UNIVERSITÀ DEGLI STUDI FIRENZE

F.I.R.M.O. Fondazione Raffaella Becagli

LE VITAMINE D ED IL LORO METABOLISMO

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Disclosures

- Dr Brandi has received honoraria from Amgen, Bruno Farmaceutici, Kyowa Kirin
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- Consultant: Alexion, Bruno Farmaceutici, Kyowa Kirin, Servier, Shire
- Speaker Bureau: Shire

The Vitamin D History

- Phytoplankton and zooplankton have been produced vitamin D for more than 500 million years
- In 1919-1924 vitamin D is discovered
- In the next decade the chemical preparation of vitamin D led to elimination of rickets
- Infantile hypercalcemia was first described in 1952, but not immediately associated with vitamin D intake
- In the 1960_s the function and metabolism of vitamin D was discovered

Sources of Vitamin D

- **Sunlight exposure**
  - Major source of vitamin D, providing the majority of the body's daily requirement
  - Vitamin D production is affected by season, duration of exposure, sunscreen use, and skin pigmentation
- **Endogenous production**
  - Ability of skin and kidneys to form and process vitamin D
- **Dietary intake**
  - Minor source of vitamin D, providing ≤100 IU/day
  - Vitamin D is rare in foods other than fatty fish, eggs, and supplemented dairy products*
  - Even vitamin D–fortified dairy products may not contain level indicated on label
  - Vitamin D can be supplied by multivitamins and supplements
  - Supplements containing vitamin D alone are not readily available
  - Patient compliance with supplementation therapy is inconsistent

*Sold in the United States, Canada, Argentina (optional), Brazil, Guatemala, Honduras, Mexico, Philippines (optional), and Venezuela

Adapted from Holick MF; Allain TJ, Dhesi J; Webb AR et al; Reid IR et al; Matsuoka LY et al; Holick MF; Lips P; Macleod CC et al; Omdahl JL et al; Chen TC et al; Holick MF et al; Heaney RP; Segal E et al; Webb AR et al; Faulkner H et al; Roche Vitamins Europe Ltd.

PRODUCTION, METABOLISM AND BIOLOGIC FUNCTIONS OF VITAMIN D

Inert Photoproducts

UVB

HEAT

Total body sun exposure easily provides 250 μg (10.000 IU) Vitamin D/d with circulating 25(OH)D levels ~140 nmol/l (56 ng/ml)

$ProD_3$ (7-DHC) → $PreD_3$ → Vitamin D_3

SKIN

chylomicrons

LIVER

25(OH)D

PROSTATE
BREAST
OVARY
COLON
OSTEOBLASTS

KIDNEY

Calciferol

Ergosterol

DIET

<2.5 μg (<100 IU)/d

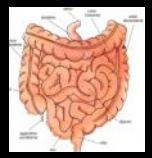
PTH (+)

(+) Low PO_4^{2-}

CALCITROIC ACID

24-OHase

1, 25$(OH)_2D$



INTESTINE

↑ Calcium and Phosphorus Absorption

BONE

↑ Mineralization Mobilizes Calcium Stores

PARATHYROID GLANDS

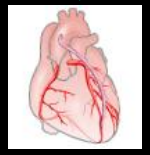
↓ PTH

MUSCLE

↑ Muscle Strength

T and B LYMPHOCYTES

Immunomodulation (Prevention of Autoimmune Diseases)



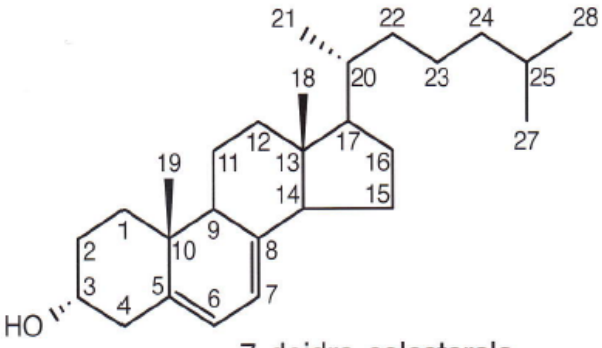
HEART

Renin-Angiotensin (Prevention CVD)

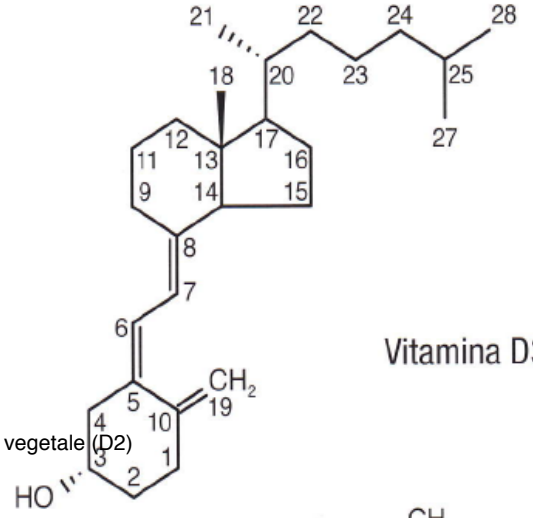
CANCER

Regulation of Cell Growth (Cancer Prevention)

Vitamina D animale (D3) e vegetale (D2)

