ROLE OF VITAMIN D SUPPLEMENTATION IN CHRONIC URTICARIA
OVERVIEW

- Vitamin D – The Basics
- Vitamin D – Role in Allergic Disease and Immunomodulation
- Chronic Urticaria – Definition and Current Therapies
- Vitamin D and Urticaria – Prior Studies
- Discussion of Journal Club article
- Conclusion
Why is Vitamin D important?
- Emerging literature in the world of Allergy/Immunology
- Patients are interested in or are already using as supplementation
- Potential adjunct treatment to help improve QOL

What are the recommended levels?

<table>
<thead>
<tr>
<th>Vitamin D 25(OH)D range guidelines from various organizations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D Council</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Deficient</td>
</tr>
<tr>
<td>Insufficient</td>
</tr>
<tr>
<td>Sufficient</td>
</tr>
<tr>
<td>Toxic</td>
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</table>
VITAMIN D

<table>
<thead>
<tr>
<th>Age</th>
<th>National Institute of Medicine</th>
<th>The Endocrine Society</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recommended Intake (IU/day)</td>
<td></td>
</tr>
<tr>
<td>Children (0–18 years)</td>
<td>400–600</td>
<td>400–1000</td>
</tr>
<tr>
<td>Adults (19–70 years)</td>
<td>600</td>
<td>1500–2000</td>
</tr>
<tr>
<td>Older Adults (&gt;70 years)</td>
<td>800</td>
<td>1500–2000</td>
</tr>
<tr>
<td>Pregnancy/Lactation</td>
<td>600</td>
<td>600–1000 (14–18 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1500–2000 (19–50 years)</td>
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<td></td>
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<td>2000–4000</td>
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<td></td>
<td>10,000</td>
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</table>
VITAMIN D - THE BASICS

Natual sunlight, fortified milk, cheese, butter/margarine, cereal, fish

<table>
<thead>
<tr>
<th>Source</th>
<th>Approx Vitamin D Content</th>
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</thead>
<tbody>
<tr>
<td>Salmon</td>
<td>600-1000 IU</td>
</tr>
<tr>
<td>Fresh, wild (3.5 oz)</td>
<td>600-1000 IU</td>
</tr>
<tr>
<td>Fresh, farmed (3.5 oz)</td>
<td>100-250 IU</td>
</tr>
<tr>
<td>Canned (3.5 oz)</td>
<td>300-600 IU</td>
</tr>
<tr>
<td>Sardines, Canned (3.5 oz)</td>
<td>300 IU</td>
</tr>
<tr>
<td>Mackerel, canned (3.5 oz)</td>
<td>250 IU</td>
</tr>
<tr>
<td>Tuna, canned (3.6 oz)</td>
<td>230 IU</td>
</tr>
<tr>
<td>Exposure to Sunlight</td>
<td>3000 IU</td>
</tr>
<tr>
<td>Fortified milk (8oz)</td>
<td>100 IU</td>
</tr>
<tr>
<td>Fortified orange juice (8 oz)</td>
<td>100 IU</td>
</tr>
<tr>
<td>Infant formulas (8 oz)</td>
<td>100 IU</td>
</tr>
<tr>
<td>Prescription vitamin d</td>
<td>50,000 IU</td>
</tr>
</tbody>
</table>

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Lower Vitamin D level in atopic patients.
Both low and very high Vitamin D values have been associated with high IgE concentrations.
Conflicting data in studies looking at Vitamin D level and atopic dermatitis, food allergies, environmental allergies and asthma.
NHANES Data Analysis - Vitamin D deficiency and prevalence of IgE sensitization
NHANES Data Analysis - Vitamin D deficiency and prevalence of IgE sensitization
Children with asthma have been noted to have low serum 25(OH)D3 values.

Brehm et al.: 616 patients, 21 w/ 25(OH)D3 level <20 ng/ml and 152 with levels between 20-30 ng/ml.

Goleva et al found an inverse correlation between serum 25(OH)D3 and IgE values and inverse relationship between daily inhaled corticosteroid doses and serum 25(OH)D3 values.

Hughes et al. found no association between any Vitamin D-related measures and childhood asthma.

