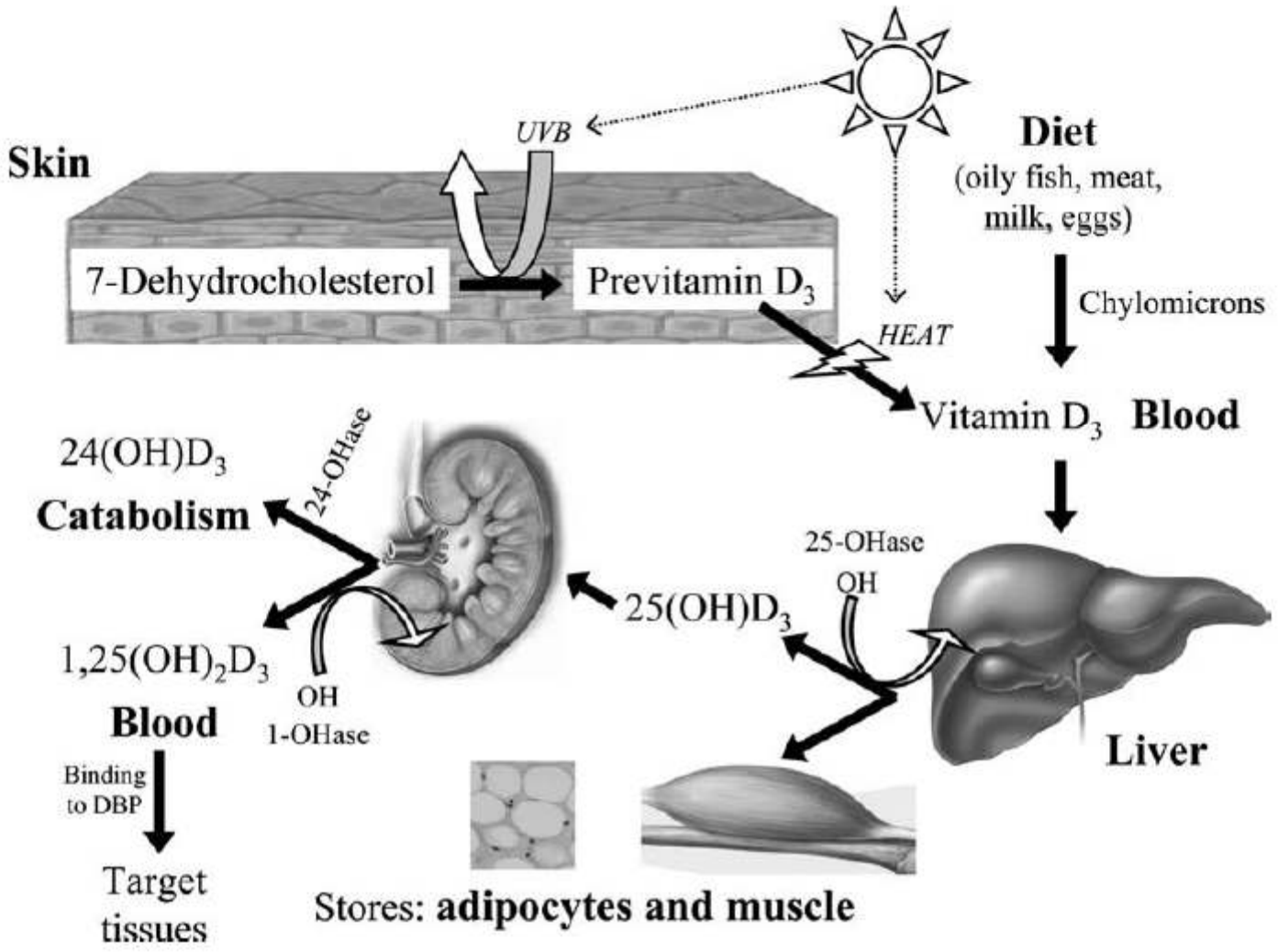
Vitamin D and Diabetes

인제의대 부산백병원 내분비내과
이순희

비타민 D의 대사

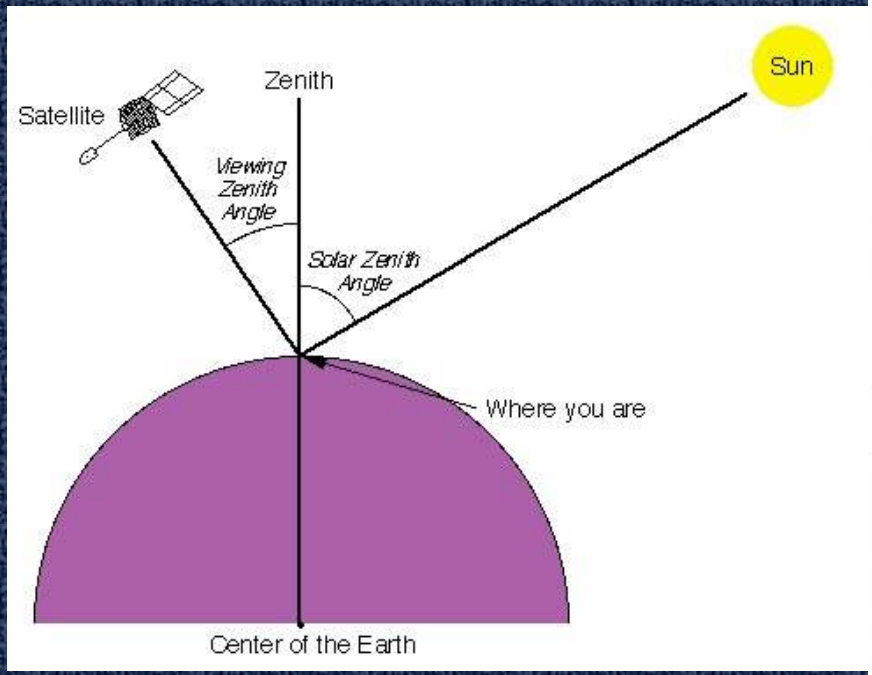


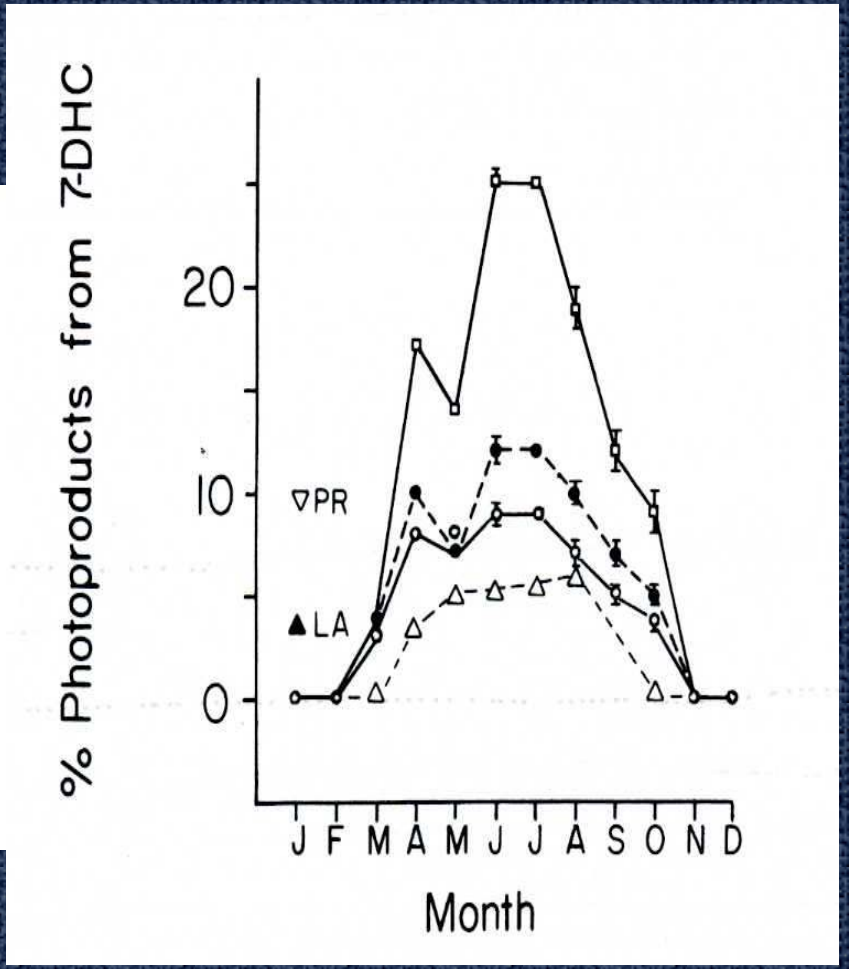
Diabetes, Obesity and Metabolism, 10, 2008, 185–197

