ng/ml
- ◆ Lower serum 25(OH) D levels are associated with:
  - increased airway hyperresponsiveness
  - impaired lung functions
  - decreased in vitro corticosteroid response



# Vitamin D Viral Infections

- ◆ Viral infections play a significant role in
  - precipitating asthma exacerbations
  - loss of lung function
  - rhinovirus
- ◆ Vitamin D deficiency is associated with:
  - ◆ Increased rate of infections overall, particularly viral respiratory and in young children
  - ◆ Increased pro-inflammatory cytokines and decreased factors for viral inactivation on airway epithelium
  - ◆ Increased markers of allergy and asthma severity, and exacerbations

## Participants with recent upper respiratory infection (URI) stratified by serum 25-hydroxyvitamin D level and season



# Vitamin D & Asthma



- ◆ Vitamin D deficiency and asthma share risk factors such as urban residence, obesity, African American ethnicity.
- ◆ Vitamin D has been positively correlated with lung function measures.
- ◆ Vitamin D deficiency may predispose to asthma or increase asthma morbidity by altering lung development in early life.
- ◆ Vitamin D may influence asthma by regulating the expression of disease-susceptibility genes.

# Vitamin D & Asthma

- Higher levels of vitamin D are correlated with improved lung function compared to individuals whose levels of the vitamin are lower.
- Childhood asthma is associated with vitamin D deficiency.
- Maternal vitamin D intake has been demonstrated to be inversely associated with increased risk of wheezing and asthma.
- Vitamin D may be involved in asthma pathogenesis through its effect on the immune system.

# Asthma and Obesity

- ◆ An inverse relationship exists between body mass index and vitamin D status.
  - secondary to decreased bioavailability.
- ◆ Vitamin D can be locked up in fat stores in obese people, who have been found to have lower levels of 25-hydroxyvitamin D and are at risk of deficiency.

# Vitamin D & Allergic Diseases

- ◆ Studies have hypothesized a relationship between vitamin D and the rising incidence of food allergies.
- ◆ Development of many skin diseases including eczema and psoriasis.
  - Eczema tends to be better controlled during the summer months. Possibly the potential effect of sun exposure and the consequent increase of vitamin D
- ◆ Vitamin D receptors (VDR) have been found in the proliferating keratin cells.

# Vitamin D & Atopic Dermatitis

- ◆ Several studies have linked vitamin D supplementation with either the decreased risk or clinical improvement of atopic dermatitis
- ◆ Patients with vitamin D deficiency have been more likely to report atopic dermatitis symptoms

Oren, et al., 2008



How do we  
screen for Vitamin D  
deficiency?



# First of all.....Who is at risk for vitamin D deficiency?

- ▶ Limited Sunlight Exposure
- ▶ People with increased skin pigmentation/dark skin
- ▶ Malabsorption syndromes
- ▶ Osteoporosis and osteopenia
- ▶ Elderly patients
- ▶ Some chronic illnesses.... asthma



# How Do we Screen for Vitamin D Deficiency?

Screening should be performed using a reliable assay for 25-hydroxy-vitamin D (25[OH]D)

**NOT** → 1,25-dihydroxy-vitamin D (1,25[OH]<sub>2</sub>D)

The prohormone 25(OH) D is an indicator of supply rather than function.

Determination of vitamin D status is NOT based on measurement of serum 1,25(OH)<sub>2</sub>D concentration.

**The most suitable indicator of  
vitamin D status  
25(OH)D**

- ◆ The most stable and plentiful metabolite of vitamin D in human serum
- ◆ Half-life of approximately 3 weeks

# Screening Vitamin D levels in Patients with Asthma

A question often asked by health care professionals is.....

should patients with asthma should be screened for vitamin D deficiency or insufficiency.

There is **no** evidence to support such screening for the purpose of asthma management.

# Screening for Vitamin D Deficiency

Two arguments can be made in regards to vitamin D screening and treatment:

1. Patients routinely should be screened for vitamin D deficiency
2. Patients with suspected vitamin D deficiency should be treated empirically.

