

Vitamin D and Immunity NASPGHAN Annual Meeting October 12, 2013

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Financial Disclosures

In the past 12 months, I have the financial relationships with the following

- Equity interest in Asklepiion Pharma, LLC.
- Funding: NCATS, NIDDK, NICHD, and CFF
- Consultant to Nordmark

None of these relationships will be discussed in the presentation




Definition of an Expert

- Travels more than 50 miles
- Has no more knowledge of the subject than members of the audience
- Has a PowerPoint® Presentation




Objectives

- IOM recommendations re: vitamin D/Ca
- IOM findings re: vitamin D and immunity
- Role of vitamin D in immunity associated with infectious diseases and immune-mediated disease
- How current recommendations re: vitamin D and its impact on immune function might influence practice

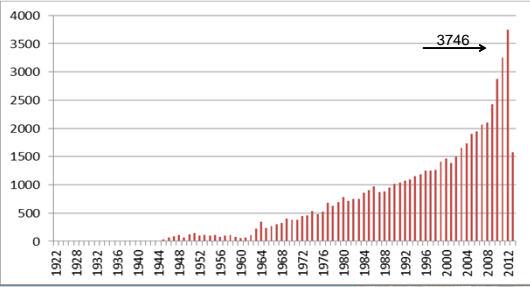


Outline of Presentation


- Function of vitamin D
- Vitamin D status in IBD patients
- Institute of Medicine (IOM) Report
- Role of Vitamin D
 - Immune function
 - Autoimmune/infectious disease
 - IBD
- Summary /Conclusions

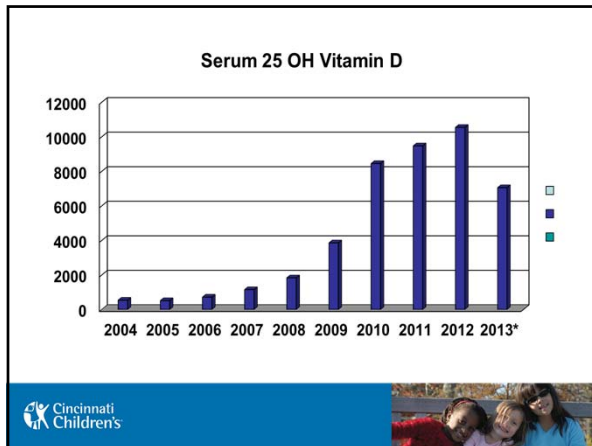


Vitamin D Publications per Year



Year	Publications
1922	0
1928	0
1932	0
1936	0
1940	0
1944	0
1948	0
1952	0
1956	0
1960	0
1964	0
1968	0
1972	0
1976	0
1980	0
1984	0
1988	0
1992	0
1996	0
2000	0
2004	0
2008	0
2012	3746





Vitamin D - Overview

- Sources:
 - Sunlight/UVB irradiation
 - 10-15 minutes total-body exposure to peak-summer sun => 20,000 IU D₃
 - Diet/supplements
 - Naturally occurring: Fatty fish, fish liver oil, egg yolk
 - Fortified food: milk, plant-based beverages
 - Assessment
 - 25 OHD (20 g/ml=50mmol/l)
 - Not 1,25(OH)₂D

Dietary Reference Intakes for Calcium and Vitamin D
http://www.nap.edu/catalog/13050.html