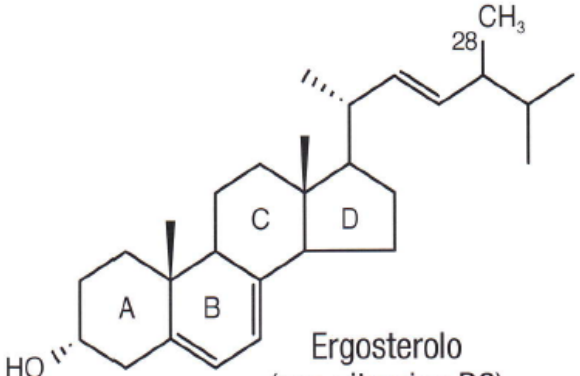


7-deidro-colesterolo
(pro-vitamina D3)

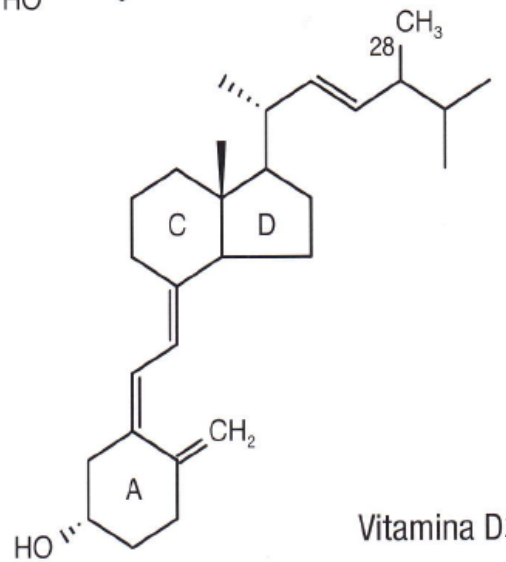


Vitamina D3

Vitamina D animale (D3) e vegetale (D2)

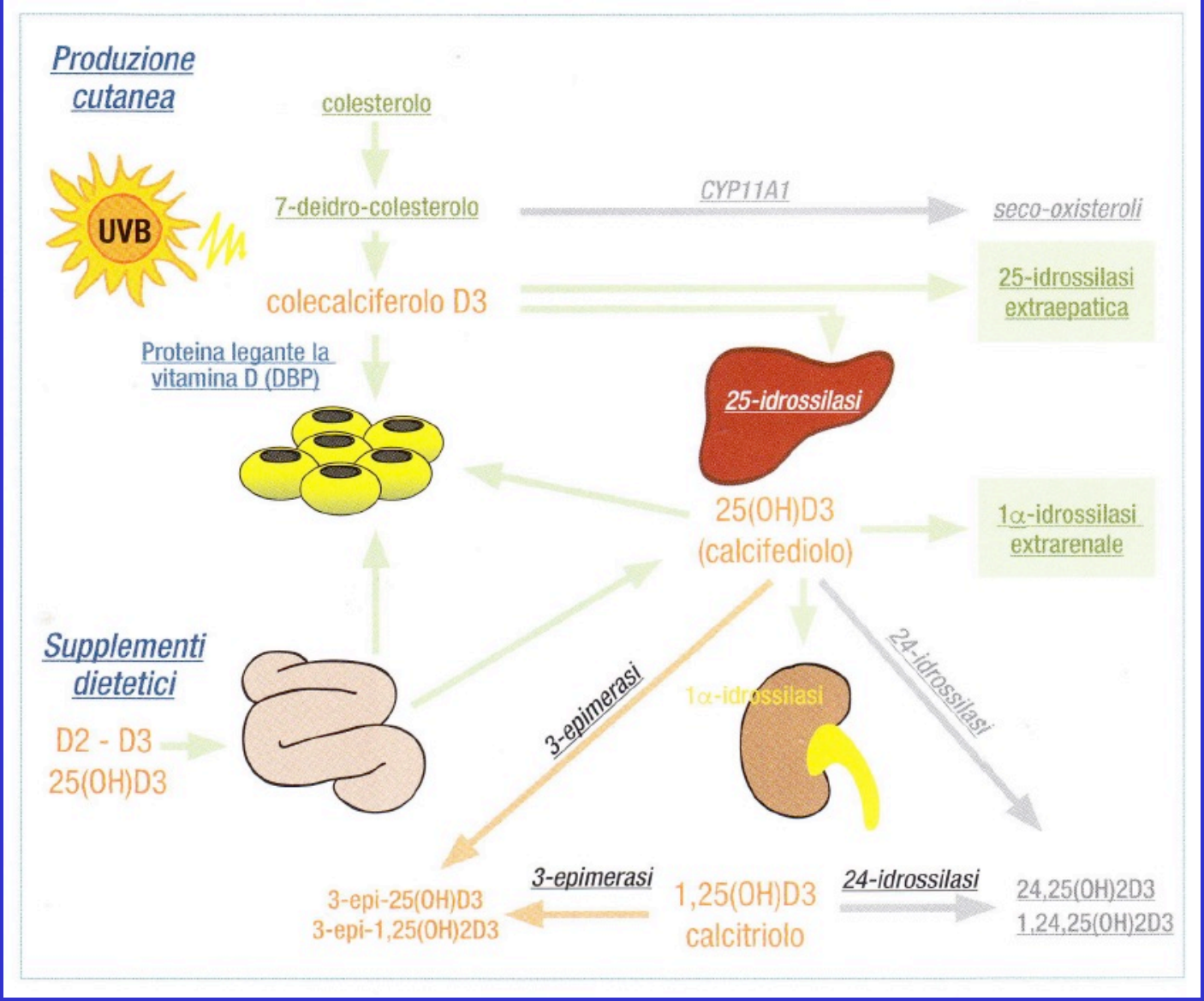


Ergosterolo
(pro-vitamina D2)



