Vitamin D and Immunity
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Financial Disclosures

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

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

None of these relationships will be discussed in the presentation

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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

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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

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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

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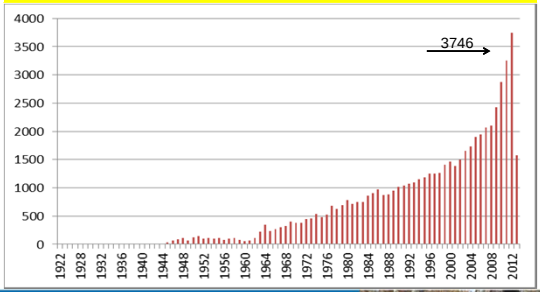
Vitamin D Publications per Year



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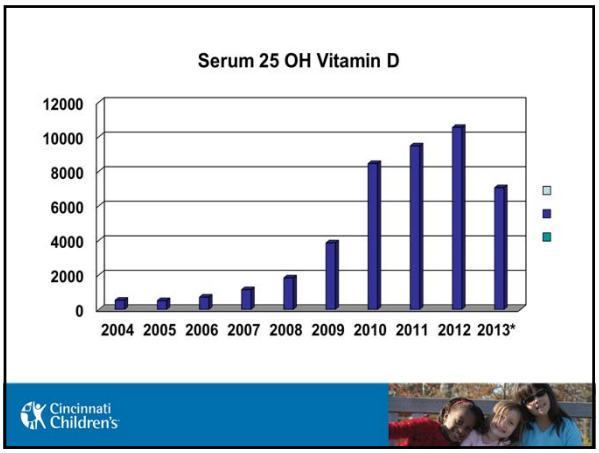
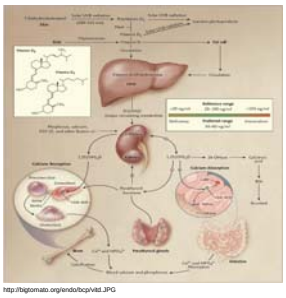


Vitamin D - Overview

- Sources:
  - Sunlight/UVB irradiation
    - 10-15 minutes total-body exposure to peak-summer sun => 20,000 IU D_3
  - Diet/supplements
    - Naturally occurring: Fatty fish, fish liver oil, egg yolk
    - Fortified food: milk, plat-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


http://bigtomato.org/endo/bcp/vitd.JPG

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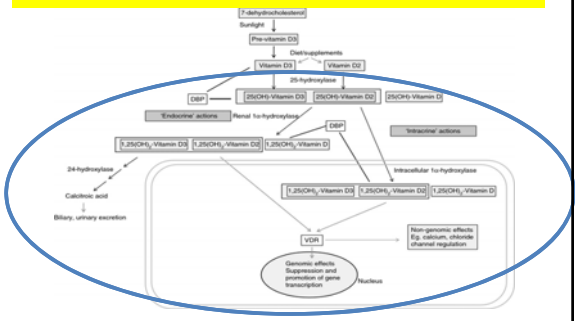
Vitamin D Metabolism/Actions



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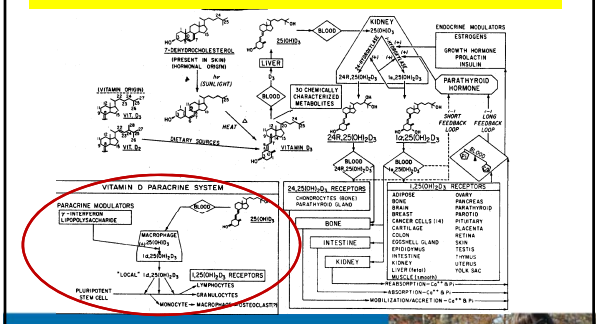
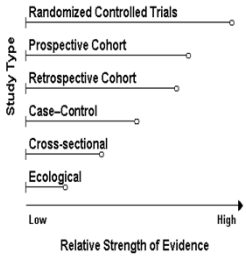
Vitamin D Paracrine System



