Vitamin D and Allergic disorders.

‘D-Lightful’, ‘sunshine vitamin’, Jua Kali!!

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Epidemiology of allergic diseases.

Allergic diseases and asthma are increasing worldwide, particularly in low and middle income countries.

In addition, the complexity and severity of allergic disorders, including asthma, continue to increase especially in children and young adults, who are bearing the greatest burden of these trends.

This upsurge in the prevalence of allergies is observed as societies become more affluent and urbanized.

An increase in environmental risk factors like outdoor and indoor pollution combined with reduced biodiversity also contributes to this rise in prevalence.

Clinical services to help patients with such diseases are either non-existent or limited and lacking in cost-effective solutions.

*statement from WAO white book on allergy 2013 update.

PREVALENCE OF VIT D DEFICIENCY.

It has been estimated that 20–100% of U.S., Canadian, and European elderly men and women still living in the community are vitamin D deficient.

Children and young and middle-aged adults are at equally high risk for vitamin D deficiency and insufficiency worldwide.

Vitamin D deficiency is common in Australia, the Middle East, India, Africa, and South America.

In addition, 42% of African-American girls and women aged 15–49 yr throughout the United States had a blood level of 25(OH)D below 15 ng/ml at the end of the winter.

Pregnant and lactating women who take a prenatal vitamin and a calcium supplement with vitamin D remain at high risk for vitamin D deficiency.

* The Endocrine Society clinical practice guideline.

Risk groups

Rickets

Osteoporosis

Chronic kidney disease

Hepatic failure

Malabsorption syndromes

Cystic fibrosis

Inflammatory bowel disease

Obese children and adults (BMI 30 kg/m2).

*allergic diseases??

Crohn's disease

Anti-seizure medications

Glucocorticoids

AIDS medications

Antifungals, e.g. ketoconazole

Cholestyramine

African-American and Hispanic children and adults

Pregnant and lactating women

Older adults with history of non-traumatic fractures

Tuberculosis

* The Endocrine Society clinical practice guideline.

SOURCES OF VIT D.

Cod liver oil ~400–1,000 IU/teaspoon vitamin D_3

Salmon, mackerel, tuna and sardines.

Shiitake mushrooms, sun-dried ~1,600 IU/3.5 oz vitamin D_2

Egg yolk ~20 IU/yolk vitamin D_3 or D_2

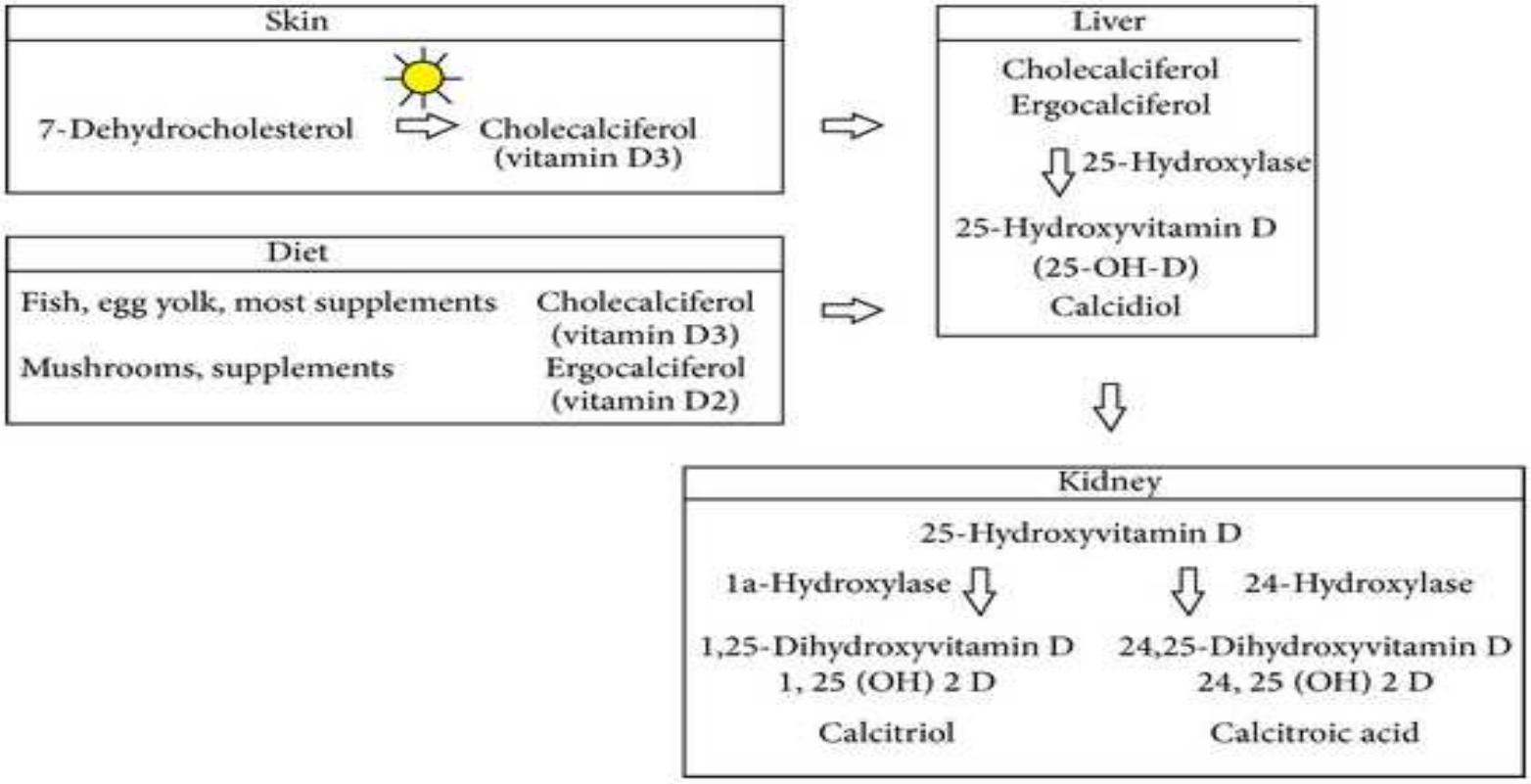
Sunlight/UVB radiation ,exposure of arms and legs equal to ingesting ~3,000 IU vitamin D_3.

