Position statement AME: deficit di vitamina D nell'adulto

Coordinatore:	Roberto Cesareo (LT)
Moderatori:	Roberto Cesareo (LT), Alfredo Scillitani (FG)
	1.Problemi diagnostici (Assunta Santonati, RM)
	2.Trattamento e monitoraggio (Alfredo Scillitani, FG)
	3.Situazioni particolari e interferenze farmacologiche (Fabio Vescini, UD)

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Abiogen

Brunofarmaceutici

Novartis

Shire

Research

JAMA | Original Investigation

Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults

A Systematic Review and Meta-analysis

Jia-Guo Zhao, MD; Xian-Tie Zeng, MD; Jia Wang, MD; Lin Liu, MD

Conclusions

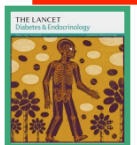
In this meta-analysis of randomized clinical trials, the use of supplements that included calcium, vitamin D, or both compared with placebo or no treatment was not associated with a lower risk of fractures among community-dwelling older adults. These findings do not support the routine use of these supplements in community-dwelling older people.

Zhao JG et al, JAMA 2017

Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis

Mark J Bolland, Andrew Grey, Alison Avenell

In summary, vitamin D supplementation did not have meaningful effects on fracture, falls, or bone mineral density, and future trials are unlikely to alter these conclusions. Therefore, there is little justification for the use of vitamin D supplements to maintain or improve musculoskeletal health, and clinical guidelines should reflect these findings.



Bolland MJ et al, Lancet Diabetes & Endocrinol 2018

DOI: 10.1002/ajpa.23646

WILEY American Journal of PHYSICAL ANTHROPOLOGY

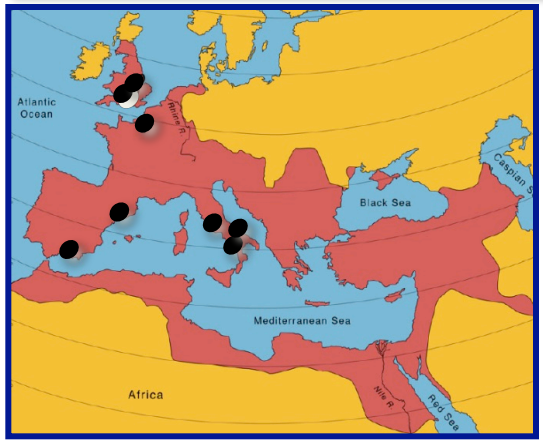
RESEARCH ARTICLE

Latitude, urbanization, age, and sex as risk factors for vitamin D deficiency disease in the Roman Empire

S. Mays[1,2,3] | T. Prowse[4] | M. George[5] | M. Brickley[4]

2787 individuals (1143 subadults, 1644 adults) from 18 cemeteries

The overall prevalence of rickets in subadults (<20 years) was 5.7%, and 3.2% of adults showed osteomalacia and/or residual rickets



Mays L et al, Am J Phys Anthropol 2018

- 4. Therapeutic Issues

- 4.1. Fortified Food for Treating Vitamin D Deficiency: What Is Their Role?

Foods, Fortificants, and Supplements: Where Do Americans Get Their Nutrients?

Usual intake from NHANES 2003–2006 compared to DRI from naturally occurring nutrients, enrichment/fortification, and dietary supplements in individuals aged ≥2 y[1]

Nutrient	Usual intake	Percentiles					<EAR	≥UL
		10	25	50	75	90		
	Mean ± SEM						*% ± SEM*	*% ± SEM*
Vitamin D, *μg/d*								
Naturally occurring	1.9 ± 0.4	0.8	1.1	1.7	2.5	3.3	100 ± 0	0.0 ± 0.0
+ Enriched/fortified	4.9 ± 0.1	1.7	2.7	4.2	6.4	8.9	93.3 ± 0.6	0.0 ± 0.0
+ Dietary supplements	8.2 ± 0.2	2.0	3.3	6.0	11.7	16.3	69.5 ± 0.9	0.1 ± 0.1
Calcium, *mg/d*								
Naturally occurring	883 ± 9	476	624	828	1084	1361	54.2 ± 0.9	0.1 ± 0.04
+ Enriched/fortified	939 ± 9	504	662	881	1152	1449	48.9 ± 0.8	0.3 ± 0.1
+ Dietary supplements	1091 ± 10	551	735	1000	1342	1740	38.0 ± 0.8	2.4 ± 0.2