Vitamina D2

Sintesi e metabolismo della vitamina D



The importance of Vitamin D for bone health is becoming better understood

Definition

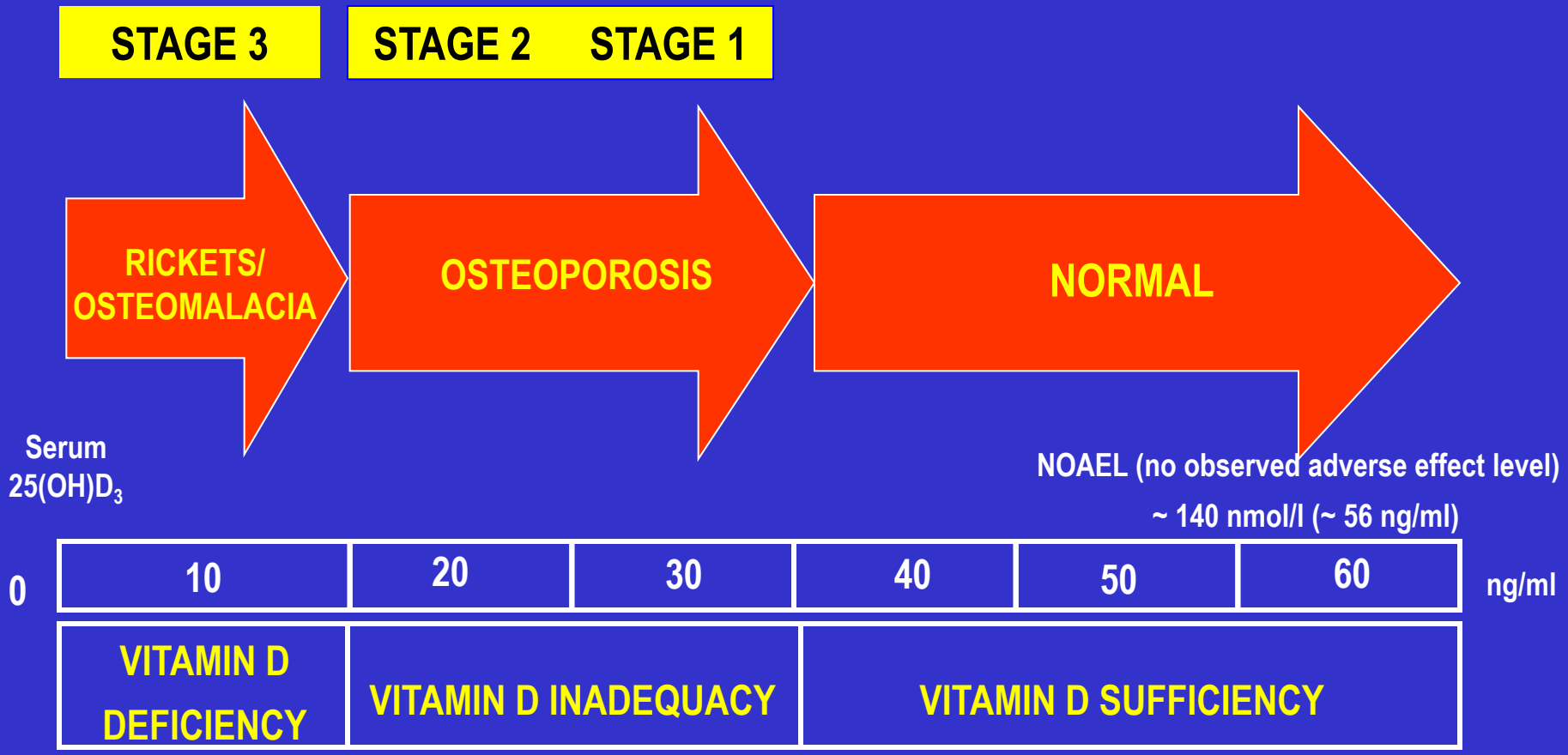
- Vitamin D is essential for ensuring intestinal absorption of calcium
  - *Intestinal absorption of dietary calcium is 10% to 15% with Vitamin D deficiency*
  - *Intestinal absorption of dietary calcium is 30% to 50% when status is adequate*
- Lack of Vitamin D leads to increased release of PTH and bone resorption

Clinical Consequences

- Evidence suggests that Vitamin D inadequacy increases risk of fracture
- Vitamin D inadequacy is common and unrecognized

Historical evolution of the classification scheme for Vitamin D-related bone disease

HYPOVITAMINOSIS D OSTEOPATHY (Parfitt A.M., 1990)



Adapted from: Parfitt A.M. In: Avioli LV, Krane SM, eds. Metabolic Bone Diseases and Clinically Related Disorders, 1990
Heaney R.P. Am. J. Clin. Nutr. 80:1706S, 2004

Vitamin D inadequacy

Definition

- No consensus on vitamin D inadequacy
- 25(OH)D concentration <30 ng/ml (75 nmol/L) suggested as indication of vitamin D inadequacy