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



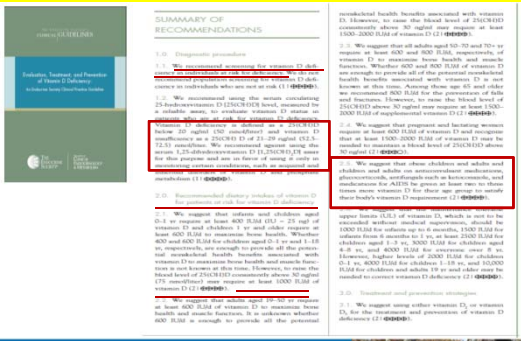
Institute of Medicine

TABLE: Dietary Reference Intakes for Calcium and Vitamin D

Life Stage Group	Calcium: Estimated Average Requirement (mg/day)	Calcium: Recommended Dietary Allowance (mg/day)	Calcium: Upper Level Intake (mg/day)	Vitamin D: Estimated Average Requirement (IU/day)	Vitamin D: Recommended Dietary Allowance (IU/day)	Vitamin D: Upper Level 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	1,100	1,300	3,000	400	600	4,000
14–18 years old	1,100	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 year 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	1,100	1,300	3,000	400	600	4,000
19–50 years old, pregnant/lactating	800	1,000	2,500	400	600	4,000

*For infants, Adequate Intake is 200 mg/day for 0 to 6 months of age and 260 mg/day for 6 to 12 months of age.
**For infants, Adequate Intake is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age.

Endocrine Society Recommendations


SUMMARY OF RECOMMENDATIONS

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PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

- Screen:
  - Non-specific symptoms: poor growth, gross motor delays, unusual irritability
  - Dark-skinned infants at higher latitudes in the winter and spring
  - Children on anticonvulsants and chronic glucocorticoids
  - Children with chronic diseases associated with malabsorption
- Possibly screen:
  - Kids with frequent fractures and low BMD

Misra M. Pedaitr 2008; 122:398-417

STATE-OF-THE-ART REVIEW ARTICLE

Vitamin D Deficiency in Children and Its Management: Review of Current Knowledge and Recommendations

TABLE 7 Treatment of Vitamin D–Deficiency Rickets: Vitamin D and Calcium Supplementation and Monitoring of Therapy

Vitamin D (ergocalciferol)

Double-dose vitamin D: 20 μg (800 IU)/d × 3–4 mo; or

Pharmacological doses of vitamin D: 25–125 μg (1000–10 000 IU) per day × 8–12 wk depending on the age of the child, then maintain at 10–25 μg (400–1000 IU) per day; or

Stoss therapy: ~2.5–15.0 mg or 100 000–600 000 IU of vitamin D orally (over 1–5 d), then maintain at 10–25 μg (400–1000 IU) of vitamin D per day, or 1.25 mg or 50 000 IU of vitamin D_2 weekly for 8 wk orally (teenagers and adults)

Calcium

30–75 mg/kg per d of elemental calcium in 3 divided doses (start at a higher dose, and wean down to the lower end of the range over 2–4 wk)

Monitoring of therapy

At 1 mo: calcium, phosphorus, ALP

At 3 mo: calcium, phosphorus, magnesium, ALP, PTH, 25(OH)-D, urine calcium/creatinine ratio (frequency depends on severity of rickets and hypocalciuria); recheck radiologic findings in 3 mo

At 1 y and annually: 25(OH)-D

Adapted with permission from Levine M, Zgajewski C, Kuppy M. Disorders of calcium, phosphate, parathyroid hormone and vitamin D metabolism. In: Kuppy MS, Allen DB, Geffner ME, eds. *Principles and Practice of Pediatric Endocrinology*. Springfield, IL: Charles C. Thomas Co; 2005:741.

