Overview of Presentation

- Essential info about vitamin D, including its role as a potent immunomodulator
- Emphasis on RCTs and IPD meta-analyses
- Major outcomes:
  - Acute respiratory infections / childhood wheezing
  - Asthma: incident asthma vs exacerbations
  - COPD exacerbations
- Vitamin D mega-trials
- Summary & clinical implications
Severe Vitamin D Deficiency \(\rightarrow\) Rickets
Vitamin D Synthesis & Metabolism

- Sun
  - 7-dehydro cholesterol
    - Skin
- Liver
  - 25-hydroxylase (CYP27A1)
- Kidney
  - 1α-hydroxylase (CYP27B1)
  - 24-hydroxylase
    - 24,25(OH)₂D
    - 1,25(OH)₂D

Diet & Suppl.

- Fish
- Milk
- Vitamin D supplements
Vitamin D Receptor (VDR)

- VDR present in most tissues and cells of body
- Growing recognition that many different cells have the enzymatic machinery to convert 25(OH)D to the active hormone, 1,25(OH)$_2$D
- >2,700 binding sites for VDR along genome
- Significant effects on activity of >220 genes
Consistent, Year-Round Exposure to UVB

Figure 1. Global climatology (1979-1992) of mean daily erythemal (i.e., “sunburning”) UV dose (from the NCAR web site http://www.acd.ucar.edu/TUV/).
Skin Color and Vitamin D

Risk Factors for Low 25(OH)D

- **Winter** at higher latitudes  
  USA: Nov – March  
  NZ: May – Sept
- Darker skin
- **Lifestyle-related** ↓ UVB exposure  
  - Newborns with exclusive breastfeeding  
  - Age 50+ (more indoors + ↓ skin conversion)  
  - Sunscreen use (only if applied correctly)
- Obesity (fat storage)
Serum 25(OH)D  
*cut-points controversial*

- **Conversion factor:** $1 \text{ ng/ml} = 2.5 \text{ nmol/L}$
- **Average varies widely across countries & by other factors** (e.g., USA $55 \text{ nmol/L}$, with black < white)
- **“Inadequate” vitamin D**
  - $<25 \text{ nmol/L}$ (few researchers)
  - $<50 \text{ nmol/L}$ (AAP, IOM)
  - $<75 \text{ nmol/L}$ (some researchers)
  - $<100 \text{ nmol/L}$ (few researchers)

**Optimal level also controversial ...**
- $\geq 75 \text{ nmol/L}$
- $100 \text{ nmol/L}$
- $100-150 \text{ nmol/L}$
- $150-200 \text{ nmol/L}$

multiple sources
Dietary Vitamin D $\rightarrow$ Serum 25(OH)D

- Dietary intake has modest effect on 25(OH)D:
  - Glass of fortified milk (100 IU) = $\uparrow$ 2.5 nmol/L
  - 10 µg (400 IU) per day = $\uparrow$ 10 nmol/L
  - 25 µg (1000 IU) per day = $\uparrow$ 25 nmol/L

- Cod liver oil: variable (400 - 1300 IU per tbsp)

Skin can create $\sim$10,000 IUs after only 15-20 minutes of direct UVB exposure
Non-Calcemic Functions of Vitamin D

Holick, J Clin Invest 2006
Cathelicidin Antimicrobial Peptide (CAMP)

Human CAMP gene is direct target of vitamin D receptor (VDR) and strongly up-regulated in myeloid cells by 1,25(OH)$_2$D3

Gombart et al, *FASEB* 2005
Immunologic Effects of Vitamin D

Remarks on the red-light treatment of small-pox.

Is the treatment of small-pox patients in broad daylight warrantable?

By Professor Niels R. Finsen, M.D.,
Director of the Finsen Medical Light Institute of Copenhagen.

Ten years have elapsed since I first advocated red light in the treatment of small-pox. During my investigations on the effect of various rays of light my attention was directed to some old reports, especially American and English, on the injurious influence of light in small-pox, which coincided with my own observations as to the effect of light upon the skin. Knowing full well, if this were so, that the injury was due to the chemical rays of light, I recommended that the patients be protected against these rays by placing them in red light, exactly in the same way that photographers protect their plates from the chemical rays. In the course of years this treatment was tried in many places, meeting everywhere with unquestionable success. At the present time about twenty physicians in various countries, mostly, however, in Scandinavia, have given this treatment a trial, and all of them, have obtained most favourable results when the treatment has been properly conducted.
1903 Nobel Prize – UVR and Lupus Vulgaris
Heliotherapy for TB
Maternal Vitamin D and Risk of Child Wheezing

ARI By Age 3 Months

• Season-adjusted odds ratio (OR) was higher among those with low cord blood 25(OH)D:

  - 75+ nmol/L: 1.00
  - 25-74: 1.39 (95%CI, 0.98-1.99)
  - <25: 2.16 (95%CI, 1.35-3.46)

• This inverse association was not materially changed by adjustment for 14 other factors