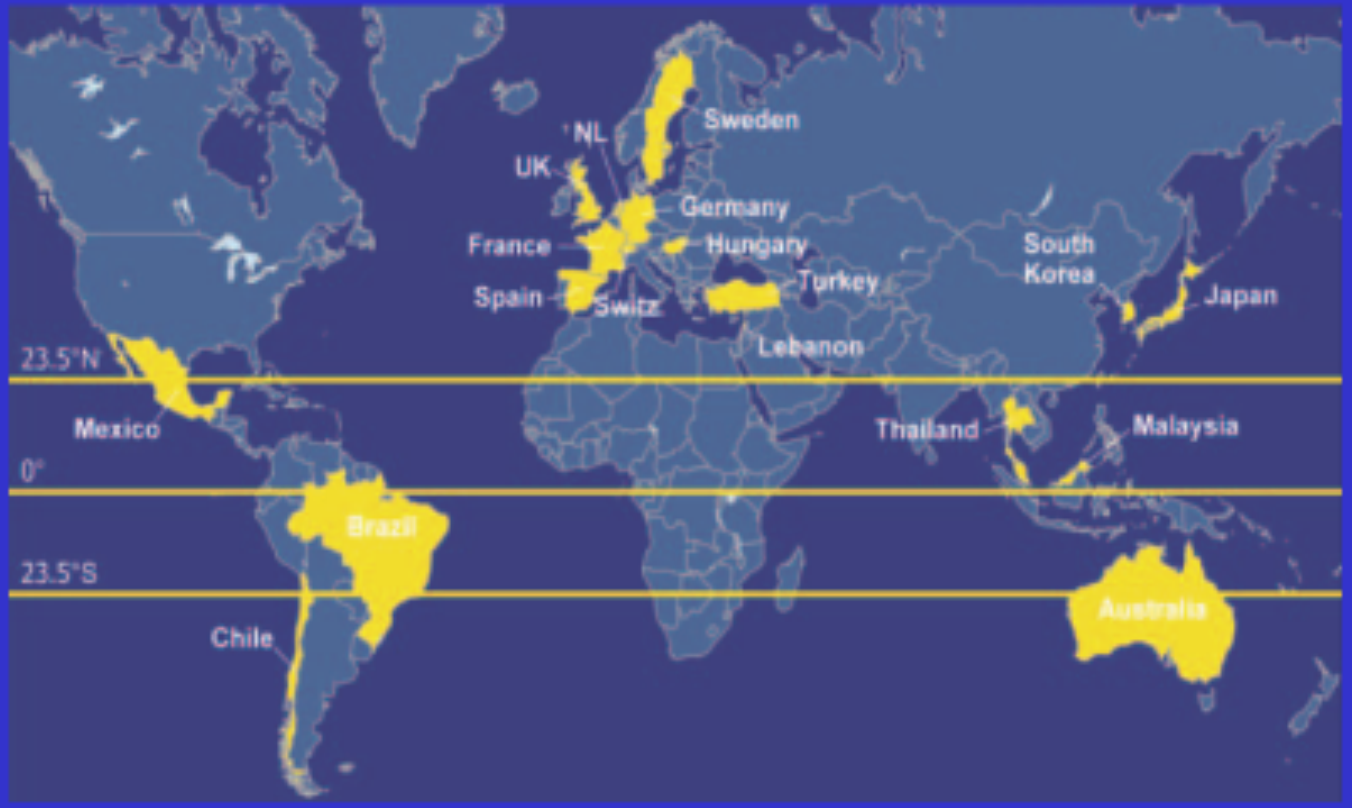
Clinical consequences

- Suboptimal calcium absorption
- Increased PTH
- Reduced Bone Mineral Density

VITAMIN D INADEQUACY AMONG 2589 COMMUNITY DWELLING POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

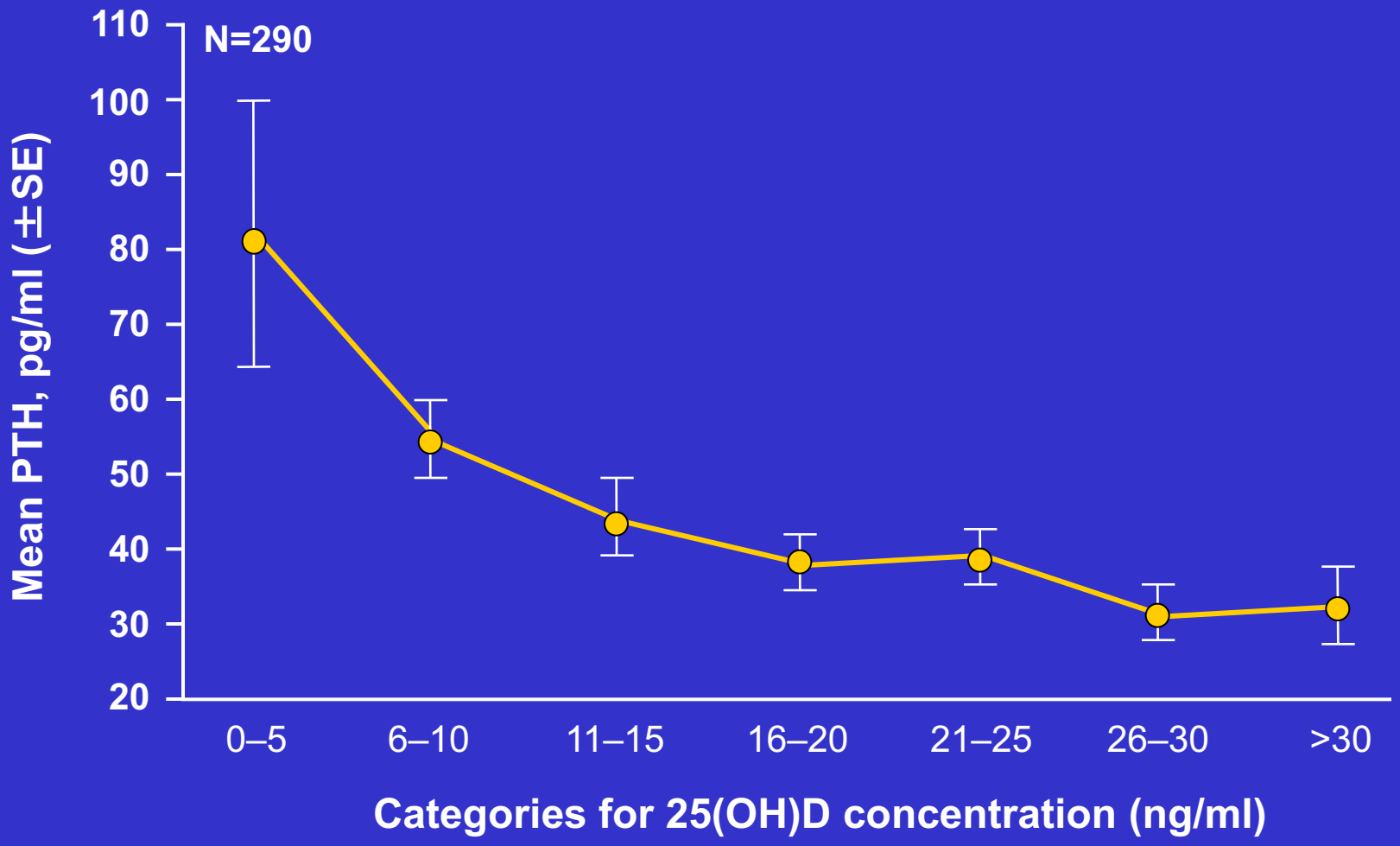
Study design: Observational, cross-sectional, single visit