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IBD and Vitamin D Status- 2 Studies

- 150 IBD : 94 CD, 36 UC
- Age 15 ±3 yrs
- 92% white
- Mean 25 OHD 20.9±10.7 ng/ml
- 35% 25 OH D ≤ 15 ng/ml: 38% CD; 25% UC
- Vitamin D supplement: 77%
- Reduced 25 OHD related to
  - Season, serum albumin
- Pappa H et al. Pediatr 2006; 118: 1950-1961

- 448 IBD: 288 CD, 143 UC
- Age 15.7 ±3.2 yrs
- 83.3 % white
- Mean 25 OHD 31± 12
- 58.5% <32 ng/ml; 14.3%<20 ng/ml
- Vitamin D supplement: 57.1%
- Serum 25 OHD related to
  - Season, serum albumin, race/ethnicity, supplements, ESR
- Pappa H et al. JPGN 2011; 53:11-25

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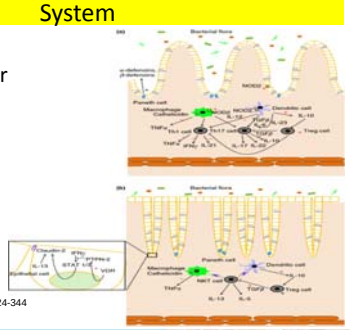
Tutorial: Relation to Vitamin D/GI and Immune System

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



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

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Vitamin D in Autoimmune-Infectious Disease

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

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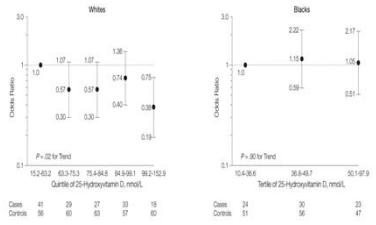
Serum 25 OHD and MS



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

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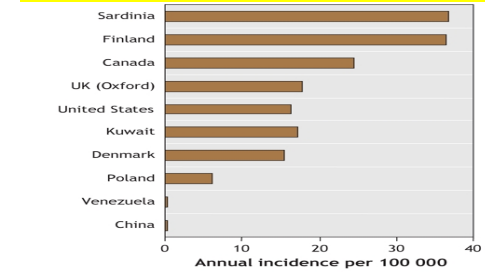
DM Incidence by Country



Gillespie KM. CMAJ 2006; 175:165-170

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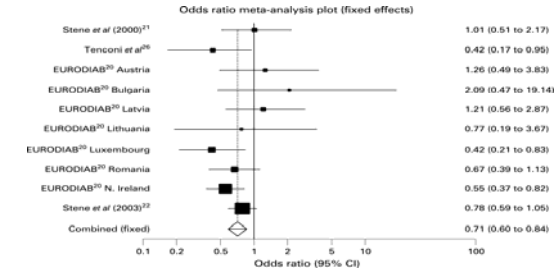
Vitamin D Supplementation and DM



Zipitis CS, Akobeng AK. Arch Dis Child 2008; 93:512- 517

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Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study

	Type 1 diabetes	Time at risk (years)	Incidence per 100 000 years at risk	RR (95% CI)	Adjusted RR (95% CI)*
Use of vitamin D supplements					
None	2	981	204	1 (reference)	1 (reference)
Irregularly	12	36 143	33	0·16 (0·04–0·72)	0·16 (0·04–0·74)
Regularly	67	276 235	24	0·12 (0·03–0·47)	0·12 (0·03–0·51)
Dose of vitamin D†					
Low	2	2 093	96	1 (reference)	1 (reference)
Recommended	63	259 779	24	0·26 (0·05–0·84)	0·22 (0·05–0·88)
High	2	13 245	15	0·14 (0·02–0·97)	0·14 (0·02–1·01)
Suspected rickets‡					
No	77	306 945	25	1 (reference)	1 (reference)
Yes	4	6 414	62	2·6 (1·0–7·2)	3·0 (1·0–9·0)

*Adjusted for sex, neonatal (parity, gestational and maternal age), length of maternal education, social status, and standardised birth weight, and growth rate in infancy (suspected rickets adjusted in addition to the increased dose of vitamin D); †in children receiving vitamin D supplementation regularly.