Fortified foods,juices, dairy , cereals and foods.

Supplements.

IU = 25 ng. Reproduced with permission from M. F. Holick: N Engl J Med 357:266–281, 2007 (3).

VITAMIN D METABOLISM



INSTITUTE OF MEDICINE(IOM) REFERENCE RANGES FOR SERUM 25(OH)D

Table 1: Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health* [1]		
nmol/L**	ng/mL*	Health status
<30	<12	Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults
30 to <50	12 to <20	Generally considered inadequate for bone and overall health in healthy individuals
≥50	≥20	Generally considered adequate for bone and overall health in healthy individuals
>125	>50	Emerging evidence links potential adverse effects to such high levels, particularly >150 nmol/L (>60 ng/mL)

** 1 nmol/L = 0.4 ng/Ml, 1mcg=40iu

Table 3. Vitamin D intakes recommended by the IOM and the Endocrine Practice Guidelines Committee

Life Stage Group	IOM Recommendations				Committee recommendations for patients at risk for vitamin D deficiency	
	AI	EAR	RDA	UL	Daily requirement	UL
INFANTS						
0 to 6 months	400 IU (10 μg)			1,000 IU (25 μg)	400–1,000 IU	2,000 IU
6 to 12 months	400 IU (10 μg)			1,500 IU (38 μg)	400–1,000 IU	2,000 IU
CHILDREN						
1–3 yr		400 IU (10 μg)	600 IU (15 μg)	2,500 IU (63 μg)	600–1,000 IU	4,000 IU
4–8 yr		400 IU (10 μg)	600 IU (15 μg)	3,000 IU (75 μg)	600–1,000 IU	4,000 IU
MALES						
9–13 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
51–70 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
> 70 yr		400 IU (10 μg)	800 IU (20 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
FEMALES						
9–13 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
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PREGNANCY						
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
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LACTATION[a]						
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU

AI, Adequate intake; EAR, estimated average requirement; UL, tolerable upper intake level.

a Mother's requirement, 4,000–6,000 IU/d (mother's intake for infant's requirement if infant is not receiving 400 IU/d).

VITAMIN D IN ASTHMA AND ALLERGY….

- Cholecalciferol from the skin or derived from nutrition is metabolized in the liver to 25-hydroxyvitamin D (25-OH-D)- Calcidiol. This is the major circulating form; thus it is usually used to measure serum vitamin D levels.
- 25-OH-D is then transported to the kidneys where it is metabolized to its active form calcitriol (1,25(OH)D,1,25-dihydroxyvitamin D.
- Guidelines from the Institute of Medicine (IOM) for bone health define “vitamin D deficiency” as serum 25(OH)D levels below 30 nmol/L (<12 ng/mL), while sufficient vitamin D levels should be considered serum levels of at least 50 nmol/L (20 ng/mL) .
- Due to evidence of vitamin D insufficiency on allergic disease prevalence, many researchers categorized vitamin D sufficiency as >75 nmol/L (30 ng/mL). Above 100nmol is high.