Participating Regions: Europe, Middle East, Asia, Latin America, Pacific Rim



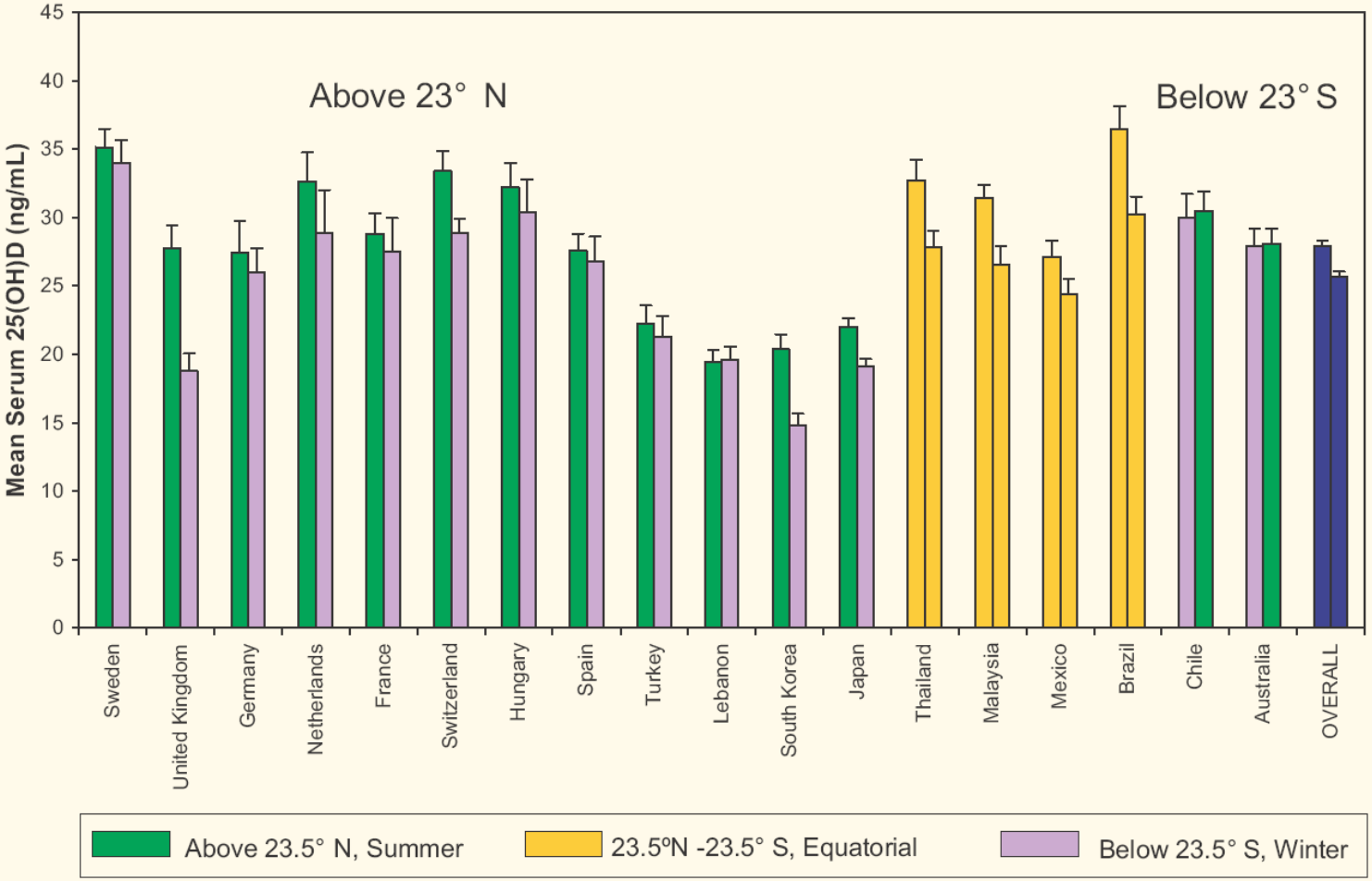
Adapted from: P. Lips et al. JBMR, 2005

Relationship Between Serum 25(OH)D and PTH in Medical Inpatients



Adapted from Thomas MK et al *N Engl J Med* 1998;338:777–783.