Table 2: **Incidence rate and rate ratio (RR) of type 1 diabetes by the use of vitamin D supplements and suspected rickets in infancy**

-Risk of Type 1 DM reduced by ~80% with *regular** Vitamin D supplementation during the first year of life

* Regular supplementation – based on mothers report

THE LANCET • Vol 358 • November 3, 2001

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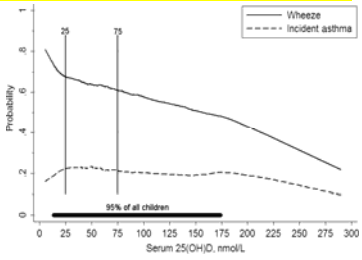
Cord Blood 25 OHD and risk of wheeze/asthma

- 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
	n/total n (%)					
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 (6.0)	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

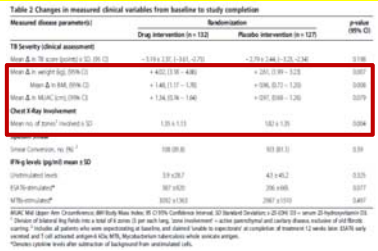


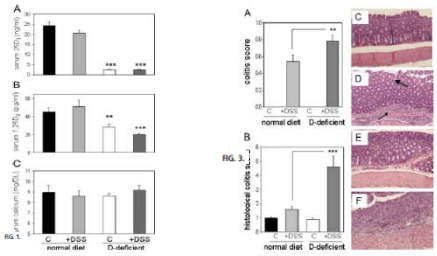
Table 2 Changes in measured clinical variables from baseline to study completion

Salahadin _____

Vitamin D in IBD models

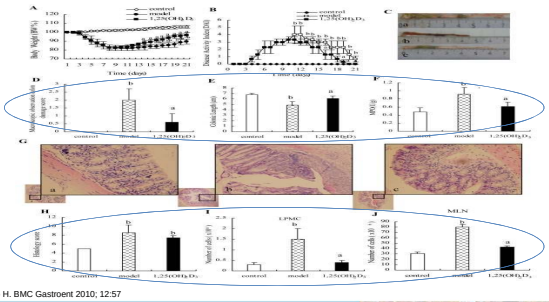
- DSS model with vitamin D deficiency
- Protective effect of 1,25 $(OH)_2D$ on epithelial barrier function and cytokine production in DSS model
- Cytokine production by non-diseased and Crohn's disease patient T-cells

Vitamin D Effect in Murine Model of Colitis



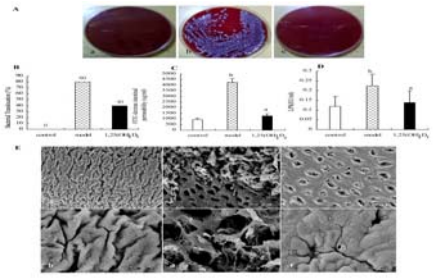
Lagishetty V et al. Endocrinology 2010; 151:2423-2432

1,25$(OH)_2D$ and Epithelial Barrier



Zhao H. BMC Gastroent 2010; 12:57

1,25(OH)$_2$D and Epithelial Barrier



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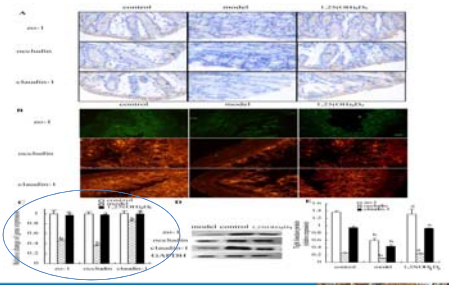
1,25(OH)$_2$D and Epithelial Barrier



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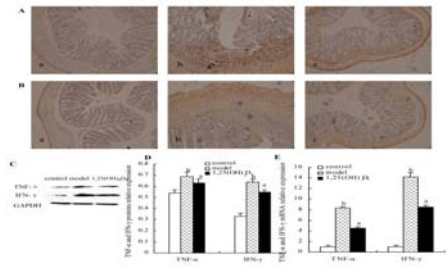
1,25 (OH)$_2$D and Cytokine Expression



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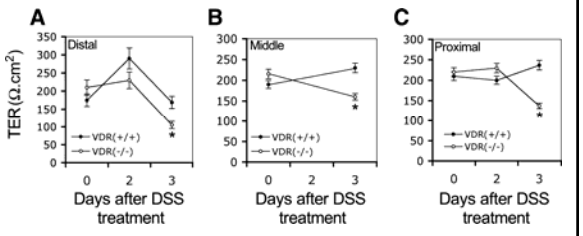
VDR Knockout and Epithelial Barrier