Other studies showed greater time in the sun in winter (between 6-15 years of age) increased the odds of having hay fever and supplementation with codliver oil in childhood increased the odds of a history of having both asthma and hay fever.
- Children with mild AD had higher 25(OH)D3 levels as compared to moderate/severe AD patients.

- Correcting serum concentrations of 25(OH)D3 led to decreased IgE levels.

- Back et al showed children who were supplemented with Vitamin D demonstrated:
  - Increased risk of either AD, AR or allergic asthma
  - Increased risk of AD at age 6 in patient with positive family history.

- Hypponen et al showed dietary intake of vitamin D during infancy promoted allergic disease at age 31.
Camaro et al. reported high 25(OH)D3 values during pregnancy decreased childhood wheezing by 50%.
- Also suggested cord blood 25(OH)D3 values are inversely associated with risk of respiratory tract infection and childhood wheezing, but NOT asthma.

Gale et al. reported high vitamin D values may be harmful
- Maternal 25(OH)D3 level >75 nmol/L had increased risk of atopic eczema and asthma at 9 months of age.

Other studies demonstrated that reduced maternal intake of Vitamin D during pregnancy was associated with increased wheezing outcomes and increased food allergies.
VITAMIN D AND ALLERGIC DISEASE

- Conflicting data
  - Mode of application important?
  - Timing (winter vs. summer months).
  - Dose dependent?
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CHRONIC URTICARIA

Images from: www.Skindermatologist.com
Definition of Chronic Urticaria:
- Urticarial episodes that last 6 weeks. Lesions may occur daily or several days per week.

Most common etiologies:
- Idiopathic
- Autoimmune
- Physical urticaria
  - Environmental or physical stimulus
  - Cholinergic, cold induced etc.

Data on Natural history of disease is limited, and based on type of referral center. Physical urticaria has the worst prognosis.

Results in significant impairment in quality of life.
CURRENT TREATMENT OPTIONS

**STEP 1**
- Monotherapy with second generation antihistamine
- Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present.

**STEP 2**
- One or more of the following:
  - Dose advancement of 2nd generation antihistamine used in Step 1
  - Add another second generation antihistamine
  - Add H1-antagonist
  - Add leukotriene receptor antagonist
  - Add 1st generation antihistamine to be taken at bedtime

**STEP 3**
- Dose advancement of potent antihistamine (e.g., hydroxyzine or doxepin) as tolerated

**STEP 4**
- Add an alternative agent
  - Omalizumab or cyclosporine
  - Other anti-inflammatory agents, immunosuppressants, or biologics

**FIG 1.** Step-care approach to the treatment for CU.

CURRENT TREATMENT OPTIONS

**STEP 1**
- Monotherapy with second generation antihistamine
- Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present.

- Begin treatment at step appropriate for patient’s level of severity and previous treatment history
- At each level of the step-approach, medication(s) should be assessed for patient tolerance and efficacy
- “Step-down” in treatment is appropriate at any step, once consistent control of urticaria/angioedema is achieved

**FIG 1.** Step-care approach to the treatment for CU.

CURRENT TREATMENT OPTIONS

STEP 4
Add an alternative agent
- Omalizumab or cyclosporine
- Other anti-inflammatory agents, immunosuppressants, or biologics

STEP 3
Dose advancement of potent antihistamine (e.g., hydroxyzine or doxepin) as tolerated

STEP 2
One or more of the following:
- Dose advancement of 2nd generation antihistamine used in Step 1
- Add another second generation antihistamine
- Add H2- antagonist
- Add leukotriene receptor antagonist
- Add 1st generation antihistamine to be taken at bedtime
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Retrospective case series of 63 patients described an association of pruritis, rash, and urticaria/angioedema with low Vitamin D level. Supplementation resulted in 70% (40/57) success rate leading to symptom resolution.

Separate case study reported resolution of CU after Vitamin D supplementation in severely deficient patient.