Mean 25(OH)D (ng/ml) by Country and Descending Latitude (North to South)



For each country: first bar = enrollment period I; second bar = enrollment period II
T= Standard Errors

Adapted from: P. Lips et al. JBMR, 2005

Is regular sunlight exposure an effective prophylaxis against Vitamin D inadequacy?

Studies in sunny countries

	POPULATION	[25(OH)D]	PREVALENCE	REASON
MIDDLE EAST	Men and Women (30-50y)	[<12 ng/ml]	73%	Customary clothing High parity
ITALY	Women (>60y)	[<12 ng/ml]	76%	Latitude not so low Scarce education
		[<5 ng/ml]	27%	
SOUTH FLORIDA	Men and Women (18-88y)	[<20 ng/ml]	39%	Sunscreen use

Adapted from: J. Bone Miner. Res. 15:1586, 2000; Osteoporos. Int. 14:577, 2003; J. Clin. Endocrinol. Metab., in press

ESCEO Guidelines 2013

Vitamin D supplementation in elderly or postmenopausal women: A 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)

R. Rizzoli, S. Boonen, M-L. Brandi, O. Bruyère, C. Cooper, J. A. Kanis, J-M. Kaufman, J. D. Ringe, G. Weryha, JY Reginster

- Valore minimo adeguato 25(OH)D sierica: 20 ng/ml (30 ng/ml in condizioni di aumentato rischio cadute e fratture) ottenibile con suppl. 800-1000IU/die
- Frequenza di somministrazione: giornaliera, settimanale, mensile (no annuale)
- Sicurezza: fino a 10000 IU/die
- Incoraggiare utilizzo cibi fortificati con calcio e vitamina D

Curr Med Res Opin 2013; 29(4):305-13

Vitamin D recommendations for adults

	Recommended vitamin D level (IU/day)				
	Age 19–50 years	Age 51–60 years	Age 61–70 years	Age >70 years	Pregnancy/ lactation
Nordic Dietary Recommendations	300	300	400	400	300
Dutch Health Council	400	400	400	800	400
Belgian Health Council (RDA)	400–600	400–600	400–600	600	800
Institute of Medicine (RDA)	600	600	600	800	600
US Endocrine Society*	600	600	600	800	800
Swiss Federal Nutrition Council*	600	600	800	800	600
DACH countries (Germany, Austria, and Switzerland)	800	800	800	800	800

*1500–2000 IU/day for patients with severe vitamin D deficiency (<25 nmol/L).
400 IU = 10 μg.
RDA = recommended daily allowance.

Adapted from: CMRO 29:305, 2013

Preparazioni: D_2 – D_3 – 25(OH)D

- **Ergocalciferolo 400000IU (fiala, monosomministrazione, os, i.m.)**
- **Ergocalciferolo 600000IU (fiala, monosomministrazione, os, i.m.)**
- **Colecalciferolo 10000 IU (flacone 10ml, 1 goccia=250 IU=6.25 µg, os)**
- **Colecalciferolo 25000 IU (flacone, monosomministrazione, os)**
- **Colecalciferolo 50000 IU (flacone, monosomministrazione, os)**
- **Colecalciferolo 100000 IU (fiala, monosomministrazione, os, i.m.)**
- **Colecalciferolo 300000 IU (fiala, monosomministrazione, os, i.m.)**
- **Calci(fe)diolo 1,5 mg (flacone 10 ml, 1 goccia=5 µg, os)**

Metaboliti alfa-idrossilati

- **Calcitriolo capsule 0,25-0,50 mcg, os**
- **Calcitriolo 1 mcg/ml, soluzione ev**
- **Alfacalcidolo capsule 0,25 – 1 mcg, os**
- **Alfacalcidolo flacone 10 ml 2 mcg/ml gocce, os**

NB: da somministrare se alterazione dell'idrossilazione renale (es. ipoparatiroidismo, osteodistrofia renale)

Supplementi vitamina D: farmacocinetica

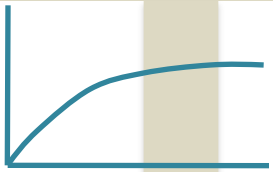
D_2 **D_3**

lipofili
> vol. distribuzione

emivita
8-10 giorni

SOMMINISTRAZIONE
giornaliera
settimanale
(mensile)