Cincinnati Children's

Vitamin D Metabolism/Actions

Cincinnati Children's

Vitamin D Paracrine System

VITAMIN D PARACRINE SYSTEM

PARACRINE MODULATORS: 1,25(OH)₂D₃, 24,25(OH)₂D₃

ENDOCRINE MODULATORS: 1,25(OH)₂D₃, 24,25(OH)₂D₃

RECEPTORS: VDR, RXR, CD141, CD142, CD143, CD144, CD145, CD146, CD147, CD148, CD149, CD150, CD151, CD152, CD153, CD154, CD155, CD156, CD157, CD158, CD159, CD160, CD161, CD162, CD163, CD164, CD165, CD166, CD167, CD168, CD169, CD170, CD171, CD172, CD173, CD174, CD175, CD176, CD177, CD178, CD179, CD180, CD181, CD182, CD183, CD184, CD185, CD186, CD187, CD188, CD189, CD190, CD191, CD192, CD193, CD194, CD195, CD196, CD197, CD198, CD199, CD200, CD201, CD202, CD203, CD204, CD205, CD206, CD207, CD208, CD209, CD210, CD211, CD212, CD213, CD214, CD215, CD216, CD217, CD218, CD219, CD220, CD221, CD222, CD223, CD224, CD225, CD226, CD227, CD228, CD229, CD230, CD231, CD232, CD233, CD234, CD235, CD236, CD237, CD238, CD239, CD240, CD241, CD242, CD243, CD244, CD245, CD246, CD247, CD248, CD249, CD250, CD251, CD252, CD253, CD254, CD255, CD256, CD257, CD258, CD259, CD260, CD261, CD262, CD263, CD264, CD265, CD266, CD267, CD268, CD269, CD270, CD271, CD272, CD273, CD274, CD275, CD276, CD277, CD278, CD279, CD280, 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CD996, CD997, CD998, CD999, CD1000.

Cincinnati Children's

Institute of Medicine Report on Vitamin D and Ca

- 2010 IOM report
 - 1016 page document with hundreds of references
 - Summarized in 4 page Report Brief
 - Task: Review evidence and update the Dietary Reference Intakes
 - Conclusions
 - Vitamin D/Ca play key role in bone health
 - Monitor with serum 25 OHD
 - Current evidence not sufficient for other benefits

Study Type

Randomized Controlled Trials

Prospective Cohort

Retrospective Cohort

Case-Control

Cross-sectional

Ecological

Low → High

Relative Strength of Evidence

Cincinnati Children's

Institute of Medicine

TABLE: Dietary Reference Intakes for Calcium and Vitamin D

Life Stage Group	Calcium			Vitamin D		
	Estimated Average Requirement (mg/day)	Recommended Dietary Allowance (mg/day)	Upper Limit Intake (mg/day)	Estimated Average Requirement (IU/day)	Recommended Dietary Allowance (IU/day)	Upper Limit Intake (IU/day)
Infants 0 to 6 months	-	-	1,000	**	**	1,000
Infants 6 to 12 months	-	-	1,500	**	**	1,500
1-3 years old	500	700	2,500	400	600	2,500
4-8 years old	800	1,000	2,500	400	600	3,000
9-13 years old	1,300	1,300	3,000	400	600	4,000
14-18 years old	1,300	1,300	3,000	400	600	4,000
19-30 years old	800	1,000	2,500	400	600	4,000
31-50 years old	800	1,000	2,500	400	600	4,000
51-70 years old	800	1,000	2,000	400	600	4,000
51-70 year old females	1,000	1,200	2,000	400	600	4,000
71+ years old	1,000	1,200	2,000	400	800	4,000
14-18 years old, pregnant/lactating	1,300	1,300	3,000	400	600	4,000
19-50 years old, pregnant/lactating	800	1,000	2,500	400	600	4,000

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Tutorial: Relation to Vitamin D/GI and Immune System

- Maintenance of epithelial barrier
- Innate Immune response
- Adaptive T-cell response

Garg M. Aliment Pharmacol Ther 2012; 36:324-344

Vitamin D in Autoimmune-Infectious Disease

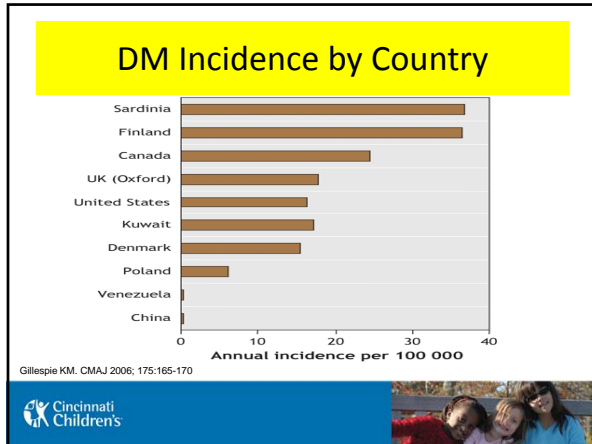
- Multiple Sclerosis
- Type 1 DM
- Respiratory Conditions
- Influenza A
- Tuberculosis