Kong J. Am J Phys 2007; 294:G208-G216

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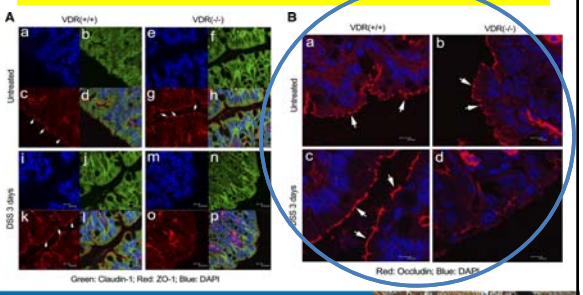
VDR Knockout and Epithelial Barrier



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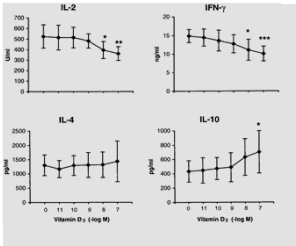
Cytokine Production by Human PBMC



Rausch-Fan X et al. Int Arch All. Immunol 2002; 128:33-41

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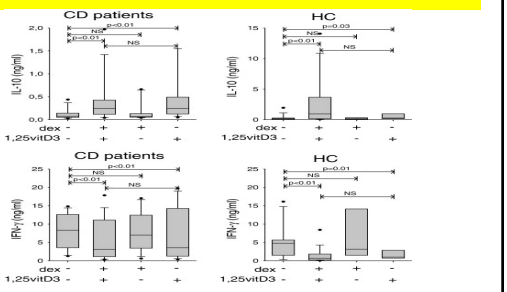
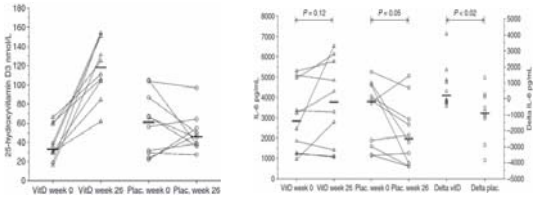
1,25 $(OH)_2$D Effect on IL-10/IFN-γ Production in CD



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_{trend}
Person-years of follow-up evaluation	380,369	384,505	377,108	378,763	
Crohn's disease					
Number of cases	37	37	22	26	
Age-adjusted HR (95% CI)	1.0	0.99 (0.63–1.56)	0.60 (0.35–1.01)	0.70 (0.42–1.15)	.059
Multivariate HR (95% CI)[a]	1.0	0.89 (0.55–1.45)	0.50 (0.28–0.90)	0.56 (0.30–1.00)	.018
Ulcerative colitis					
Number of cases	35	36	29	23	
Age-adjusted HR (95% CI)	1.0	1.02 (0.64–1.62)	0.84 (0.51–1.37)	0.66 (0.39–1.12)	.096
Multivariate HR (95% CI)[a]	1.0	0.98 (0.59–1.63)	0.84 (0.47–1.48)	0.68 (0.35–1.31)	.17

[a]Adjusted for age, smoking (ever or never), oral contraceptive use (current, past, or never), postmenopausal hormone therapy use (premenopausal, current, past, or never), physical activity (quintiles), 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_{trend}
Person-years of follow-up evaluation	380,151	380,256	380,299	380,039	
Crohn's disease					
Number of cases	34	33	28	27	
Age-adjusted HR (95% CI)	1.0	0.96 (0.59–1.54)	0.80 (0.48–1.32)	0.76 (0.46–1.26)	.24
Multivariate HR (95% CI)[a]	1.0	0.96 (0.60–1.56)	0.80 (0.49–1.32)	0.76 (0.46–1.27)	.22
Ulcerative colitis					
Number of cases	34	37	31	21	
Age-adjusted HR (95% CI)	1.0	1.08 (0.68–1.72)	0.91 (0.56–1.48)	0.61 (0.35–1.05)	.04
Multivariate HR (95% CI)[a]	1.0	1.10 (0.69–1.76)	0.93 (0.57–1.52)	0.64 (0.37–1.10)	.04

[a]Adjusted for age, smoking (ever or never), oral contraceptive use (current, past, or never), postmenopausal hormone therapy use (premenopausal, current, past, or never), physical activity (quintiles), and body mass (kg/m²) index (<21, 21–22.9, 23–24.9, 25–28.9, ≥29).