식품의 비타민 D 함량

식품	함량 (IU/100g or IU/dL)
Egg yolk(난황)	Usually no more than 50 IU per yolk
Salmon(연어)	360 IU (3.5 ounces=100 g)
Mackerel(고등어)	345
Halibut(넙치)	40
Herring (청어)	320
Sardines (정어리)	1100-1500
Shrimp(새우)	150
Liver (간)	0-70
Butter(버터)	35
Cheese(치즈)	12-15
우유나 주스를 포함한 비타민 D 강화 식품	100 IU (8 ounces)

비타민 **D** 와 위도


Sun
Zenith
Satellite
Viewing Zenith Angle
Solar Zenith Angle
Where you are
Center of the Earth


% Photoproducts from 7-DHC
20
10
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▽PR
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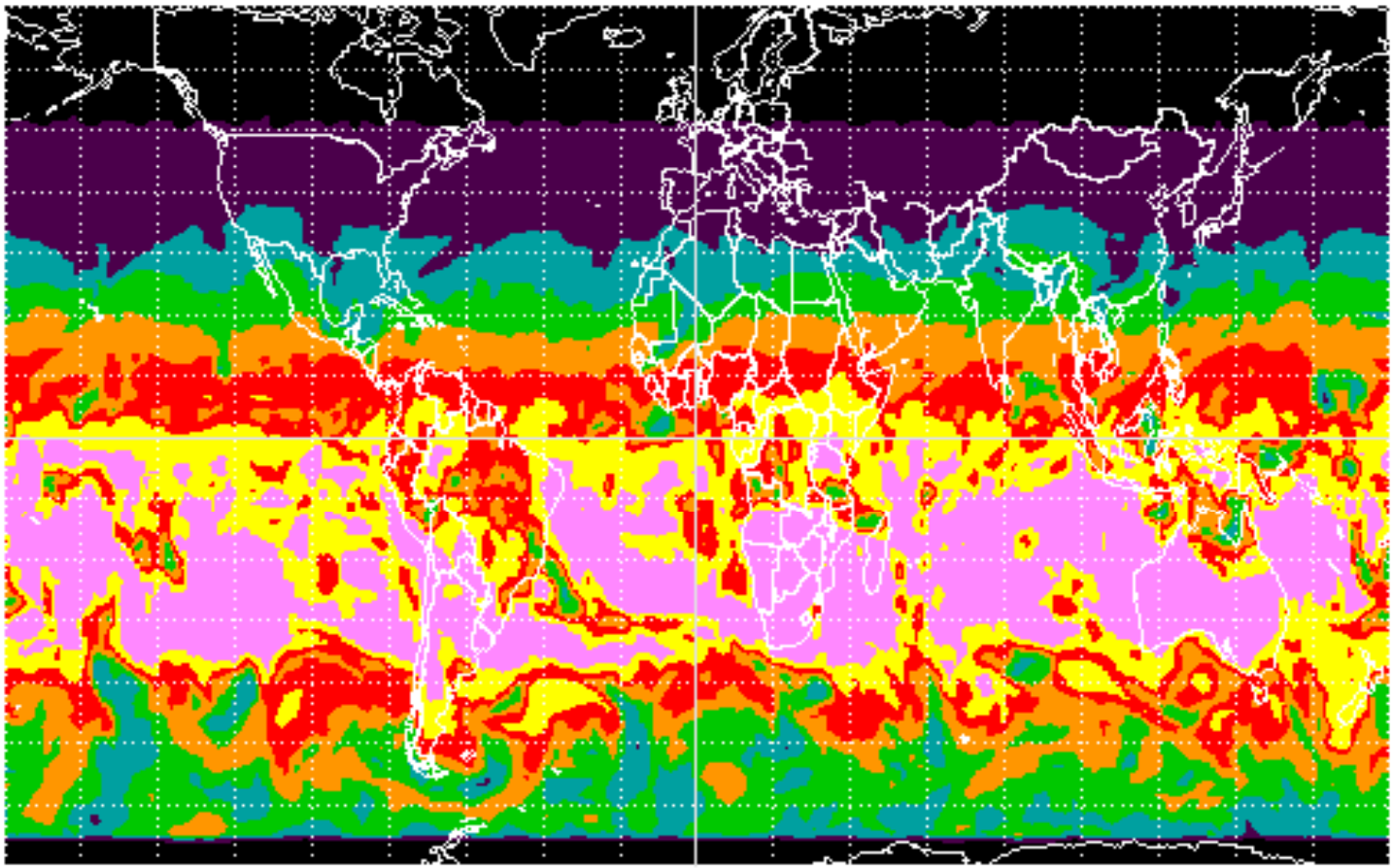
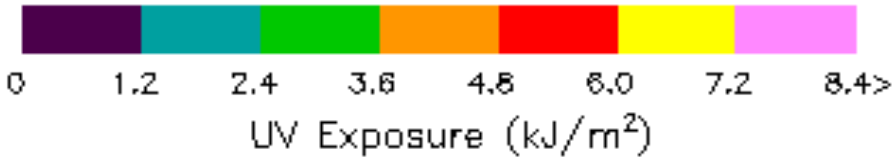
J F M A M J J A S O N D
Month