# Screening Vitamin D levels in Patients with Asthma

It may be advisable to measure a serum vitamin D level in children and adults who belong to groups at high risk for vitamin D deficiency

→ African Americans and individuals who are obese or have limited sun exposure

**Treatment with  
vitamin D may improve  
clinical outcomes in  
patients with asthma.**

# **Reference**

## **Adult and Pediatric Prevention & Treatment Recommendations**



# Pediatrics

## Prevention of vitamin D deficiency

### Breast-fed infants

- ◆ 400 IU/day beginning in the first few days of life.
- ◆ Continue supplementation until infant is weaned to  $\geq 1,000$  mL/day or 1 qt/day of vitamin D-fortified formula or whole milk

→ whole milk given after 12 months of age

### Formula-fed infants

- ◆ ingesting  $< 1,000$  mL of vitamin D-fortified formula: 400 IU/day

### Premature neonates:

- ◆ 400 to 800 IU/day or 150 to 400 IU/kg/day

# Pediatrics

## Prevention of vitamin D deficiency

- ◆ Children 400 IU/day -- ingesting <1,000 mL of vitamin D-fortified milk
- ◆ Children with increased risk of vitamin D deficiency:
  - use laboratory testing 25(OH)D, PTH, bone mineral status to evaluate
- ◆ Adolescents without adequate intake:  
400 IU/day

# Pediatrics

## Treatment vitamin D deficiency

- ◆ **Infants:** 2,000 IU daily or 50,000 IU once weekly for 6 weeks to achieve a serum 25(OH)D level >20 ng/mL -- followed by a maintenance dose of 400 to 1,000 IU daily.
- ◆ **Children and Adolescents:** 2,000 IU daily or 50,000 IU once weekly for 6 to 8 weeks to achieve serum 25(OH)D level > 20 ng/mL -- followed by a maintenance dose of 600 to 1,000 IU daily.

In addition to calcium and phosphorus supplementation

# Adults

## Treatment of vitamin D deficiency

- ◆ 6,000 units daily or 50,000 IU once weekly for 8 weeks to achieve serum 25(OH)D level >30 ng/mL
- ◆ Maintenance dose → 1,500 to 2,000 IU daily.

Holick 2011

# Adults

## Prevention of vitamin D deficiency

- ◆ Adults 19 to 70 years: RDA: 600 IU/day (IOM 2011)
- ◆ Adults >70 years: RDA: 800 IU/day (IOM 2011)
- ◆ 1,500 to 2,000 units daily to maintain serum 25(OH)D levels >30 ng/mL (Holick 2011)
- ◆ Female: Pregnancy/Lactating: RDA: 600 IU/day (IOM 2011)
- ◆ Osteoporosis prevention (off-label): Adults  $\geq$ 50 years 800 to 1,000 IU/day (National Osteoporosis Foundation Guidelines, 2014)

# Role of Health Care Professionals

- ◆ Identification of patients at risk for vitamin D deficiency
- ◆ Appropriate screening
- ◆ Education → health care professionals and patients!

# Take Home Message



- ◆ Vitamin D deficiency is prevalent worldwide.
- ◆ 5-10 minutes of direct exposure to the arms and legs = 3000 IU of vitamin D3
- ◆ Vitamin D deficiency associated with:
  - ◆ Increased rate of infections overall, particularly viral respiratory and in young children
  - ◆ Increased pro-inflammatory cytokines and decreased factors for viral inactivation on airway epithelium
  - ◆ Increased markers of allergy and asthma severity, and exacerbations
- ◆ Need for RCTs to document improvement in outcomes with vitamin D supplementation



# Take Home Message

- ◆ Current evidence most consistently favors a beneficial effect of vitamin D on asthma morbidity by prevention of viral infections and enhanced steroid responsiveness.
- ◆ Vitamin D influences process such as immune regulation, host defense, inflammation, or cell proliferation.
- ◆ Vitamin D is now recognized as an immunomodulator.
- ◆ Vitamin D deficiency can increase risk for more serious diseases.
- ◆ Conflicting data indicate the need for RCTs to demonstrate the effect of vitamin D on the prevention and control of asthma and allergic disease.



**Now go out there and make  
sure your patients are not  
vitamin D deficient!**



# Thank YOU!



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