Mehmet Hoxha,1 Maria Zoto, Leonard Deda, and Gentian Vyshka. Vitamin D and Its Role as a Protective Factor in Allergy. International Scholarly Research Notices. Volume 2014 (2014) .http://dx.doi.org/10.1155/2014/951946

Immunomodulation…..

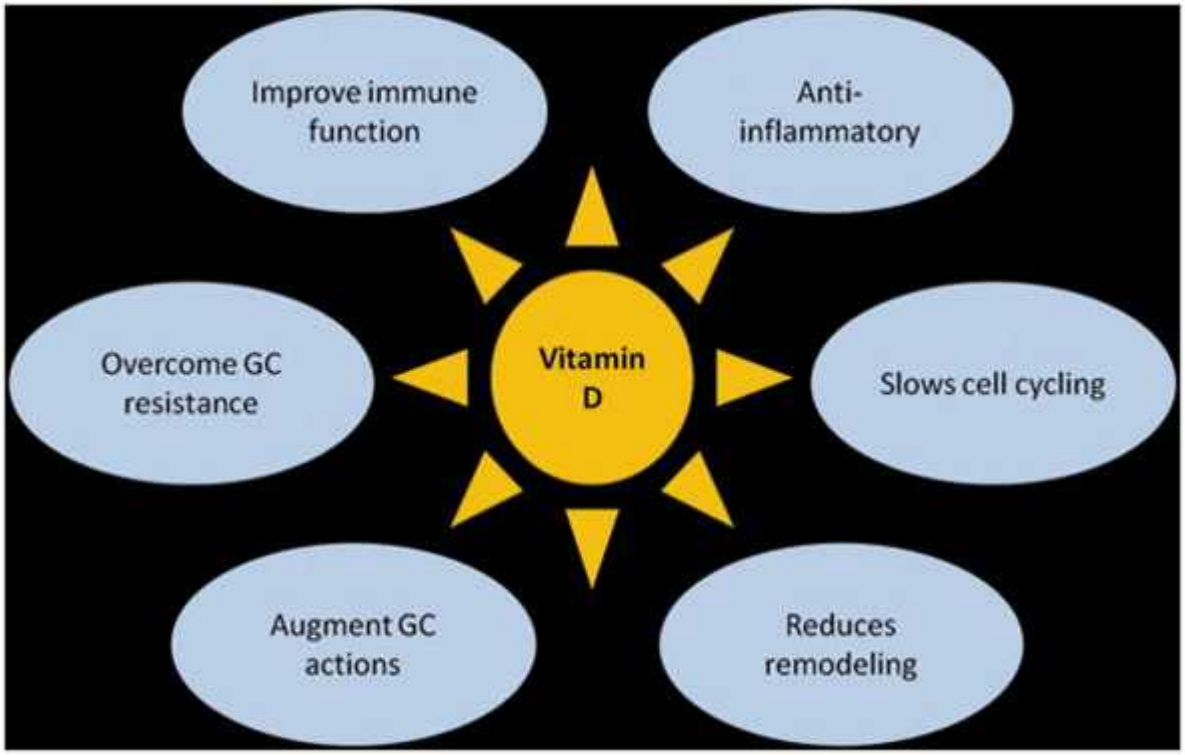
Studies on naïve cd4/cd8 cord cells shows inhibitory effects of IFN-Y production thus th2 response suppression.

- Murine models on Vit D deficiency or defective receptor signalling favors a TH1 response.
- Knockout mice did not develop asthma but were noted to have an increased production of TH2 related genes. Receptor polymorphisms may be a phenotype of severe asthma.
- Inn atopic dermatitis, Cathelicidin levels, an antimicrobial peptide is associated with deficiency.
- VDR is expressed in proliferative keratinocytes ad associated with faster healing.
- Increases PGDF syntheisis that promotes wound healing.

Immunomodulation….

- Increases TNF-α production useful for keratinocyte differentiation.
- Vit D deficiency is associated with reduced level of proteins necessary for permeability barrier function including filaggrin and delays skin barrier recovery after disruption.
- Vit D shifts dendritic cell production to a tolerogenic form and increases T-Reg cell production.