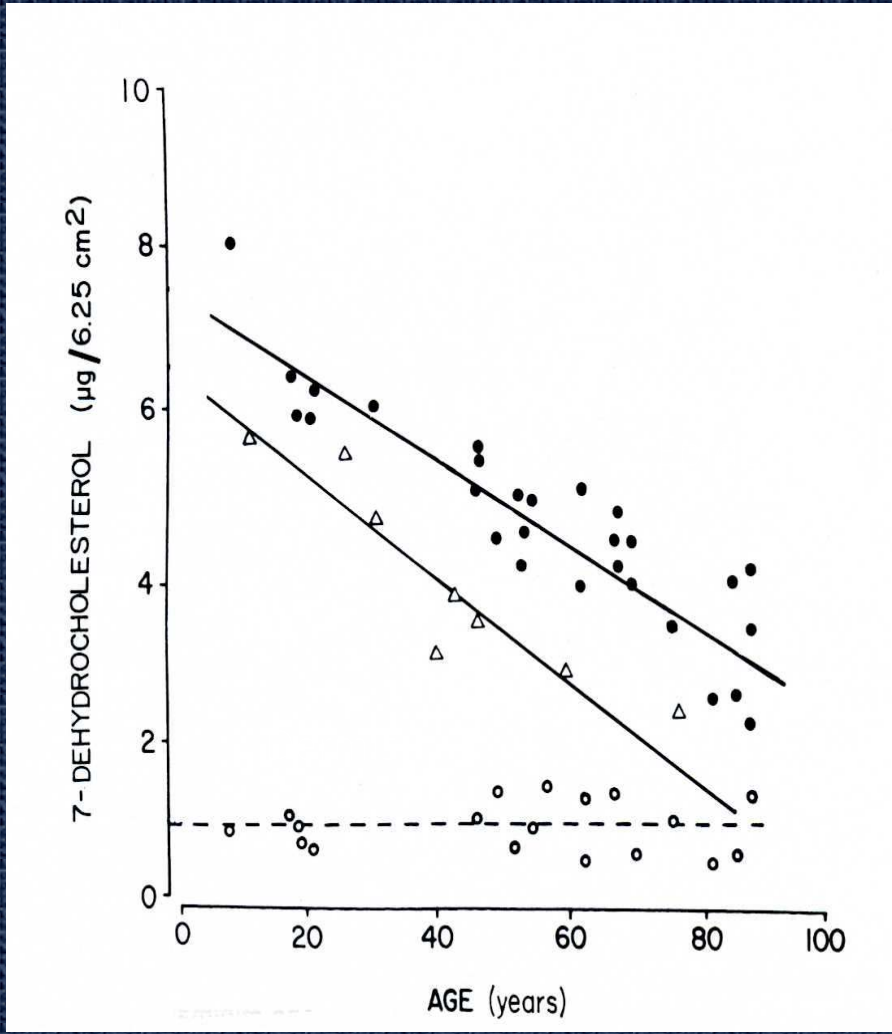
Earth Probe TOMS UV Erythemal Exposure on January 15, 2003



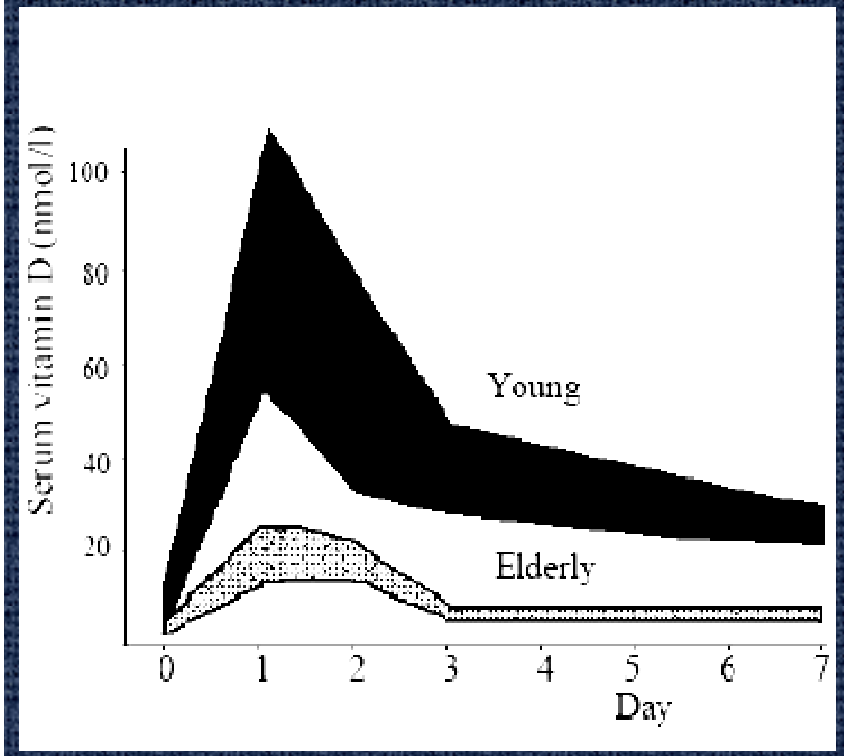


Goddard Space Flight Center

비타민 D 와 나이



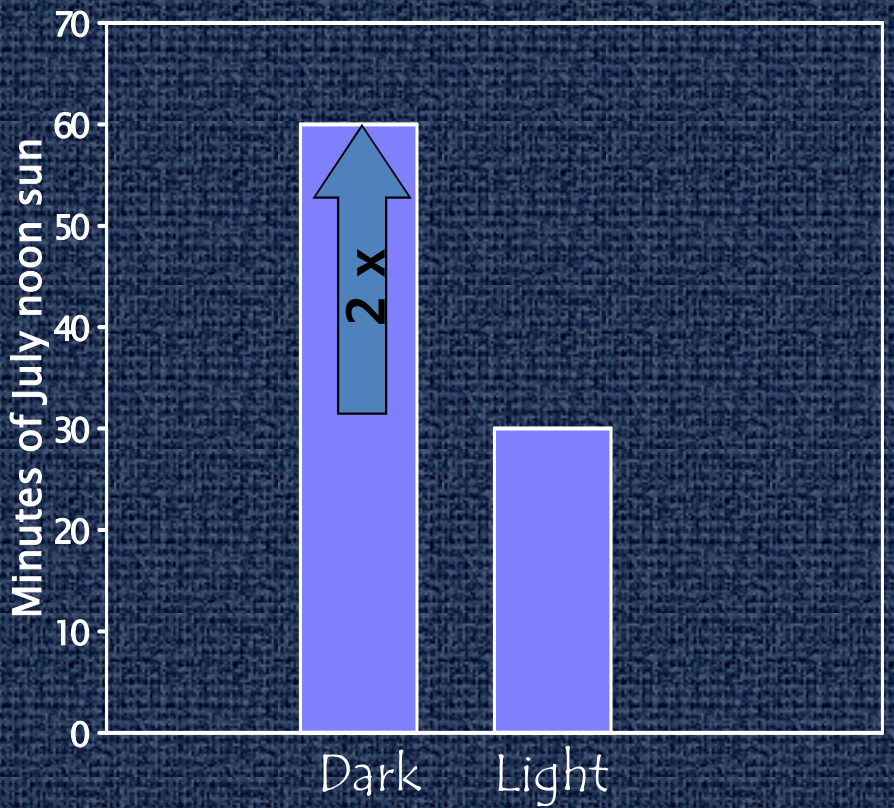
McLaughlin & Holick
JCI 1985 76:1536–38



Holick et al
Lancet 1989

비타민 D와 피부색

피부색이 검은 사람은 흰 사람에 비해 동일한 양의 비타민 D 생성을 위해 2배 더 많은 UVB 를 필요로 한다



Armas L. et al. 2007
J Am Acad Dermatol 57:588

비타민 **D**의 기능:
잘 알려진 것 들

- 소장과 신장에서 칼슘 흡수
- 소장에서 인 흡수
- 뼈 건강을 위해 중요

  (결핍시 소아에서 구루병, 성인에서 골연화증,

  골다공증)

비타민 D의 기능:
덜 알려진 기능들

근거 중심(Evidence Based)

질병	근거의 정도
골관절염/류마티스관절염	+
낙상/신경근육계 기능	++++
다발성경화증	++
섬유근통	++
제1형당뇨병	++
제2형당뇨병	+
인슐린민감도	++
심혈관질환	++
치주질환	++
다양한 종양	++++
결핵	+++
고혈압	++

비타민 D가 뼈, 소장, 신장 외에 다른 말초 조직에 영향을 미치는 간접 증거

- $1,25(OH)_2D_3$ 수용체는 장과 뼈 외에도 뇌, 심장, 췌장, 활성화된 T 임파구, B 임파구, 피부, 생식선 등의 다양한 다른 조직에도 존재

  - J Bone Miner Res. 1998 Mar;13(3):325-49.