Camargo et al, *Pediatrics* 2011
Cord Blood 25(OH)D, Wheeze, and Asthma

Camargo et al, *Pediatrics* 2011
Study Designs & Causal Inference

**Weak**
- case report
- case series
- cross-sectional study
- case-control study
- cohort study
- nonrandomized trial
- multiple time series

**Strong**
- randomized controlled trial
Continued Role for Observational Research

• To generate new hypotheses

• To address questions that are impractical or even unethical to test with RCT, such as:
  – Associations among those with suboptimal care (including very low baseline 25(OH)D levels)
  – Dose-response across wide range of vitamin D (including NOT taking any vitamin D supplement)

• Even with outstanding adherence to protocol, high statistical power, and so forth… most RCTs provide answers for very specific questions only
Interpretation of RCTs on Vitamin D

Participants
- Age (eg, infants vs adults)
- Baseline 25(OH)D (eg, <25 vs 75 nmol/L)
- Genetic factors (eg, VDR, DBP)
- Comorbidities (eg, asthma, immunodeficiency)

Vitamin D regimen
- Dose (eg, 400 IU vs 2000 IU)
- Frequency (eg, daily vs monthly)
- Duration (eg, <3 months vs 12 months)
- Adherence with protocol
Acute Respiratory Infections

• Location
  – Upper respiratory (eg, common cold)
  – Lower respiratory (eg, pneumonia)

• Pathogen
  – Virus (eg, rhinovirus, influenza)
  – Bacteria (eg, pneumococcus, Staph aureus)
  – Fungus

• Importance of ARI in asthma and COPD

• Thus, we should anticipate “noise” when using ARI (composite outcome) in heterogenous populations
Two RCTs on Vitamin D and ARI

- **Mongolian children (n=247)**
  - Daily ingestion of fortified vs non-fortified cow’s milk over one winter (Jan to March) – only 300 IU daily
  - Primary outcome: parental report of ARI in past 3 months
  - Serum 25(OH)D: baseline 17 nmol/L → 47 nmol/L
  - ↓ risk of ARI: OR 0.50 (95%CI, 0.28-0.88)

- **NZ adults (n=322)**
  - 100,000 IU vitamin D₃ monthly x 18 months
  - Primary outcome: number of URI episodes
  - Serum 25(OH)D: baseline 72 nmol/L → 125+ nmol/L
  - No difference in ARI: OR 0.97 (95%CI, 0.85-1.11)

IPD Meta-Analysis of RCTs – Vit D & ARI

• 25 RCTs from around world; n=11,321 participants

• Random effects adjusting for age, sex, study duration, and clustering by study. Pre-specified subgroup analysis by baseline 25(OH)D and dosing regimen.

• Vit D supplementation reduced risk of ARI among all participants (aOR 0.88, 95%CI 0.81-0.96, P=0.003)

• Subgroup analyses: stronger effects among those with baseline 25(OH)D < 25 nmol/L (aOR 0.62), and those not receiving one or more bolus doses (aOR 0.81).

Martineau et al, BMJ 2017
RCTs on Persistent/Recurrent Wheezing

• **ABCvitaminD** (Bisgaard)  
  - 600 women, ages 18+ years, GA 22-26 weeks  
  - 2,800 IU daily during pregnancy (vs 400 IU daily)  
  - Primary outcome: “persistent wheeze” at age 3y  
    High 16% vs Low 20%; **HR 0.8** (0.5-1.1; P=0.16)  

• **VDAART** (Weiss)  
  - 870 women, ages 18-39 years, GA 10-18 weeks  
  - 4,400 IU daily during pregnancy (vs. 400 IU daily)  
  - Primary outcome: “recurrent wheeze” at age 3y  
    High 24% vs Low 30%; **HR 0.8** (0.6-1.0; P=0.051)  

SR of RCTs – Vit D & Wheezing

- 2 RCTs; n=1,387 children

- Vit D supplementation reduced risk of persistent wheeze (aOR 0.81, 95%CI 0.67-0.98).

- “As early childhood wheeze is not necessarily the same as asthma, longer-term follow-ups of these trials are required to establish the efficacy of vitamins in prevention of actual asthma in later childhood.”

Vahdaninia et al, JACI Pract 2017
Asthma Exacerbations

• Prospective cohort data suggest **benefit**
  – Childhood wheezing studies
  – USA (Brehm, *J Allergy Clin Immunol* 2010)
    n=1024 children, baseline 25(OH)D, 4 years:  P=0.01

• First published RCTs of asthma
    n=234 children, 1200 IU daily x 4 months:  P<0.01
  – Poland (Majak, *J Allergy Clin Immunol* 2011)
    n=48 children, 500 IU daily x 6 months:  P<0.01
  – USA (Castro, *JAMA* 2014)
    n=408 adults, 100k then 4000 IU daily x 28 weeks:  P=0.54
    Primary outcome = time to 1st treatment failure (composite)
Adding Vitamin D to ICS in Adult Asthma