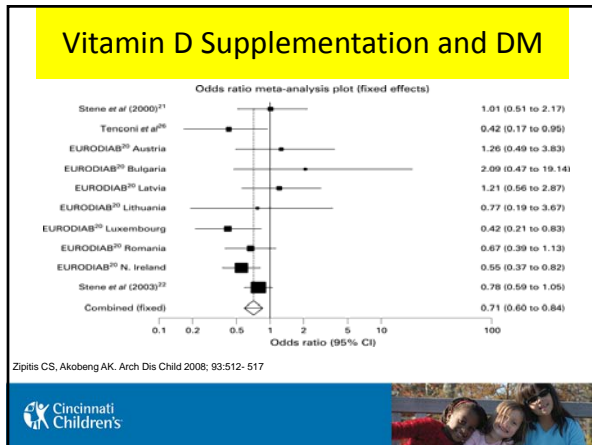
Serum 25 OHD and MS

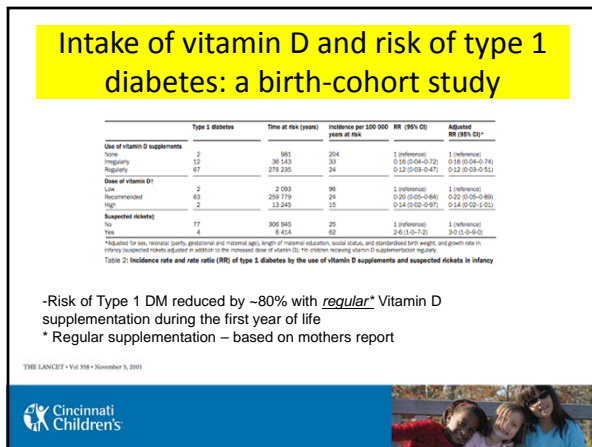
Quartile of 25-Hydroxyvitamin D, nmol/L	OR (95% CI)
15.2-62.2	1.00
63.2-71.3	1.07 (0.37-3.07)
73.4-84.9	1.07 (0.30-3.80)
84.9-99.1	1.07 (0.40-2.91)
102-152.9	1.38 (0.33-5.91)

Quartile of 25-Hydroxyvitamin D, nmol/L	OR (95% CI)
15.4-36.6	1.00
36.9-67.7	1.11 (0.39-3.17)
68.4-97.9	1.05 (0.31-3.61)

Munger KL et al JAMA 2006; 296:2832-2838







Cord Blood 25 OHD and risk of wheeze/asthma

- Cord-blood 25-OH Vitamin D levels inversely correlated with risk of wheezing
- No correlation with asthma

Camargo CA Jr et al. *Pediatr* 2011;127:e180-e187.

Vitamin D Supplementation-Influenza A

Subjects with influenza A

	Vitamin D ₃	Placebo	Relative risk	95% CI	P value	P value
<i>n/total n (%)</i>						
Influenza A	18/167 (10.8)	31/167 (18.6)	0.58	0.34, 0.99	0.04	
Additional vitamin D						0.04
None	8/140 (5.0)	22/140 (16.5)	0.36	0.17, 0.79	0.006	
At least once per week	10/34 (29.4)	9/34 (26.5)	1.11	0.52, 2.39	0.79	
Starting age of nursery school						0.04
<3 y	10/59 (16.9)	7/49 (14.3)	1.19	0.49, 2.88	0.71	
≥3 y	8/107 (7.5)	24/117 (20.5)	0.36	0.17, 0.78	0.005	

Urashima M et al. *Am J Clin Nutr* 2010; 91:1255-1260

SUCCINT Trial in TB

Table 2. Changes in measured clinical variables from baseline to study completion

Measured disease parameter†	Randomization		P value
	Drug intervention (n = 122)	Placebo intervention (n = 127)	
TB Severity (clinical assessment)			
Mean Δ in the number of sputum-positive days	-2.0 (95% CI, -3.60, -0.70)	-1.7 (95% CI, -3.20, -0.20)	0.98
Mean Δ in weight loss (kg)	+4.2 (95% CI, 3.29, 5.10)	+3.1 (95% CI, 2.19, 4.12)	0.07
Mean Δ in BMI (kg/m ²)	+1.48 (95% CI, 1.17, 1.78)	+1.06 (95% CI, 0.75, 1.37)	0.008
Mean Δ in MRC (mg/dL)	+1.34 (95% CI, 0.98, 1.70)	+0.97 (95% CI, 0.69, 1.26)	0.019
Chemotherapy involvement			
Number of doses††	120 (97.5%)	100 (78.7%)	<.001
Number of doses†††	108 (88.5%)	89 (69.3%)	0.004
Salahadin			
Mean Δ in weight loss (kg)	1.9 ± 0.87	4.1 ± 0.2	0.025
Mean Δ in BMI (kg/m ²)	0.97 ± 0.02	2.06 ± 0.06	0.017
Mean Δ in MRC (mg/dL)	0.92 ± 0.02	2.06 ± 0.06	0.007