- 대장, 전립선, 유방, 피부, 췌장 등의 조직에는 $1,25(OH)_2D_3$ 를 생산할 수 있는 1α-hydroxylase 가 존재

  - J Bone Miner Res. 1998 Mar;13(3):325-49.

- 인슐린종 베타세포주에서 $1,25(OH)_2D_3$ (10 nM for 72 h)에 반응하여 비타민 D 수용체 발현이 대조군에 비해 313% 증가

  - Endocrinology. 1994 Apr;134(4):1602-10

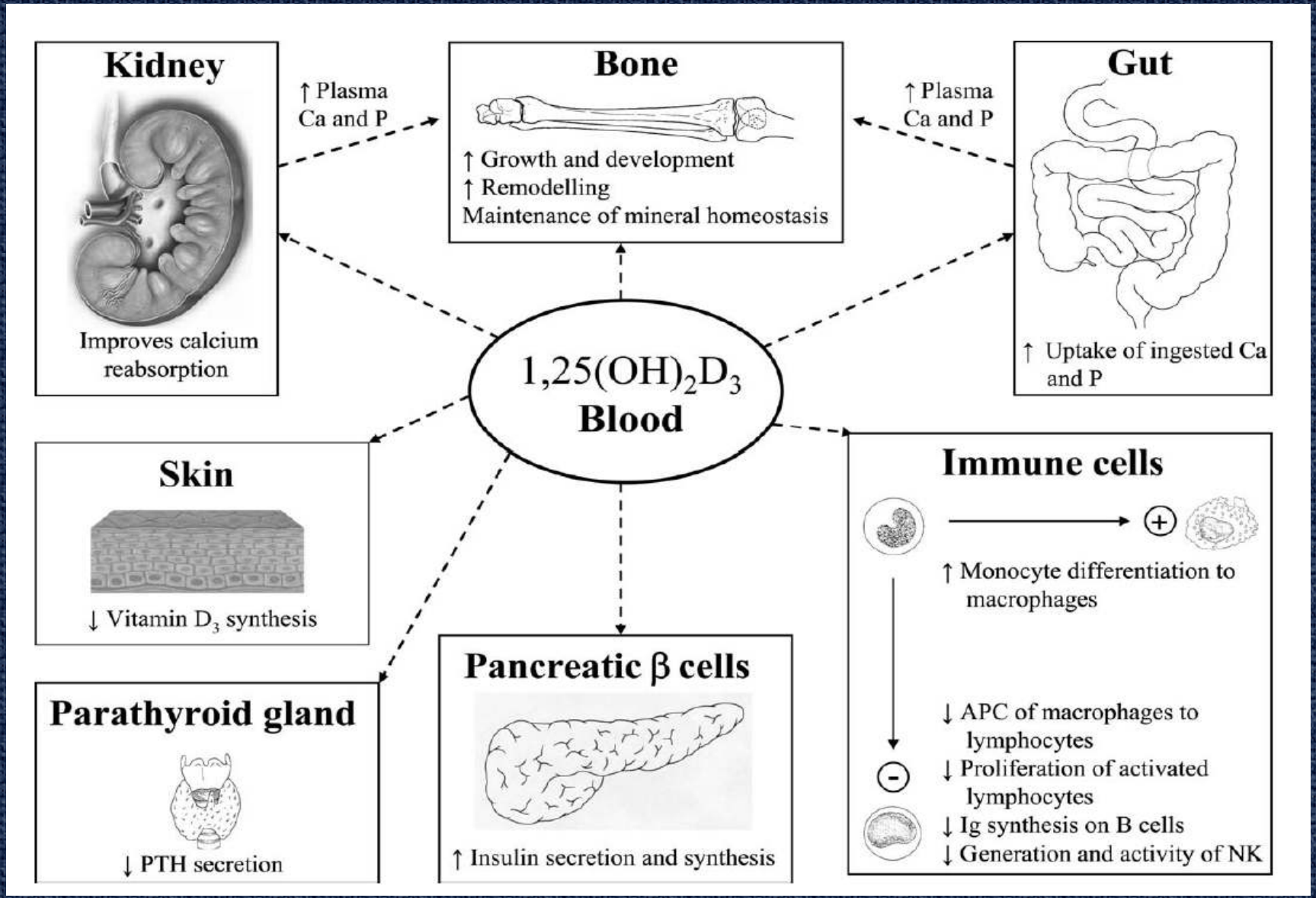
$1,25(OH)_2D_3$의 표적 장기

Classification	*Target tissue or cell**	*Specific effects†*
Immune system	monocytes/macrophages[53] and T-lymphocytes (helper type 1)[53,57]	suppression of γ-interferon[202] and IL-1 through IL-6[53,159,203]
Central nervous system	dorsal root ganglia,[204] glial cells, and hippocampus[70,107]	production of NGF,[65,66,205] neurotrophin-3,[64] and leukemia inhibitory factor[63]
Epithelium	epidermal skin/keratinocyte[206]	differentiation[17,211]
	hair follicle[207]	differentiation[16,17,212]
	female reproductive tract[208]	uterine development[16]
	mammary[108]	↓ cell growth[213]
	prostate[209]	↓ cell growth[173]
	colon[210]	↓ cell growth[170,214]
	lung[108]	surfactant[215]
Endocrine system	thyrotrope[216]	TRH receptor[218]
	thyroid[108]	↓ TSH action[219]
	pancreatic β-cell[217]	insulin secretion[51]
	ovary[208]	folliculogenesis[16] and ↓ cell growth[220]
Muscle	heart[221]	↓ ANP[222,223]
Adipose	adipocyte[224]	lipoprotein lipase[225]
Many systems	diverse cells and cancer cell lines[173,226,227]	↓ cell growth (c-*fos*[179]; ↓ c-*myc*[58,157]), differentiation (p21[228]; p27[229]; *Mad*-1[230]) and apoptosis[213] (↓ *Bcl*-2[231,232])

*Detected by autoradiographic ligand localization in the nucleus, VDR immunocytochemistry, or responsiveness of cultured cells.
†Effects of $1,25(OH)_2D_3$ are positive unless otherwise noted and are selected examples rather than a comprehensive list.

J Bone Miner Res. 1998 Mar;13(3):325-49.