emivita
25-30 giorni

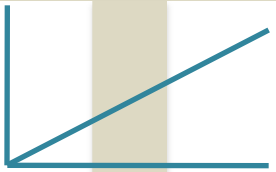


SOMMINISTRAZIONE
giornaliera
settimanale
mensile

$25(OH)D_3$

idrofilo
< vol. distribuzione
> escrezione

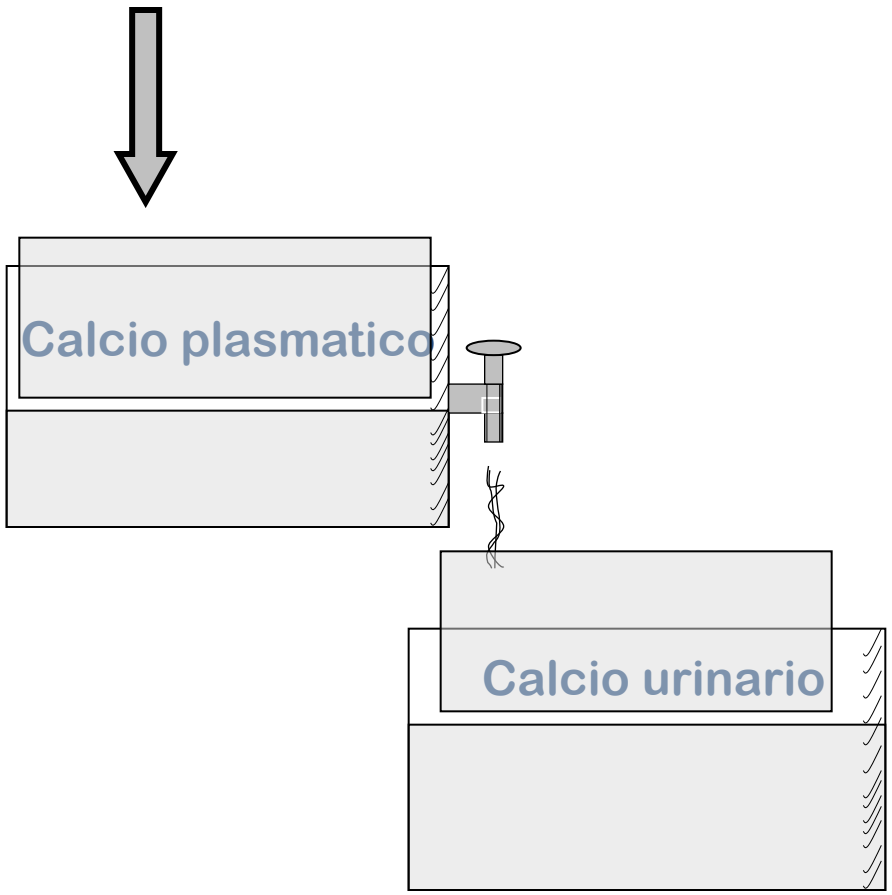
Emivita
10-15 giorni



SOMMINISTRAZIONE
giornaliera
settimanale

Monitoraggio terapia D_2, D_3, 25(OH)D: sicurezza

- Calcemia
- Calciuria



S Kimball, R Vieth. Ann Clin Biochem 2008; 45: 106–110.

The Story of Calcidiol

- It began in 1967: vitamin D injected i.v. in humans is converted into a more polar metabolite
- In 1969 the conversion to a 25-hydroxy metabolite was localized in the liver
- In 1970 it was identified as a pro-hormone that needed another hydroxylation step to become active
- First patented by H.F. De Luca in 1971 (USPN 3, 607, 888)
- A radiostereoassay to measure calcidiol in biological fluids was developed by J.G. Haddad, becoming soon a significant commercial enterprise

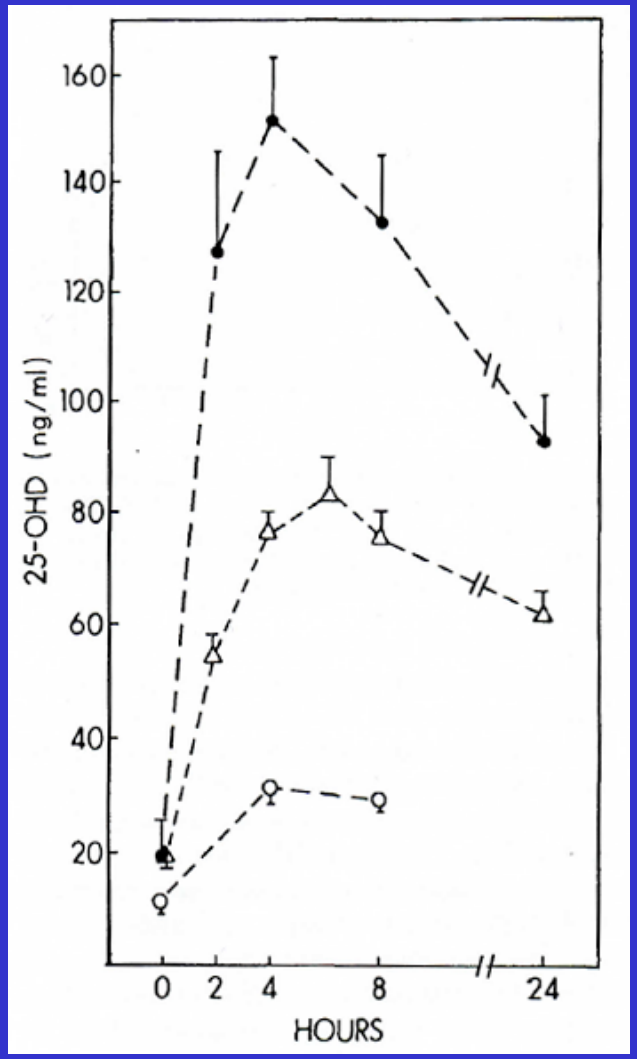
Adapted from: JCI 46:983, 1969; JCI 48:2032, 1969; Nature 228:764, 1970; JCEM 33:992, 1971