VITAMIN D IN ASTHMA AND ALLERGY.



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Investig Med. 2011 Dec; 59(8): 1200–1202. **The Mechanism of Action of Vitamin D in the Asthmatic Lung**
Sabah F Iqbal, MD[1,2,3] and Robert J Freishtat, MD, MPH[1,2,3]

VITAMIN D IN ASTHMA AND ALLERGY…

Immune regulation of Treg cells by vitd and IL-10 production(anntiinflammatory) ,both factors known to be behind th2 responses and dyregulation in allergic diseases.

- Decreasing inflammation, which may reduce acute asthma symptomology,
- Reducing remodelling, which can reduce chronic lung dysfunction,
- Augmenting GC function, which may allow lower total doses of steroids to be administered.
- The main source of vitamin D in humans is solar UV-B (290–315 nm wavelengths) radiation, which influences the formation of cholecalciferol.

J Investig Med. 2011 Dec; 59(8): 1200–1202. **The Mechanism of Action of Vitamin D in the Asthmatic Lung**

Sabah F Iqbal, MD[1,2,3] and Robert J Freishtat, MD, MPH.

Maternal Vit D intake and Eczema incidence

- 1354 mother child pairs studied in Japan.
- Maternal intake during pregnancy monitored.
- Infants 23-29 months assessed.
- Higher maternal intake of total dairy products, cheese, yogurt, and calcium during pregnancy may reduce the risk of infantile eczema, physician-diagnosed asthma, physician-diagnosed atopic eczema, and physician-diagnosed atopic eczema, respectively.
- Higher maternal intake of vitamin D during pregnancy may increase the risk of infantile eczema.

Miyake Y[1], Tanaka K[2], Okubo H[3], Sasaki S[3], Arakawa M[4] **Maternal consumption of dairy products, calcium, and vitamin D during pregnancy and infantile allergic disorders.** Ann Allergy Asthma Immunol. 2014 Jul;113(1):82-7. doi: 10.1016/j.anai.2014.04.023.

Vit D ,asthma and Rhinitis

We examined data from 44,825 women enrolled during pregnancy in the longitudinal Danish National Birth Cohort (1996–2002).

We estimated vitamin D intake from diet and supplements based on information from a validated food frequency questionnaire completed in gestational week 25. 2/3 on supplements. Median intake 400iu.

Asthma incidence at 18 months physician diagnosed, asthma and allergic rhinitis at 7 years as per ISAAC study criteria and national registry records.

In multivariable analysis, mothers in the highest (vs. lowest) quintile of total vitamin D intake were less likely to have children classified with current asthma at 7 years and they were less likely to have children admitted to the hospital due to asthma .We found no associations with child asthma at 18 months or with allergic rhinitis at 7 years.

Higher intake levels of Vit D need to be studied to ascertain the protective threshold against asthma.

*Maslova et al. BMC Pregnancy and Childbirth 2013, 13:199 .http://www.biomedcentral.com/1471-2393/13/199

Vitamin D Insufficiency and asthma.

- Cohort studies in children have attempted to perform longitudinal analyses to correlate Vitamin D and allergy development .In the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort of over 300 children, serum vitamin D concentrations at age 4 years were inversely associated with asthma at ages 4–8 years.

- Hollams *et al.*,in a cohort of over 600 Australian children, showed that higher vitamin D levels at age 6 were protective against the development of asthma, rhino conjunctivitis, and atopy at age 14. These effects appeared to be stronger for boys than for girls.

van Oeffelen AA, Bekkers MB, Smit HA, *et al.* Serum micronutrient concentrations and childhood asthma: the PIAMA birth cohort study. Pediatr Allergy Immunol 2011; 22:784–793.

Hollams EM, Hart PH, Holt BJ, *et al*. Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. Eur Respir J 2011; 38:1320–1327.

Vitamin D insufficiency……..

Gupta *et al.* studied 86 children with a mean age of 11.6 years – 36 severe, therapy-resistant asthmatic, 26 moderate asthmatic, and 24 nonasthmatic controls.

Among 19 severe, therapy-resistant asthmatic children who had adequate endobronchial biopsy specimens, vitamin D levels were found to be inversely related to the airway smooth muscle mass.

This finding is consistent with previous findings that vitamin D can prevent airway smooth muscle proliferation, and has implications on airway remodelling.

Gupta A, Sjoukes A, Richards D, *et al.* Relationship between serum vitamin D, disease severity and airway remodelling in children with asthma. Am J Respir Crit Care Med 2011; 184:1342–1349.