Ananthakrishnan AN. Gastroent 2012; 142:482-489

QI Efforts and CD

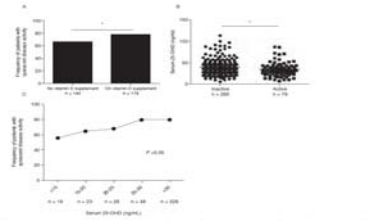
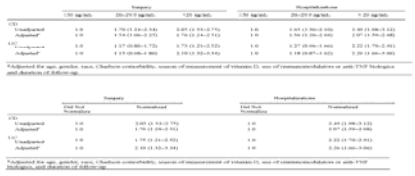


FIGURE 2. Vitamin D status and remission rate. A, For the year 2010, the frequency of patients with quiescent disease activity that were taking a vitamin D supplementation compared with those without any vitamin D supplementation, $P_1 = 0.02$. B, For the year 2010, serum 25-hydroxyvitamin D (25-OHD) was compared between patients with inactive (quiescent) and active (mild, moderate, or severe) disease activity. $^*P = 0.03$. C, For the year 2010, patients were stratified based on their most serum 25-OHD level and proportion of patients with a quiescent physician global assessment was determined.

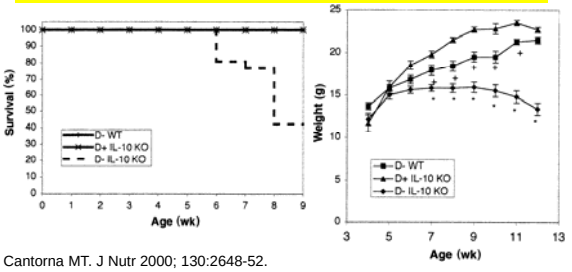
Samson CM. JPGN 2012; 55:679-688

Serum 25 OHD and Surgery in IBD



Ananthakrishnan AN. Inflamm Bowel Dis 2013; 19:1921-27

1,25 $(OH)_2D$ in Murine IBD



Cantorna MT. J Nutr 2000; 130:2648-52.

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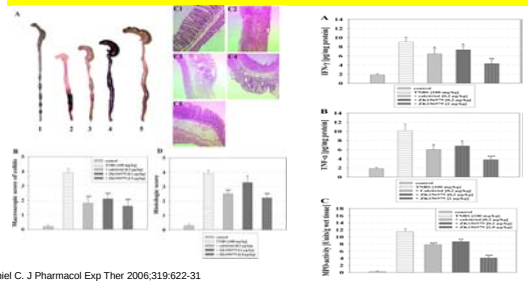
1,25 $(OH)_2D$ /Analogues in Murine IBD



Daniel C. J Pharmacol Exp Ther 2006;319:622-31

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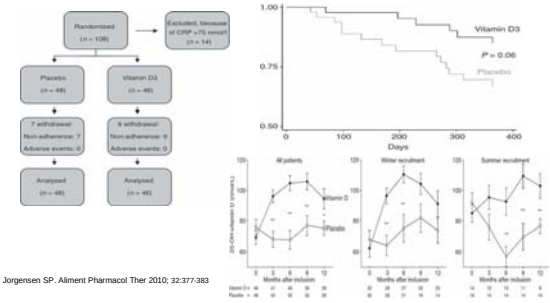
Vitamin D Treatment in CD



Jorgensen SP. Aliment Pharmacol Ther 2010; 32:377-383

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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.

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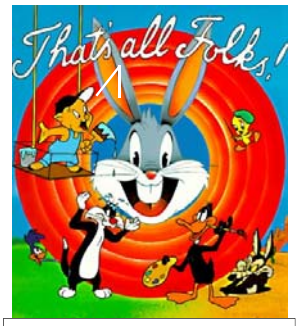

Questions?

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