Goetz DW. W V Med J. 2011 Jan-Feb;107(1):14-20
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Beneficial role for supplemental vitamin D₃ treatment in chronic urticaria: a randomized study

Andy Rorie, MD*; Whitney S. Goldner, MD†; Elizabeth Lyden, MS‡; and Jill A. Poole, MD*

*Pulmonary, Critical Care, Sleep, and Allergy Division, Department of Medicine, College of Medicine, University of Nebraska Medical Center, The Nebraska Medical Center, Omaha, Nebraska
†Diabetes, Endocrinology and Metabolism Division, Department of Medicine, College of Medicine, University of Nebraska Medical Center, The Nebraska Medical Center, Omaha, Nebraska
‡Department of Biostatistics, College of Public Health; University of Nebraska Medical Center, The Nebraska Medical Center, Omaha, Nebraska

- **Subjects**
  - Adult >19 years of age
  - Physician diagnosed CU
  - Tertiary care institution’s A/I clinics

- **Inclusion Criteria**
  - History of urticaria and/or angioedema daily or almost daily for >6 weeks.
  - Patients with Dermatographism/delayed pressure urticaria not excluded
  - NSAID intolerance and Alcohol-exacerbating hives included.

- **Exclusion Criteria**
  - Patient with pure physical urticaria
  - HAE or AAE
  - Hypercalcemia
  - Renal insufficiency
  - Primary hyperparathyroidism
  - Sarcoidosis or other granulomatous diseases
  - Malignancy
  - Pregnancy/lactation
Prospective, double-blinded, randomized, single-center

Enrollment → Randomization → Standardized treatment and action plan → 1 week Telephone interview → 6 week MD visit → 12 week Study completion

Low dose Vitamin D3 (600 IU/d) → High dose Vitamin D3 (4,000 IU/d)

Primary Outcome: Number of allergy pills used on a daily basis.
STUDY DESIGN

• Treatment algorithm modified from: Third International Consensus meeting on Urticaria (2008)
  • 10 mg Cetirizine BID (increase to QID PRN)
  • 150 mg Ranitidine BID
  • 10 mg of Montelukast

• Rescue Prednisone for intolerable or uncontrollable symptoms. MD could also add Hydroxychloroquine if symptoms were uncontrolled.

• Written action plan
  • Decrease the use of 1 allergy pill every 7 days if symptom free, or increase if symptoms flared.
  • Order of de-escalation:
    • Ranitidine
    • Montelukast
    • Cetrizine
  • If symptoms tolerable, patient was advised to remain on current regimen.
DATA COLLECTION

- Serum evaluation at enrollment, 6 and 12 week clinic visits
  - Serum 25(OH)D, Ca, Albumin, PO4, Cr, serum urea nitrogen, inorganic phosphorus, intact ptH
- Urine calcium
- Questionnaire at enrollment and study completion
- Medical record
  - Basophil CD203c expression, TSH, free thyroxine, Anti-TPO Ab, Anti-thyroglobulin, ANA, and allergy skin prick tests results (as available).
- Urticaria Symptom Score (USS) and allergy medications for CU were recorded at enrollment, 1 week, 6 weeks, and 12 weeks.
URTICARIA SYMPTOM SEVERITY SCORE

Answer each question according to how your skin has affected your life over the past week. Please answer every question.

1. Over the past week, how uncomfortable or itchy has your skin been?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>a little</th>
<th>a lot</th>
<th>very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. How many days over the past week did you have hives or itch?

| 0 1 2 3 4 5 6 7 |

3. On average, how many hours did you have hives or itch each day?

| <1 1-2 3-4 5-6 7-8 9-10 11-12 >12 |
| 0 1 2 3 4 5 6 7 |

3a. What was the maximum number of hours your hives or itch lasted each day?

| <1 1-2 3-4 5-6 7-8 9-10 11-12 >12 |
| 0 1 2 3 4 5 6 7 |

4. On average, on which parts of your body were there hives or itch? (Circle all that apply)

- head/ neck
- chest/ abdomen
- back
- right arm
- left arm
- right leg
- left leg
- genitals and/or buttocks

4a. On the worst day, on which parts of your body was there hives or itch? (Circle all that apply)

- head/ neck
- chest/ abdomen
- back
- right arm
- left arm
- right leg
- left leg
- genitals and/or buttocks
5. On average, how many pills did you take each day?
   a. Antihistamine (Benadryl or other)
      | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
   b. Prednisone or Methylprednisolone
      | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