Vitamin D supplementation for prophylaxis against allergy and asthma in children……..

- Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in pregnant women to determine whether prenatal supplementation can prevent the development of asthma and allergies in the women's offspring.

- A secondary aim is to determine whether vitamin D supplementation can prevent the development of pregnancy complications, such as preeclampsia, preterm birth, and gestational diabetes.

- Women were randomized to the treatment arm of 4,000 IU/day of vitamin D_3 plus a daily multivitamin that contained 400 IU of vitamin D_3 or the placebo arm of placebo plus a multivitamin that contained 400 IU daily of vitamin D_3.

- Women who were between the gestational ages of 10–18 weeks were randomized from three clinical centers across the United States.

- Litonjua AA[1], Lange NE[2], Carey VJ[3], Brown S[4], Laranjo N[4], Harshfield BJ[4], O'Connor GT[5], Sandel M[6], Strunk RC[7], Bacharier LB[7], Zeiger RS[8], Schatz M[8], Hollis BW[9], Weiss ST[3]. **The Vitamin D Antenatal Asthma Reduction Trial (VDAART): rationale, design, and methods of a randomized, controlled trial of vitamin D supplementation in pregnancy for the primary prevention of asthma and allergies in children.** Contemp Clin Trials. 2014 May;38(1):37-50. doi: 10.1016/j.cct.2014.02.006. Epub 2014 Mar 12.

Vitamin D supplementation for prophylaxis against allergy and asthma in children……..

- Supplementation took place throughout pregnancy. Monthly monitoring of urinary calcium to creatinine ratio was performed in addition to medical record review for adverse events.
- Offspring are being evaluated quarterly through questionnaires and yearly during in-person visits until the 3rd birthday of the child.
- Ancillary studies will investigate neonatal T-regulatory cell function, maternal vaginal flora, and maternal and child intestinal flora.

- Litonjua AA[1], Lange NE[2], Carey VJ[3], Brown S[4], Laranjo N[4], Harshfield BJ[4], O'Connor GT[5], Sandel M[6], Strunk RC[7], Bacharier LB[7], Zeiger RS[8], Schatz M[8], Hollis BW[9], Weiss ST[3]. **The Vitamin D Antenatal Asthma Reduction Trial (VDAART): rationale, design, and methods of a randomized, controlled trial of vitamin D supplementation in pregnancy for the primary prevention of asthma and allergies in children.** Contemp Clin Trials. 2014 May;38(1):37-50. doi: 10.1016/j.cct.2014.02.006. Epub 2014 Mar 12.

Vitamin D supplementation for prophylaxis against allergy and asthma in Adults……..

- To evaluate if vitamin D supplementation would improve the clinical efficacy of inhaled corticosteroids in patients with symptomatic asthma and lower vitamin D levels.

- Oral vitamin D_3 (100 000 IU once, then 4000 IU/d for 28 weeks; n = 201) or placebo (n = 207) was added to inhaled ciclesonide (320 µg/d). If asthma control was achieved after 12 weeks, ciclesonide was tapered to 160 µg/d for 8 weeks, then to 80 µg/d for 8 weeks if asthma control was maintained.

- The primary outcome was time to first asthma treatment failure (a composite outcome of decline in lung function and increases in use of β-agonists, systemic corticosteroids, and health care).

- Vitamin D_3 did not reduce the rate of first treatment failure or exacerbation in adults with persistent asthma and vitamin D insufficiency. These findings do not support a strategy of therapeutic vitamin D_3 supplementation in patients with symptomatic asthma.

Mario Castro, MD, MPH, Tonya S. King, PhD,et al. **Effect of Vitamin D_3 on Asthma Treatment Failures in Adults With Symptomatic Asthma and Lower Vitamin D Levels**
The VIDA Randomized Clinical Trial. JAMA. 2014 May; 311(20): 2083–2091. doi: 10.1001/jama.2014.5052.PMCID: PMC4217655.NIHMSID: NIHMS619559

SUMMARY.

- Vitamin D is an immunomodulator and insufficiency is inversely associated with severity of asthma and development of allergic diseases.
- Cathelicidin, an antimcrobial peptide,T-reg cells and beta defensins production and regulation are regulated by Vit D and play a role in atopic dermatitis.

However, the optimal level of vitamin D that decrease both the risk for development and severity of these disorders remains elusive. Results of ongoing clinical trials of vitamin D supplementation will be needed before recommendations can be firmly established.