MRC, Mean Δ in the number of sputum-positive days; CI, confidence interval; BMI, body mass index; MRC, mean red cell count; TB, tuberculosis; Δ, change from baseline; †, change from baseline to study completion; ††, change from baseline to study completion; †††, change from baseline to study completion.

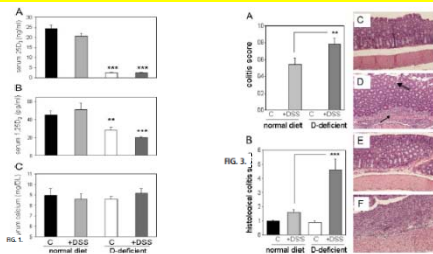
Salahadin _____

Vitamin D in IBD models

- DSS model with vitamin D deficiency
- Protective effect of 1,25 (OH)₂D on epithelial barrier function and cytokine production in DSS model
- Cytokine production by non-diseased and Crohn's disease patient T-cells



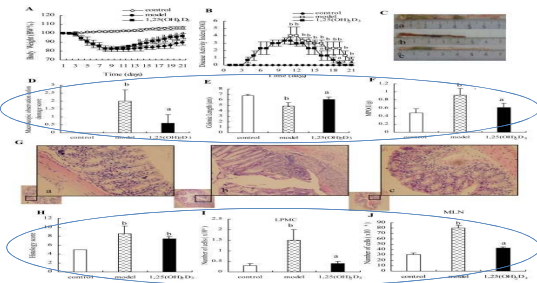
Vitamin D Effect in Murine Model of Colitis