6. How many days did you have episodes of swelling over the past week?
   | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

7. How many nights did your hives or itch interfere with sleeping?
   | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

8. Did your skin interfere with work or school?
   Not at all → a little → a lot → very much
   | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

9. Did your skin interfere with your social life?
   Not at all → a little → a lot → very much
   | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
SAFETY ASSESSMENT

- Criteria for discontinuation:
  - Pregnancy
  - Serum 25(OH)D level >200 ng/ml
  - Serum Calcium level >10.3 mg/dl

- “Safety guidelines implemented”
  - Spot urine Calcium level >30 mg/dl
  - GFR < 50 ml/min/1.73 m²
RESULTS – SUBJECT CHARACTERISTICS

N = 42
Predominantly female
Caucasian
Baseline differences not statistically significant - Low Vitamin D group with:

- increased use of Vitamin D supplementation
- More alcohol consumption
- More alcohol worsened hives
RESULTS – VITAMIN D LEVELS

- **Enrollment – Low** Vitamin D3 treatment group had a higher mean serum 25(OH)D level (37.1 vs 28.8)
- **Significant increase in** 25(OH)D level in high vitamin D3 treatment arm.
- **12 weeks –** 25(OH)D levels were significantly higher in high Vitamin D3 treatment arm.
RESULTS - MEDICATION USE

• No difference in primary outcome of number of allergy pills used on a daily basis.

• No difference in number of subjects using hydroxychloroquine or prednisone
• 33% Decrease in total USS score 1 week after treatment in both arms.
• Further decrease (40%) in total USS score at study completion in high Vit D3 arm
• No difference between the two groups in USS scores.

Figure 2. Total Urticarial Symptom Severity score over time in the high and low vitamin D₃ treatment groups. Data are presented as mean and SE (bars), with statistical significance denoted by lines and asterisks.
Figure 3. Individual Urticarial Symptom Severity score components shown between high and low vitamin D₃ treatment groups at week 12. Data are presented as mean and SE (bars), with statistical significance denoted by asterisks.
RESULTS – SAFETY AND COMPLIANCE

- No significant adverse events
- All subjects in high vitamin D3 treatment arm completed the study, 4 subjects in low vitamin D3 treatment group withdrew.
- Elevated spot urine Ca level and low GFR values repeated and were within normal limits.
- No hypercalcemia.
- Pill counts showed excellent compliance (1 subject <80%)
DISCUSSION
SUMMARY OF FINDINGS

- Primary outcome of decreased allergy medication use for CU not met.

- High dose vitamin D3 supplementation improved total USS scores over time in patients with CU. Difference most notable between 6 to 12 weeks of therapy.

- Low dose vitamin D3 supplementation did not show similar benefit.

- Improvement was irrespective of baseline vitamin D status.

- No correlation between 25(OH)D level and USS score.
## DISCUSSION – STUDY STRENGTHS AND LIMITATIONS

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ First well designed study looking at this specific question.</td>
<td>▪ Stopped at 12 weeks</td>
</tr>
<tr>
<td>▪ Adequate minimum study duration</td>
<td>▪ No placebo group</td>
</tr>
<tr>
<td>▪ Use of current standard therapy</td>
<td>▪ Baseline differences in groups</td>
</tr>
<tr>
<td></td>
<td>▪ Limitations of questionnaires used</td>
</tr>
<tr>
<td></td>
<td>▪ Limitations of using 25(OH)D levels</td>
</tr>
<tr>
<td></td>
<td>▪ Sample not reflective of general population (few minorities, obese)</td>
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<td></td>
<td>▪ Xolair?</td>
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</tbody>
</table>
DISCUSSION – TAKE HOME POINTS

- Vitamin D has been found to have immunomodulatory role and may be protective in allergic disease.

- Add-on supplementation with high-dose vitamin D3 could be considered a potentially safe and inexpensive immunomodulator to benefit patients with CU.
IT'S OKAY – THEY'RE VITAMIN-ENRICHED CHOCOLATES!
REFERENCES


VITAMIN D IN IMMUNOMODULATION