말초조직에 대한 비타민 D의 작용

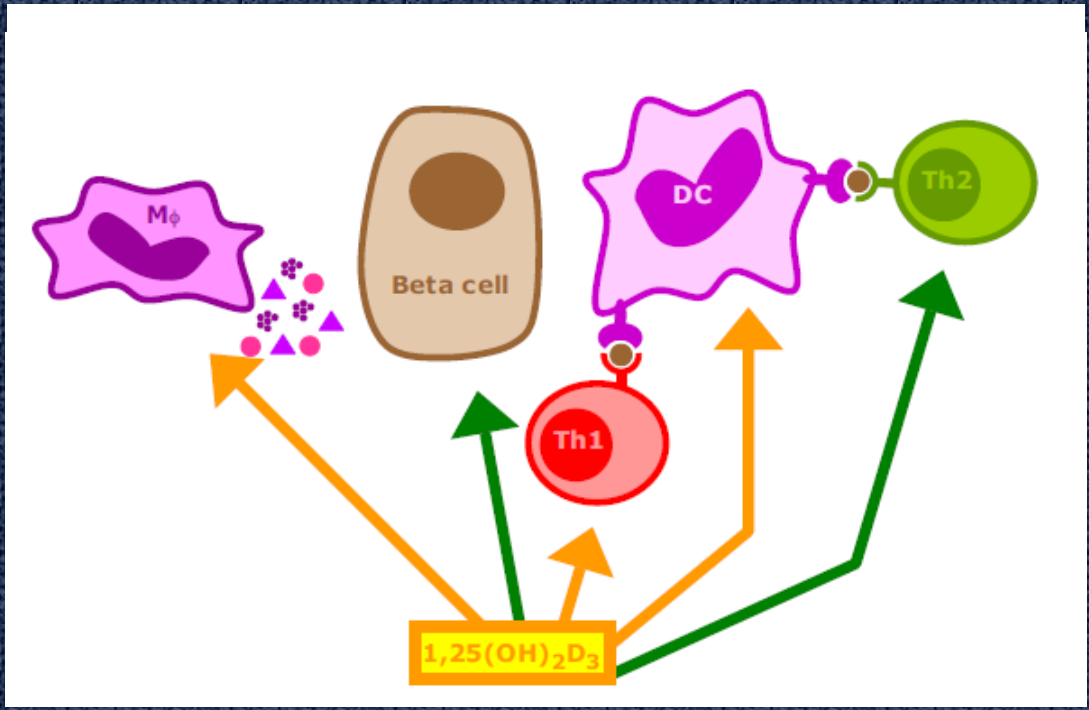


Diabetes, Obesity and Metabolism, 10, 2008, 185–197

비타민 D 와 제1형 당뇨병

- 동물모델에서 제1형 당뇨병은 $1,25(OH)_2D_3$ 에 의해 예방
- 사람에서 예방효과가 있다는 일부 증거들이 있음

제1형 당뇨병에서 $1,25(OH)_2D_3$ 의 작용기전



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

Elina Hyppönen, Esa Läärä, Antti Reunanen, Marjo-Riitta Järv rtanen

Lancet 2001;358:1500-1503

북부 핀란드의 1966년 코호트 연구

- 핀란드의 가장 북부에 위치한 두 지역 (Oulu and Lapland) 에서 1966년에 출산 예정인 모든 산모들을 대상 -> 12,058 live births
- 1세때 비타민 D 섭취량과 상태에 대한 정보를 수집 (n=10,366)
- 1997년 12월까지 제1형 당뇨병 발생 여부에 대한 추적 검사

Hyppönen et al. Lancet 2001;358:1500-1503

유아기에 비타민 D 보충 여부에 따른 제1형 당뇨병의 발생률

	Cases	Incidence /100,000 years at risk	Crude RR (95% CI)	Adjusted* RR (95% CI)
Use of vitamin D supplements				
Not at all	2	204	1 (reference)	1 (reference)
Irregularly	12	33	0. 16 (0.04-0.72)	0.16 (0.04-0.74)
Regularly	67	24	0.12 (0.03-0.47)	0.12 (0.03-0.51)

* Adjusted for neonatal, social and anthropometric factors.

Hyppönen et al. Lancet 2001;358:1500-1503

비타민 D의 용량에 따른 제1형 당뇨병의 발생률

	Cases	Incidence /100,000 years at risk	Crude RR (95% CI)	Adjusted* RR (95% CI)
Dose of Vitamin D†				
Low	2	96	1 (reference)	1 (reference)
Recommended	63	24	0.20 (0.05-0.84)	0.21 (0.05-0.88)
High	2	15	0.14 (0.02-0.97)	0.14 (0.02-1.01)

* Adjusted for neonatal, social and anthropometric factors.

† Dose has been presented for infants receiving vitamin D regularly

Hyppönen et al. Lancet 2001;358:1500-1503

유아기에 구루병 의심 유무에 따른 제1형 당뇨병의 발생률

	Cases	Incidence /100,000 years at risk	Crude RR (95% CI)	Adjusted* RR (95% CI)
Suspected rickets				
No	77	25	1(reference)	1 (reference)
Yes	4	62	2.6 (1.0-7.2)	3.0 (1.0-9.0)

* Adjusted for neonatal, social and anthropometric factors.

Hyppönen et al. Lancet 2001;358:1500-1503

제1형 당뇨병 발생률 증가와 비타민 D 권장량 감소의 연관성?
(핀란드)

- 제1형 당뇨병의 발생률 증가

AND

- 유아에서 비타민 D 권장량의 감소
  - 1956: 4000-5000 IU
  - 1964: -> 2000 IU
  - 1975: -> 1000 IU
  - 1992: -> 400 IU
- 비타민 D를 보충하는 순응도의 변화 ?
- 1980년대에 구루병의 발생률의 증가

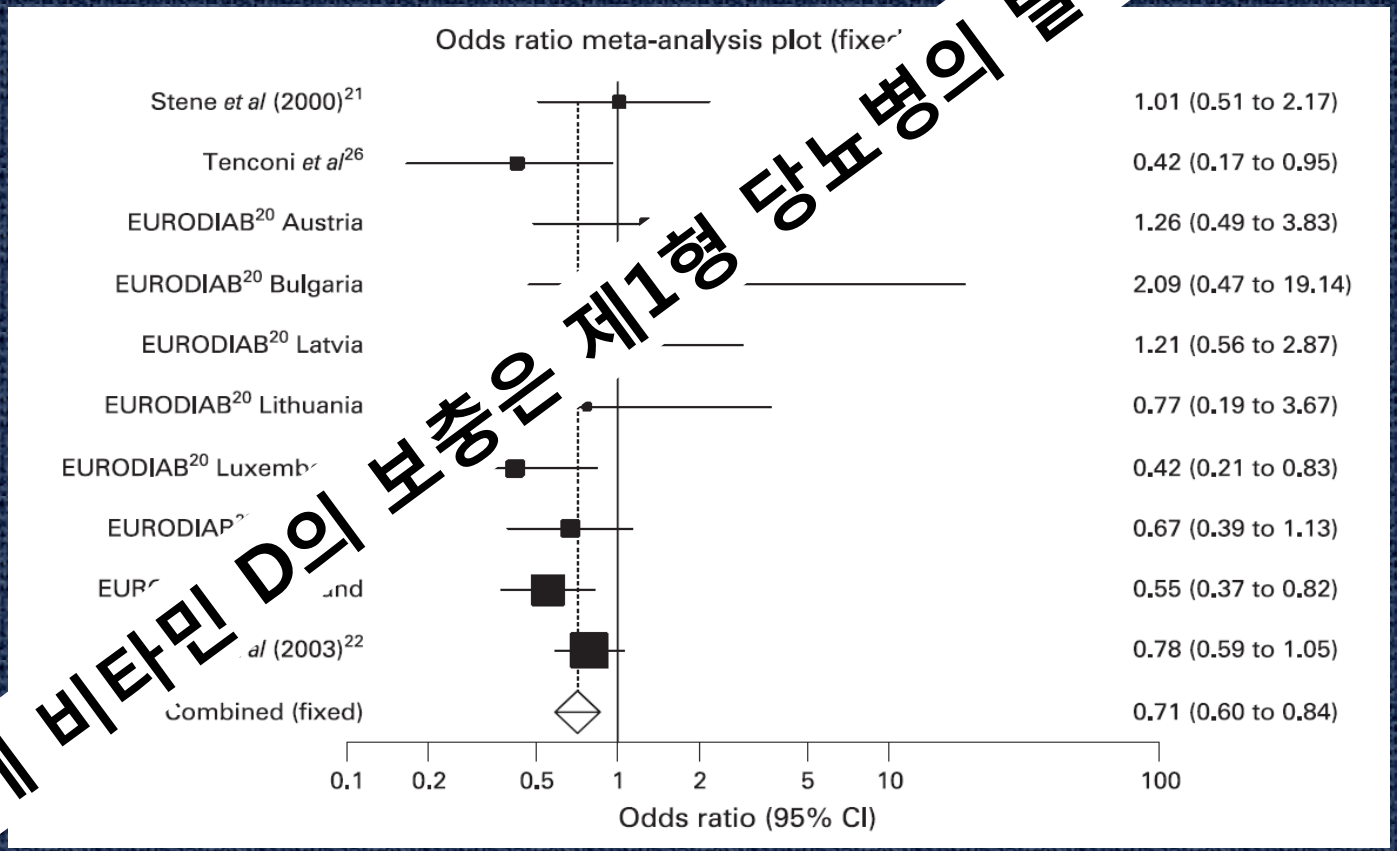
Hyppönen et al. Lancet 2001;358:1500-1503