Lagishetty V et al. Endocrinology 2010; 151:2423-2432

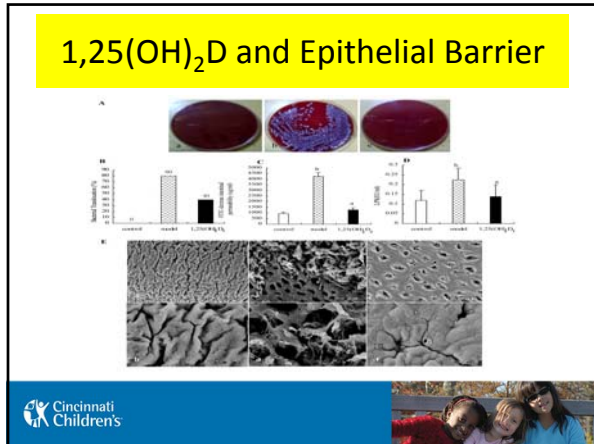


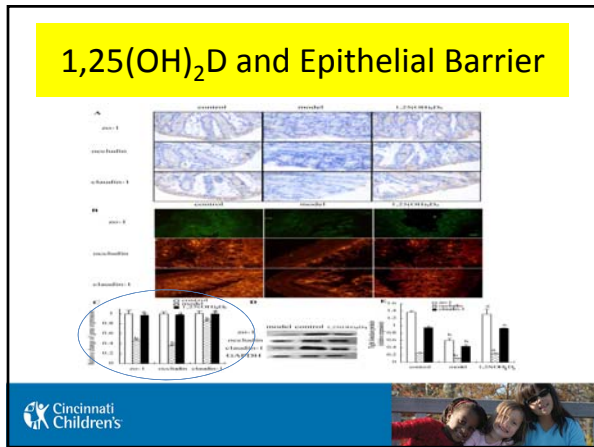
1,25(OH)₂D and Epithelial Barrier

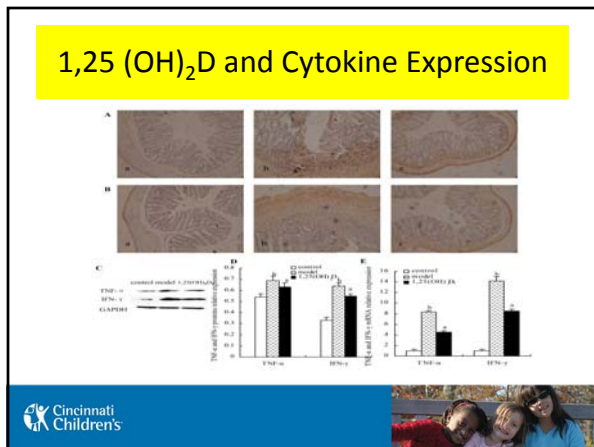


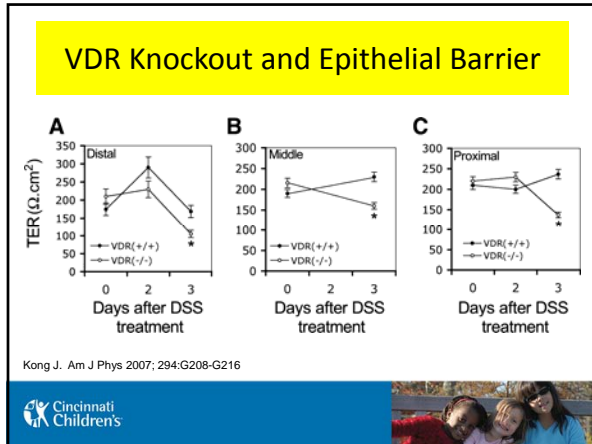
Zhao H. BMC Gastroent 2010; 12:57

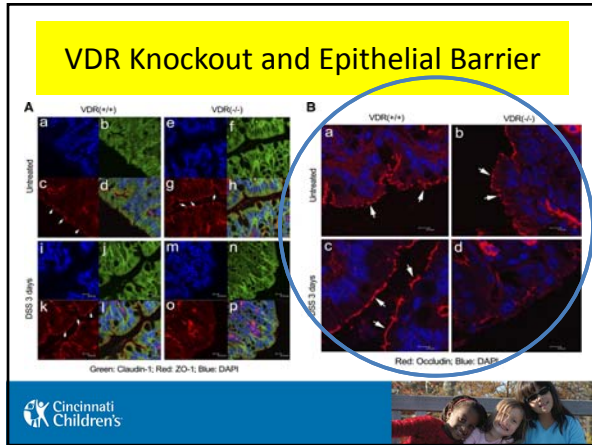


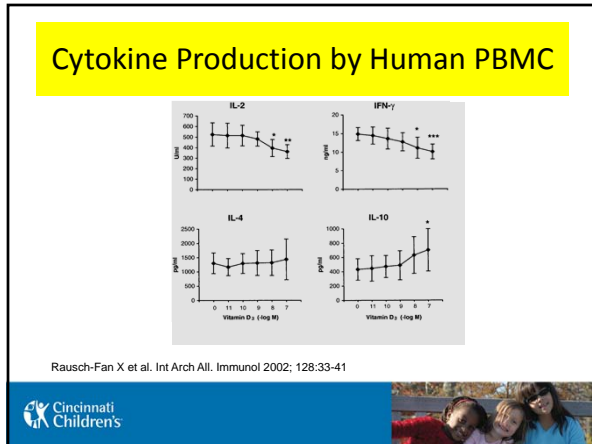




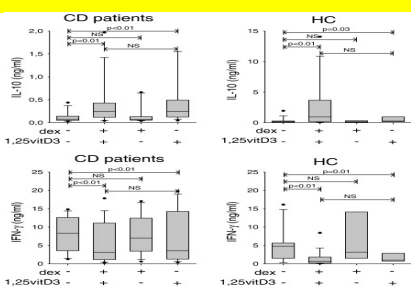








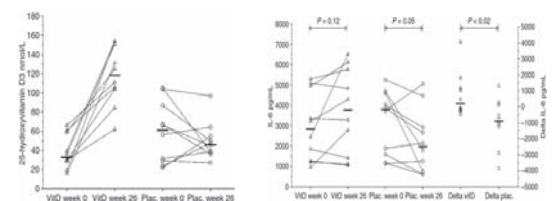
1,25 (OH)₂D Effect on IL-10/IFN-γ Production in CD