Pharmacokinetics of Vitamin D

- The synthesis of calcidiol is regulated through a kidney/parathyroid feedback mechanism
- The synthesis of calcidiol depends only on the individual synthetic potential (**CYP2R1,** CYP24A1, CYP3A4, CYP2D25)
- The mechanisms of control of **CYP2R1** are unknown, even if there are limited data of a control by calcitriol, phenobarbital and antiretroviral drugs
- Calcidiol administration produces rapid (in hours) increases in plasma levels of 25(OH)D_3

Adapted from: Mol Pharmacol 75:1392, 2009; Clin Sci 44:39, 1973; Am J Med 57:57, 1974

Serum 25(OH)D responses to the single **oral** administration of 1.5 μg/Kg (O), 5 μg/Kg (▲), or 10 μg/Kg (●) dose of calcidiol in human healthy volunteers (27 males and females, 21-40 years)



Peak responses were observed at 4-8 hours

Adapted from: J Clin Endocrinol Metab 42:284,1976

Condizioni in cui la somministrazione del calcidiolo e' preferibile al colecalciferolo

- Malassorbimento di grassi
- Diminuita biodisponibilita' (sequestro tessuto adiposo)
- Insufficienza epatica
- Inibizione iatrogena della 25OHasi epatica (es. anticonvulsivanti, glucocorticoidi)
- CKD – osteodistrofia renale
- Sindrome nefrosica (proteinuria)
- Ipogonadismo maschile
- Altre condizioni (es. diabete mellito I, post-trapianto)
- Osteomalacia *long-lasting*
- Mutazioni inattivanti di geni codificanti la 25OHasi epatica

Cianferotti L. et al Endocrine (2015) 50:12-26

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ADministration of DIfferent Doses (ADDI-D) of Calcidiol

ADDI-D Study

Multicenter, randomized, open label, three arm, parallel group, and comparative Phase III Study [EudraCT number: 2013-002648-10]

The aims of the study were to further analyze the therapeutic regimens of Calcidiol in terms of intervals of administration and long-term effects on mineral and bone metabolism

ADDI-D Study

Population:	87 Caucasian postmenopausal women (aged ≥55 years) with 25(OH)D3 circulating levels <30 ng/ml (75 mmol/L) and adequate calcium intake (1000 mg/die)
Study Duration:	3 months with evaluations at 0, 7, 14, 21, 28, 60, and 90 days
Patient Groups:	1) Daily oral calcidiol 20 µg (Didrogyl® 4 drops) [27 patients] 2) Daily oral calcidiol 40 µg (Didrogyl® 8 drops) [28 patients] 3) Weekly oral calcidiol 125 µg (Didrogyl® 25 drops) [29 patients]
Biochemical Parameters:	Serum 25(OH)D3, VDBP, calcium, phosphate, albumin, ionized calcium, creatinine, AP, BAP, CTX, PTH, 1,25(OH)D3, FGF23, DBP, calcium and phosphate in the 24 hrs urines, urinary DPD, routine exams
Efficacy Endpoints:	Primary: to compare the effects of three different therapeutic regimens of calcidiol on the increase of serum 25(OH)D3 Secondary: measurement of biochemical parameters
Safety Endpoints:	Incidence of AEs Serum calcium, ionized calcium, phosphate and creatinine, CTX, FGF23, 24 hours urinary calcium and urinary DPD

CONCLUSIONS

- The ADDI-D study demonstrates for the first time the efficacy of calcidiol as well as its safety on multiple parameters related to mineral and bone metabolism
- Increased muscle performance has been shown in postmenopausal women supplemented with calcidiol with respect to cholecalciferol. These properties make calcidiol a good alternative to cholecalciferol in the treatment of vitamin D deficiency and related muscle skeletal consequences (osteomalacia, falls, fractures)
- Calcidiol is also the supplement of choice when specific conditions hamper the efficacy of parental vitamin D

Osteoporos Int (2010) 21:1133–1149
DOI 10.1007/s00198-009-1136-2

REVIEW

The efficacy of calcitriol therapy in the management of bone loss and fractures: a qualitative review

L. J. Peppone · S. Hebl · J. Q. Purnell · M. E. Reid · R. N. Rosier · K. M. Mustian · O. G. Palesh · A. J. Huston · M. N. Ling · G. R. Morrow

Studies using calcitriol monotherapy, although non conclusive, found that calcitriol slowed the rate of bone loss in a variety of populations. Calcitriol in combination with other therapeutic bone agents was shown to have additional bone-preserving effects when compared to the use of therapeutic bone agents alone. A common side effect of calcitriol therapy whose hypercalcemia and hypercalciuria, but the degree of hypercalcemia was mild. Recent research found that intermittent dosing can reduce hypercalcemia rates. Calcitriol, alone or in combination with other agents, should be considered for the therapy of osteoporosis.

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2004 US Surgeon General's* Report on Bone Health and Osteoporosis

- **Objective of the report**
  - Increases public awareness
  - Provide information on prevention, diagnosis, and treatment
- **Consequences of osteoporosis**
  - High fracture rate
  - Hospitalizations
  - Increased risk of mortality
  - Disability and loss of independence
- **Importance of Vitamin D**
  - Necessary for calcium absorption
  - May not be common in the diet
  - Vitamin D supplements necessary when dietary intake is inadequate

*The Surgeon General is the chief health educator in the United States

Adapted from U.S. Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General.* Rockville, Md: U.S. Department of Health and Human Services, Office of the Surgeon General, 2004; Holick MF *Osteoporos Int* 1998;8(suppl 2):S24–S29.