Original article

Vitamin D supplementation in early childhood a… risk of type 1 diabetes: a systematic review meta-analysis

C S Zipitis,[1] A K Akobeng[2]

제1형 당뇨병의 발생에 미치는 유아기에 비타민 D 보충 효… 비 (95% 신뢰구간)



유아기에 비타민 D의 보충은 제1형 당뇨병의 발생을 예방할 가능성

Arch Dis Child 2008;93:512–517.

인슐린 분비능과 비타민 D

- 비타민 D의 결핍은 동물모델과 사람 모두에서 인슐린 분비 장애 유발

-Science. 1980 Aug 15;209(4458):823-5
-Endocrinology 1983 113:1511–1518
-Endocrinology 1986 119:84–90

- 비타민 D의 보충은 이러한 인슐린 분비장애를 교정

-J Clin Invest 1984 73:759–766
-Endocrinology 1984 115:191–197
-Acta Endocrinol (Copenh) 1984 105:528–533

Epidemiology/Health Services Research
BRIEF REPORT

Serum 25-Hydroxyvitamin D Concentration and Subsequent Risk of Type 2 Diabetes

CATHARINA MATTILA, MSC
PAUL KNEKT, PHD
SATU MÄNNISTÖ, PHD
HARRI RISSANEN
MAARIT A. LAAKSONEN, MSC
JUKKA MONTONEN, PHD
ANTTI REUNANEN, PHD, MD

혈청 25(OH)D 의 사분위간에 제2형 당뇨병의 상대위험도

제2형 당뇨병과 혈청 25(OH)D 간에 역의 상관관계

	25OHD quartile*			
	1	3	4	*P* for trend
N	1,051	986	981	—
n	62	39	30	—
Mean serum 25OHD (nmol/l)	35.5	47.9	70.9	—
Model†				
1	1.18 (0.81–1.72)	0.79 (0.51–1.22)	0.60 (0.36–0.98)	0.01
2	1.00	1.15 (0.79–1.69)	0.83 (0.53–1.29)	0.70 (0.42–1.16)	0.07
3	1.00	1.10 (0.75–1.61)	0.80 (0.51–1.25)	0.67 (0.41–1.11)	0.05
4	1.00	1.23 (0.80–1.89)	0.97 (0.59–1.58)	0.58 (0.32–1.06)	0.06

Data … CI) unless otherwise indicated. *Quartile 1, <30 nmol/l; 2, 30–41 nmol/l; 3, 42–55 nmol/l; and 4, >55 nmol/l. †Model 1: RRs adjusted for … variable), sex, and month of collecting blood samples; *N* (all data) = 4,097 and *n* (type 2 diabetes cases) = 183. Model 2: RRs were adjusted for all of … in model 1 plus BMI (<23, 23–24.9, 25–27.4, 27.5–29.9, or ≥30 kg/m^2), leisure-time exercise (little, occasionally, or regularly), smoking (never smoker, ex-smokers, a cigar or pipe or <20, 20–29, or >29 cigarettes/day), and education (<7, 7–9, 10–12, or >12 years); *N* = 4,083 and *n* = 183. Model 3: RRs were adjusted for all of the factors in model 2 plus blood pressure (normotension, borderline hypertension, mild hypertension, or definite hypertension); *N* = 4,030 and *n* = 181. Model 4: RRs were adjusted for all of the factors in model 2, and the first 5 years of follow-up were excluded; *N* = 4,044 and *n* = 144.

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(6):2017–2029

doi: 10.1210/jc.2007-0298

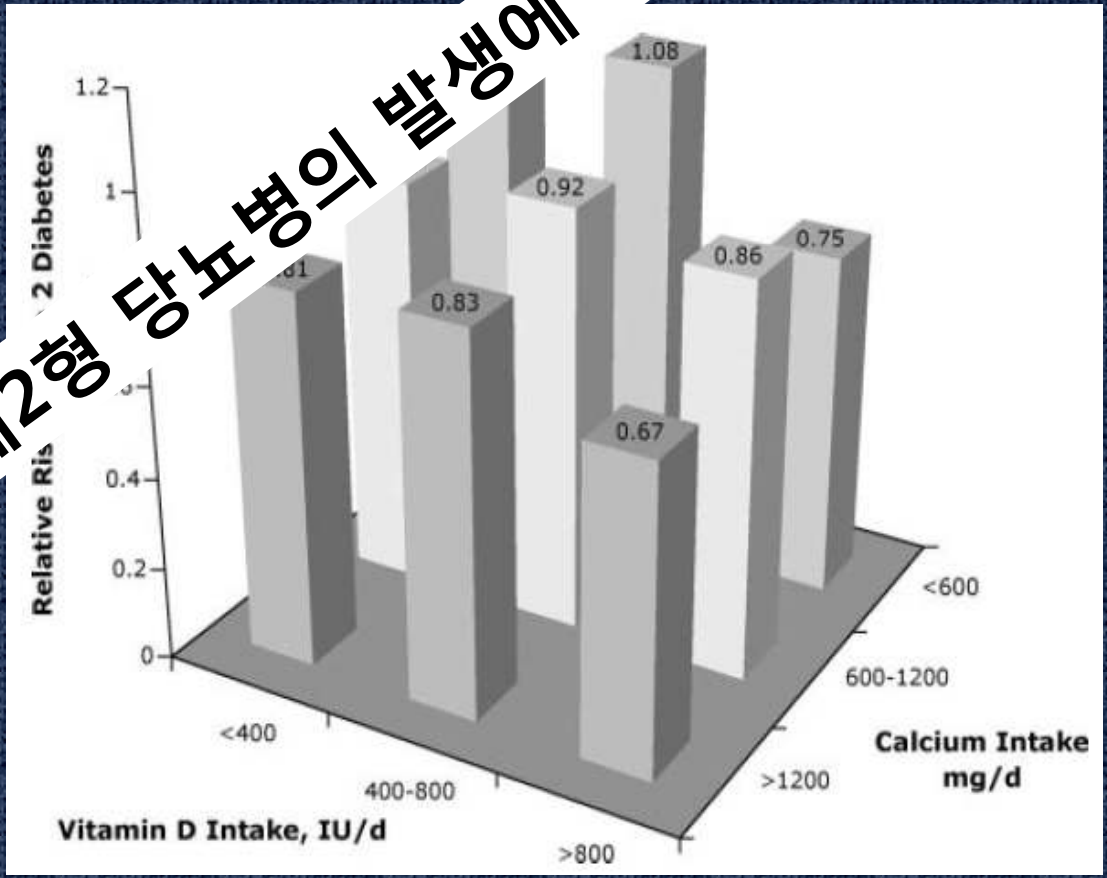
REVIEW: The Role of Vitamin D and Calcium in T… Diabetes. A Systematic Review and Meta-Analys…