Bartels LE. International Immunopharm 2007; 7:1755-1764



Vitamin D Treatment Effects on Cytokines in CD



Bendix-Struve M. Aliment Pharmacol Ther 2010; 32:1364-1372



Effect of Vitamin D on CD

- Predicted vitamin D status and risk of CD
- Serum 25 OHD and QI efforts in CD
- Serum 25OH D and surgery risk in CD
- Clinical Trials of vitamin D in CD
 - Animal Models
 - Human



Predicted Vitamin D Status and CD

Table 2. Risk of CD and UC According to Quartiles of Predicted Plasma 25(OH)D Level

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P _{total}
Person-years of follow-up (median)	380,369	384,626	377,038	376,763	
CD or UC cases	37	37	22	26	
Number of cases	1.0	0.89 (0.55-1.46)	0.60 (0.36-1.01)	0.70 (0.42-1.14)	.068
Age-adjusted HR (95% CI)*	1.0	0.89 (0.55-1.46)	0.50 (0.28-0.93)	0.55 (0.33-1.00)	.018
Adjusted OR†					
Number of cases	36	36	20	23	.096
Age-adjusted HR (95% CI)	1.0	1.02 (0.64-1.62)	0.84 (0.51-1.37)	0.68 (0.39-1.21)	.17
Multivariate HR (95% CI)*	1.0	0.98 (0.59-1.62)	0.84 (0.47-1.46)	0.68 (0.35-1.31)	.17

*Adjusted for age, smoking (never or current), total creatinine (mg/dL), past, or recent, and/or recreational hormone therapy use (topical, parent, current, past, or never), physical activity (quartiles), and body mass (kg/m²) index (≤21, 21-22.9, 23-24.9, 25-28.9, ≥29).

Table 3. Risk of CD and UC According to Quartiles of Dietary and Supplemental Vitamin D Intake

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P _{total}
Person-years of follow-up (median)	380,111	380,256	380,369	380,039	
CD or UC cases	34	33	28	27	
Number of cases	1.0	0.90 (0.58-1.44)	0.80 (0.48-1.32)	0.76 (0.46-1.20)	.34
Age-adjusted HR (95% CI)	1.0	0.96 (0.60-1.54)	0.80 (0.48-1.32)	0.76 (0.46-1.27)	.22
Adjusted OR†					
Number of cases	34	33	31	23	.04
Age-adjusted HR (95% CI)	1.0	1.08 (0.68-1.72)	0.91 (0.55-1.48)	0.63 (0.36-1.06)	.04
Multivariate HR (95% CI)*	1.0	1.10 (0.69-1.76)	0.93 (0.57-1.52)	0.64 (0.37-1.10)	.04

*Adjusted for age, smoking (never or current), total creatinine (mg/dL), past, or recent, and/or recreational hormone therapy use (topical, parent, current, past, or never), physical activity (quartiles), and body mass (kg/m²) index (≤21, 21-22.9, 23-24.9, 25-28.9, ≥29).

Ananthakrishnan AN. Gastroenterology 2012; 142:482-489



QI Efforts and CD

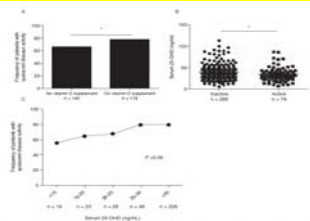


FIGURE 7. Vitamin D status and mean serum 25(OH)D level. A, For the year 2010, the frequency of patients with optimal disease activity that were taking a vitamin D supplementation compared with those without any vitamin D supplementation. *P=0.02. B, For the year 2010, serum 25(OH)D level (25(OH)D) was compared between patients with inactive (top) and active (bottom) disease activity. *P=0.03. C, For the year 2010, patients were stratified based on their most recent serum 25(OH)D level and proportion of patients with a therapeutic response (disease activity) was determined.

Samson CM. JPGN 2012; 55:679-688



Serum 25 OHD and Surgery in IBD

	Surgery		No surgery	
	OR (95% CI)	P	OR (95% CI)	P
UC				
25(OH)D ¹	1.76 (1.00-3.10)	.05	1.00 (0.60-1.70)	1.00
Adjusted†	1.74 (1.00-3.10)	.05	1.00 (0.60-1.60)	1.00 (1.00-1.00)
UC				
25(OH)D ¹	1.07 (0.60-1.90)	1.00	1.00 (0.60-1.60)	1.00 (1.00-1.00)
Adjusted†	1.13 (0.66-1.90)	1.00 (1.00-1.00)	1.00 (0.60-1.60)	1.00 (1.00-1.00)