Figure 2. Primary Treatment Failure Outcome

HR 0.9 (0.6-1.3), P=0.54

Castro et al, JAMA 2014
Adding Vitamin D to ICS in Adult Asthma

Figure 3. Secondary Exacerbation Outcome

HR 0.63 (0.39-1.01), P=0.05

Castro et al, JAMA 2014
SR of RCTs – Vit D & Severe Asthma Exac

- 9 RCTs; n=1,093 with mild-to-moderate asthma
- Primary outcome: severe asthma exacerbation (i.e., requiring systemic CS), for which there were 3 RCTs with 680 participants; high-quality evidence.
- Vit D supplementation reduced risk of severe exacerbations (RR 0.63, 95%CI 0.45-0.88)
- Unclear if beneficial effect is confined to people with lower baseline 25(OH)D and role of dosing; children were under-represented

Martineau et al, Cochrane Database Syst Rev 2016
IPDMA– Vit D & Severe Asthma Exac

• 7 RCTs from around world; n=955 participants

• Mixed effects adjusting for age, sex, and clustering by study. Primary outcome: severe asthma exacerbation (i.e., requiring systemic CS). Pre-specified subgroup analysis by baseline 25(OH)D.

• Vit D supplementation reduced risk of severe asthma exacerbations among all participants (aIRR 0.74, 95%CI 0.56-0.97, P=0.03)

• Subgroup analyses: potentially stronger effect among those with baseline 25(OH)D < 25 nmol/L (aOR 0.33).

Jolliffe et al, Lancet Respir Med 2017
IPDMA– Vit D & Mod-to-Severe AECOPD

• 3 RCTs from Europe; n=469 participants

• Fixed effects adjusting for age, sex, GOLD stage, and clustering by study. Primary outcome: mod-to-severe AECOPD (i.e., requiring systemic CS, antibiotics, both). Pre-specified subgroup analysis by baseline 25(OH)D.

• Vit D supplementation did not reduce risk of moderate-to-severe AECOPD among all participants (aIRR 0.94, 95%CI 0.78-1.13, P=0.52)

• Subgroup analyses: protective effect among those with baseline 25(OH)D < 25 nmol/L (aIRR 0.55; 0.36-0.84).

Jolliffe et al, Thorax 2019
Vitamin D Mega-Trials

• Defined (somewhat arbitrarily) as RCTs with ≥5000 subjects and ≥1000 IU “daily”

• To date, there are at least 7 mega-trials
  – ViDA
  – VITAL
  – TIPS-3
  – FIND
  – D-Health
  – ViDiKids Mongolia, South Africa = 2 trials

• Highlights of each mega-trial & comparisons

  Intervention <1000 IU daily
  - Smith, 2007 = 9,440 in UK
  - Avenell, 2012 = 5,292 in UK
Location of Vitamin D Mega-trials

ViDA  VITAL  TIPS-3  FIND  D-Health  ViDiKids
• Vitamin D Assessment Study
• ACTRN12611000402943
• Robert Scragg (NZ) & Carlos Camargo (USA)
• n=5,110 (age 50-84) closed
• Exclude >600 IU (age 50-70) or >800 IU (age 71-84)
• 2 groups: vit D₃ vs placebo
• Vit D₃ 100,000 IU monthly (~3300 IU daily)
• Main outcomes: CVD … ARI, fall/fracture
• Enrollment started 2011 → results in 2018
ViDA: monthly vitamin D and ARI

Camargo et al, Clin Infect Dis 2019
ViDA: monthly vitamin D and A/C Exac

HR 1.08
95%CI, 0.84-1.39

Camargo et al, unpublished
VITAL USA

• Vitamin D and Omega-3 Trial
• NCT01169259
• JoAnn Manson & Julie Buring – USA
• n=25,874 (M age 50+, W age 55+) closed
• Exclude >800 IU daily
• 2x2 factorial: vit D₃ x omega-3, with placebo
• Vit D₃ 2000 IU daily
• Main outcomes for D₃: cancer, CVD
• Enrollment started 2011 → results in 2019
ViDiKids Mongolia

• Trial of vitamin D supplement in Mongolian primary school children – Adrian Martineau (UK) & D. Ganmaa (Mongolia)
• n=8,200 (age 6-8) closed
• Exclude >400 IU daily
• 2 groups: vit D₃ vs placebo
• Vit D₃ 14,000 IU weekly (~2000 IU/day)
• Main outcomes: latent TB … active TB, etc.
• Enrollment started 2015 → results in 2021
Summary & Clinical Implications

• Low vitamin D status is common, and associated with:
  – \( \uparrow \) ARIs = \( \uparrow \) wheezing & asthma exacerbations = poor control
  – Little (if any) association with incident asthma at ages 5-6y

• Many recent RCTs with “mixed” results …. Null findings may be related to populations (eg, baseline vitD status), comparisons (eg, both groups taking vitD), interventions (eg, bolus dosing; given during pregnancy only), or outcomes (eg, time to failure for a seasonal event).

• The emerging pattern is supported by recent IPDMAs:
  – As expected, higher 25(OH)D + any dosing = \textit{no benefit}
  – Lower 25(OH)D + frequent (not bolus) dosing = \( \downarrow \) ARI
  – Very low 25(OH)D + \textit{any} dosing = \( \downarrow \) asthma/COPD exac