Anastassios G. Pittas, Joseph Lau, Frank B. Hu, and Bess Dawson-Hughes

Divisions of Endocrinology, Diabetes and Metabolism (A.G.P., B.D.-H.), and Clinical Researc… …s-New England Medical Center, Boston, Massachusetts 02111; Harvard School of Public Health and Char… …ory (F.B.H.), Boston, Massachusetts 02115; and Bone Metabolism Laboratory (B.D.-H.), Jean Mayer U.S. Der… …griculture Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts 02111

Nurse Health Study 에서 칼슘과 비타민 D 섭취에 따른 제2형 당뇨병 발생의 … 정된 상대위…

비타민 D와 칼슘 모두 제2형 당뇨병의 발생에 영향을 … 가능성



The Journal of Clinical Endocrinology & Metabolism 92(6):2017–2029

제2형 당뇨병과 비타민 D 수용체, 비타민 D 결합 단백, 1α-hydroxylase 유전자의 다형성의 관계

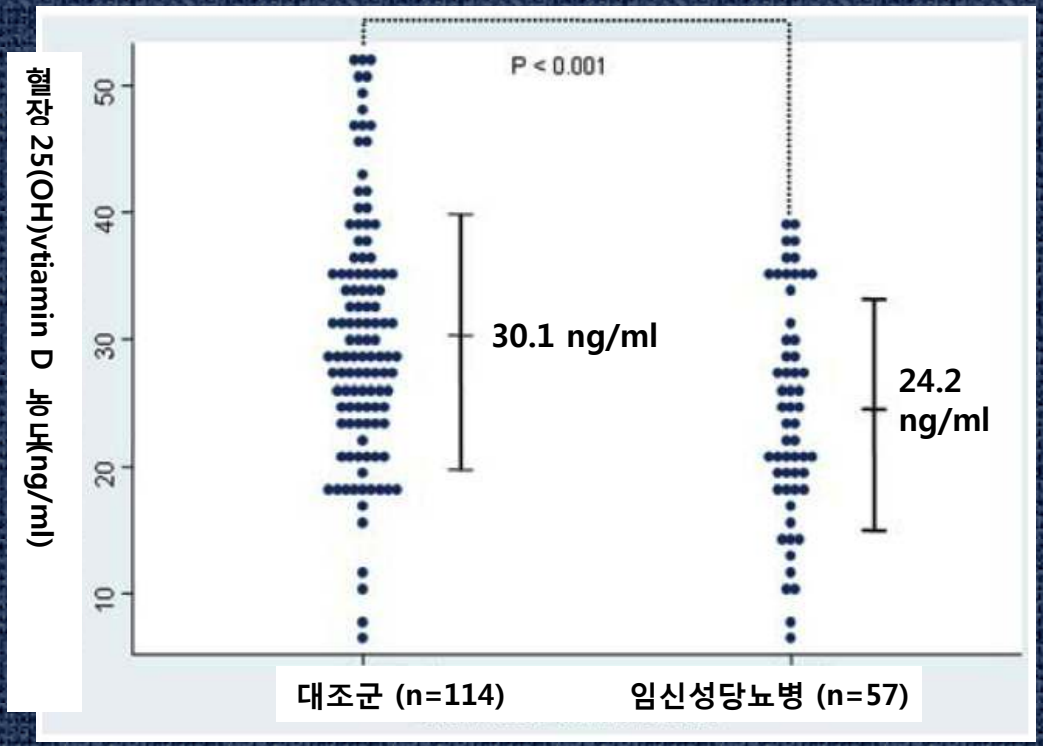
Gene	Polymorphism (base change)	Genotype	Reported association*	Population	Reference
VDR	*Apa*I (T/G)	aa	+ (lower insulin secretion)	Bangladeshi Asians population at risk of DM2 living in London	Hitman *et al.* [73]
		aa	+ (fasting plasma glucose, glucose intolerance)	Older adults without diabetes (Rancho Bernardo study)	Oh and Barrett-Connor [74]
		aa	− (DM2), + (obesity)	French Caucasians	Ye *et al.* [72]
	*Bsm*I (G/A)	bb	+ (reduced insulin secretory capacity)	Bangladeshi Asian population at risk of DM2 living in London	Ogunkolade *et al.* [16]
		bb	− (DM2), + (obesity)	French Caucasians	Ye *et al.* [72]
		B−	+ (altered calcium absorption, elevated PTH, DM2 and elevated fasting glucose)	Healthy young subjects	Ortlepp *et al.* [14]
		BB	+ (higher levels of postprandial serum C-peptide)	Obese diabetic subjects	Speer *et al.* [75]
	*Fok*I (T/C)	FF	+ (increased insulin sensitivity)	Healthy glucose-tolerant Caucasians	Chiu *et al.* [54]
	*Taq*I (A/C)	TT	+ (reduced insulin secretory capacity)	Bangladeshi Asian population at risk of DM2 living in London	Ogunkolade *et al.* [16]
		T−	+ (reduced insulin secretion)	Subjects with 25(OH)D_3 insufficiency	Ogunkolade *et al.* [16]
		TT	− (DM2), + (obesity)	French Caucasians	Ye *et al.* [72]
	*Tru9*I (A/G)	u−	− (DM2)	French Caucasians	Ye *et al.* [72]
DBP		Gc−	+ (glucose tolerance), − (DM2 prevalence)	Non-diabetic Pima Indians	Baier *et al.* [87], Pratley *et al.* [13]
		Gc1−	+ (DM2)	Polynesian and Japanese subjects	Kirk *et al.* [90], Hirai *et al.* [91]
		Gc1s−	+ (fasting insulin, plasma glucose)	Subarctic Amerindians	Szathmary [92]
		Gc1f-1f	+ (lower levels of fasting insulin)	Non-diabetic Dogrib Indians from Canada	Szathmary [93]
		Gc1f-1f	− (fasting insulin levels)	Hispanic population of San Luis Valley (USA)	Iyengar *et al.* [12]
		Gc−	− (DM2)	American, French and Polish Caucasians	Klupa *et al.* [94], Ye *et al.* [69], Malecki *et al.* [99]
CYP1alpha		TC	− (DM2)	Polish Caucasians	Malecki *et al.* [99]
			+ (DM2)	Obese Polish Caucasians	Malecki *et al.* [99]

DBP, vitamin D–binding protein; DM2, type 2 diabetes mellitus; PTH, parathyroid hormone; VDR, vitamin D receptors.
*Denotes positive (+) or negative (−) association with the corresponding phenotype reported in brackets.