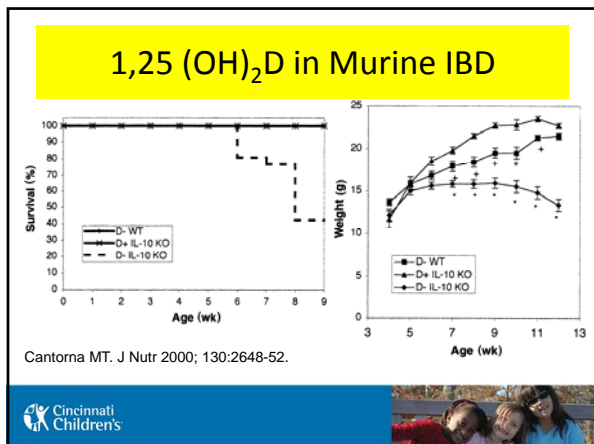
*Adjusted for age, gender, race, Crohn's disease, history of immunosuppressive use of immunosuppressants or anti-TNF biologics and history of surgery.

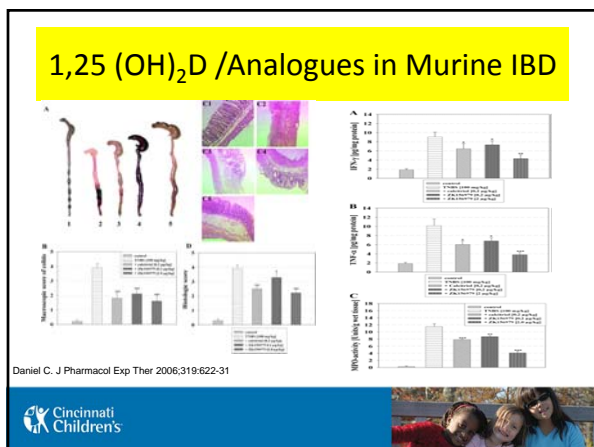
	Surgery		No surgery	
	OR (95% CI)	P	OR (95% CI)	P
UC				
25(OH)D ¹	2.01 (1.13-3.55)	.02	1.00 (0.60-1.60)	1.00 (1.00-1.00)
Adjusted†	1.76 (1.00-3.10)	.05	1.00 (0.60-1.60)	1.00 (1.00-1.00)
UC				
25(OH)D ¹	1.08 (0.64-1.84)	1.00	1.00 (0.60-1.60)	1.00 (1.00-1.00)
Adjusted†	1.10 (0.64-1.84)	1.00	1.00 (0.60-1.60)	1.00 (1.00-1.00)

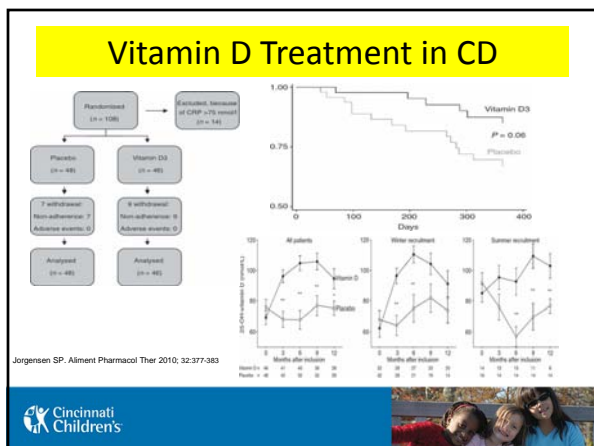
*Adjusted for age, gender, race, Crohn's disease, history of immunosuppressive use of immunosuppressants or anti-TNF biologics and history of surgery.

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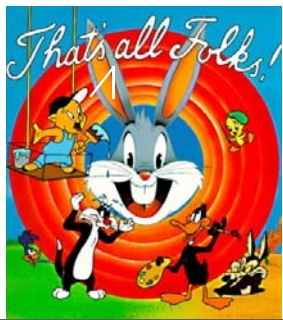




Summary/Conclusions

- Biologic plausibility for vitamin D role in pathogenesis of immune mediated diseases such as IBD
- No clear evidence of direct relationship between vitamin D status and CD course
- Current recommendation: Monitor vitamin D status with serum 25 OHD and maintain level ≥ 20 ng/ml or 50 nmol/l.





Questions?