Diabetes, Obesity and Metabolism, 10, 2008, 185–197

비타민 D와 임신성 당뇨병

- 비타민 D의 매 5 ng/ml 감소는 임신성 당뇨병의 위험성을 29% 증가시킴 [승산비(95% 신뢰구간): 1.29 (1.05-1.60)].
- 임신 16주에 혈장 25(OH)D 농도는 임신성 당뇨군에서 대조군에 비해 의미 있게 낮음 (24.2 vs. 30.1 ng/ml, P,0.001).



임신 16주

PLoS One. 2008;3(11):e3753

비타민 D와 당뇨병간의 전향적 관찰 코호트 연구

Table 1
Prospective (longitudinal) observational cohort studies of vitamin D status and diabetes.

Study, year (reference) cohort [country]	Gender, mean baseline age (range), y	Vitamin D measure; comparison[a]	Mean follow-up, y	Results, adjusted RR, OR, or HR (95% CI)	Ascertainment method of diabetes	Adjustments
Type 1 diabetes						
Hypponen et al., 2001 [11] [Finland]		Vitamin D supplementation during infancy; "regular" vs. "none"	14	0.12 (0.03, 0.51)	Central drug national registry	Neonatal, anthropometric and social
Type 2 diabetes						
Liu et al., 2005 [16] Women's Health Study [US]	Women, 52 (45–75)	Vitamin D intake (total); ≥511 IU/d vs. ≤159 IU/d	9	0.73 (0.54, 0.99)	Validated self-report	Age
Pittas et al., 2006 [17] Nurses Health Study [US]	Women, 46 (30–55)	Vitamin D intake (total); >800 IU/d vs. ≤200 IU/d	20	0.87 (0.69, 1.09)	Validated self-report	Age, BMI, exercise, residence, family history of diabetes, hypertension, calcium intake, smoking, alcohol, coffee, other dietary factors
Knekt et al., 2008 [18] Finnish Mobile Clinic Health Examination Survey [Finland]	Men, ND (40–74)	25(OH)D; 75 nmol/L vs. 25 nmol/L	9	0.49 (0.15, 1.64)	Medication-treated, registry-based	Age, BMI, exercise, season, residence, smoking, education, medications
	Women, ND (40–74)	25(OH)D; 61 nmol/L vs. 22 nmol/L		0.91 (0.37, 2.23)		
Knekt et al., 2008 [18] Mini-Finland Health Survey [Finland]	Men, 53 (40–69)	25(OH)D; 75 nmol/L vs. 22 nmol/L	9	0.17 (0.05, 0.52)	Medication-treated, registry-based	Age, BMI, exercise, season, residence, smoking, education, medications
	Women, 53 (40–69)	25(OH)D; 61 nmol/L vs. 20 nmol/L		1.45 (0.58, 3.62)		

Only studies where the predictor (vitamin D status) was assessed prior to the outcome (type 1 or type 2 diabetes) are included. 25(OH)D, serum or plasma 25-hydroxyvitamin D; BMI, body mass index; HR, hazard ratio; IU, international units; ND, no data; OR, odds ratio; RR, relative risk. To convert 25(OH)D concentration from nmol/L to ng/mL divide by 2.459.

[a] Highest/lowest risk category vs. reference category.

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당뇨병의 outcome과 비타민 D의 Randomized Controlled Trials

Study, year (reference) [country]	Mean baseline age (range), y	Participants	Baseline, mean 25(OH)D, nmol/L	Interventions (*n*)	Study duration	Outcome (units) [vitamin D vs. placebo, change or incidence] [reported *P* value]
Type 1 diabetes						
No studies						
Type 2 diabetes						
Nilas et al., 1984 [19] [Denmark]	ND (45–54)	Postmenopausal, healthy	ND	D_3 2000 IU/d (*n* = 25) vs. placebo (*n* = 103). All received calcium 500 mg/d	2 y	FPG (mmol/L) [0.12 vs. 0.13] [NS]
Pittas et al., 2007 [21] [US]	71 (ND)	Normal fasting glucose	75	D_3 700 IU/d + calcium citrate 500 mg/d (*n* = 108) vs. placebo (*n* = 114)	3 y	FPG (mmol/L) [0.15 vs. 0.12] [*P* = 0.55]
	71 (ND)	Impaired fasting glucose	75	D_3 700 IU/d + calcium citrate 500 mg/d (*n* = 45) vs. placebo (*n* = 47)	3 y	FPG (mmol/L) [0.02 vs. 0.34] [*P* = 0.042]
De Boer et al., 2008 [22] [US]	ND (50–79)	Postmenopausal without diabetes	<79	D_3 400 IU/d + calcium carbonate 1000 mg/d (*n* = 16,999) vs. placebo (*n* = 16,952)	7 y	Diabetes[a] (% cohort) [96 vs. 95] HR 1.01 (0.94, 1.10) [*P* = 0.95]
Sugden et al., 2008 [20] [UK]	64 (ND)	Stable type 2 diabetes	37	D_2 100,000 IU orally once (equivalent to 1785 IU/d) (*n* = 17) vs. placebo (*n* = 17)	8 wk	Hemoglobin A1c (%) [0.01 vs. −0.05] [*P* = 0.74]
von Hurst et al., 2009 [25] [New Zealand]	42 (23–68)	Insulin resistance without diabetes and 25(OH)D <50 nmol/L	Median ~20	D_3 4000 IU/d (*n* = 42) vs. placebo (*n* = 39)	26 wk	FPG (mmol/L) [0.1 vs. 0.1] [*P* = 0.82]
Zittermann et al., 2009 [24] [Germany]	48 (18–70)	Healthy, BMI >27 kg/m^2	30	D3 3332 IU/d (*n* = 100) vs. placebo (*n* = 100). All received weight reduction advice for 24 wk	1 y	Hemoglobin A1c (%) [−0.25 vs. −0.25] [*P* = 0.96] FPG (mmol/L) [−0.21 vs. −0.27] [*P* = 0.39]
Jorde et al., 2009 [23] [Norway]	56 (21–75)	Stable type 2 diabetes	59	D3 40,000 IU weekly (equivalent to 5714 IU/d) (*n* = 16) vs. placebo (*n* = 16)	26 wk	Hemoglobin A1c (%) [−0.2 vs. −0.2] [*P* = 0.90] FPG (mmol/L) [−0.2 vs. 0.4] [*P* = 0.43]

25(OH)D, serum or plasma 25-hydroxyvitamin D; FPG, fasting plasma glucose; ND, no data. To convert FPG from mmol/L to mg/dL, divide by 0.0555. * Δ, net difference (vitamin D minus placebo); HR, hazard ratio; RR, relative risk.

[a] Incident diabetes, self-reported by study participants.

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요약 및 결론

- 비타민 D의 여러기능
  - 무기질 균형
  - 세포 성장과 분화
  - 면역 조절자
  - 항염증 작용
  - 정상적인 베타세포의 인슐린 분비를 위해 필요
- 관찰연구들은 비타민 D와 당뇨병의 연관성 시사
- 노출변수로 25(OH)D를 측정한 대규모의 전향적 관찰 연구 필요
- 일차 종말점으로 당뇨병에 대해 비타민 D의 효과를 측정하기 위해 특이적으로 디자인된 무작위 대조군 연구 필요