Fulgoni III VL et al, J Nutr 2011

Position statement AME: deficit di vitamina D nell'adulto

Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE) Position Statement: Clinical Management of Vitamin D Deficiency in Adults

The dietary contribution to the desirable plasma levels of 25(OH)D is considerably lower in Italy than in US, due to the composition of diet (with less animal fats) and to the lack of appropriate fortification and supplementation of foods. In Italy, diet provides approximately 300 IU/day, so in Winter, when sun exposure is virtually absent, supplements for 1200–2000 IU/day must be guaranteed [68].

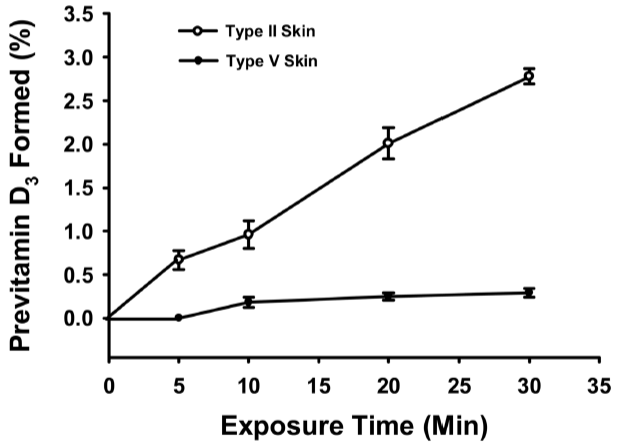
Cesareo R et al, Nutrients 2018

- 4. Therapeutic Issues

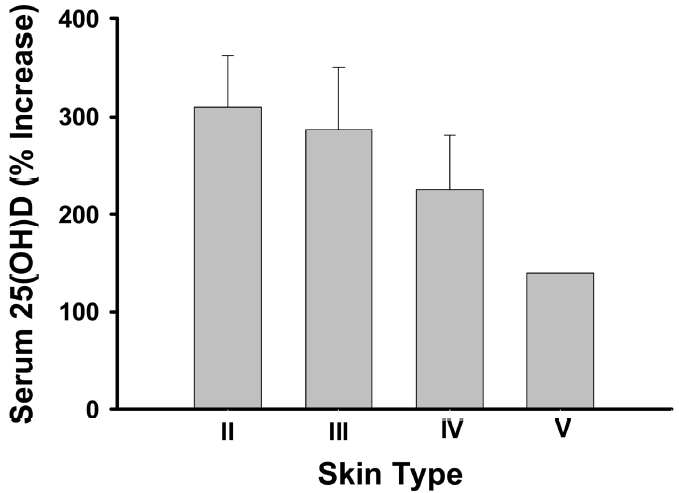
- 4.1. Fortified Food for Treating Vitamin D Deficiency: What Is Their Role?
- **We suggest not to consider the dietary sources as adequate for the achievement of an optimal vitamin D status in Italy**

- 4.2. What about the Sun Exposure for the Treatment of Vitamin D Deficiency?

Factors that Influence the Cutaneous Synthesis and Dietary Sources of Vitamin D



The conversion of epidermal 7-dehydrocholesterol to previtamin D3 in Type II and Type V skin after exposing to noon sunlight in June at Boston (42 °N)



The serum 25-hydroxyvitamin D levels in volunteers with different skin types after weekly exposure to simulated sunlight for 12 weeks

Chen TC et al, Arch Biochem Biophys 2007

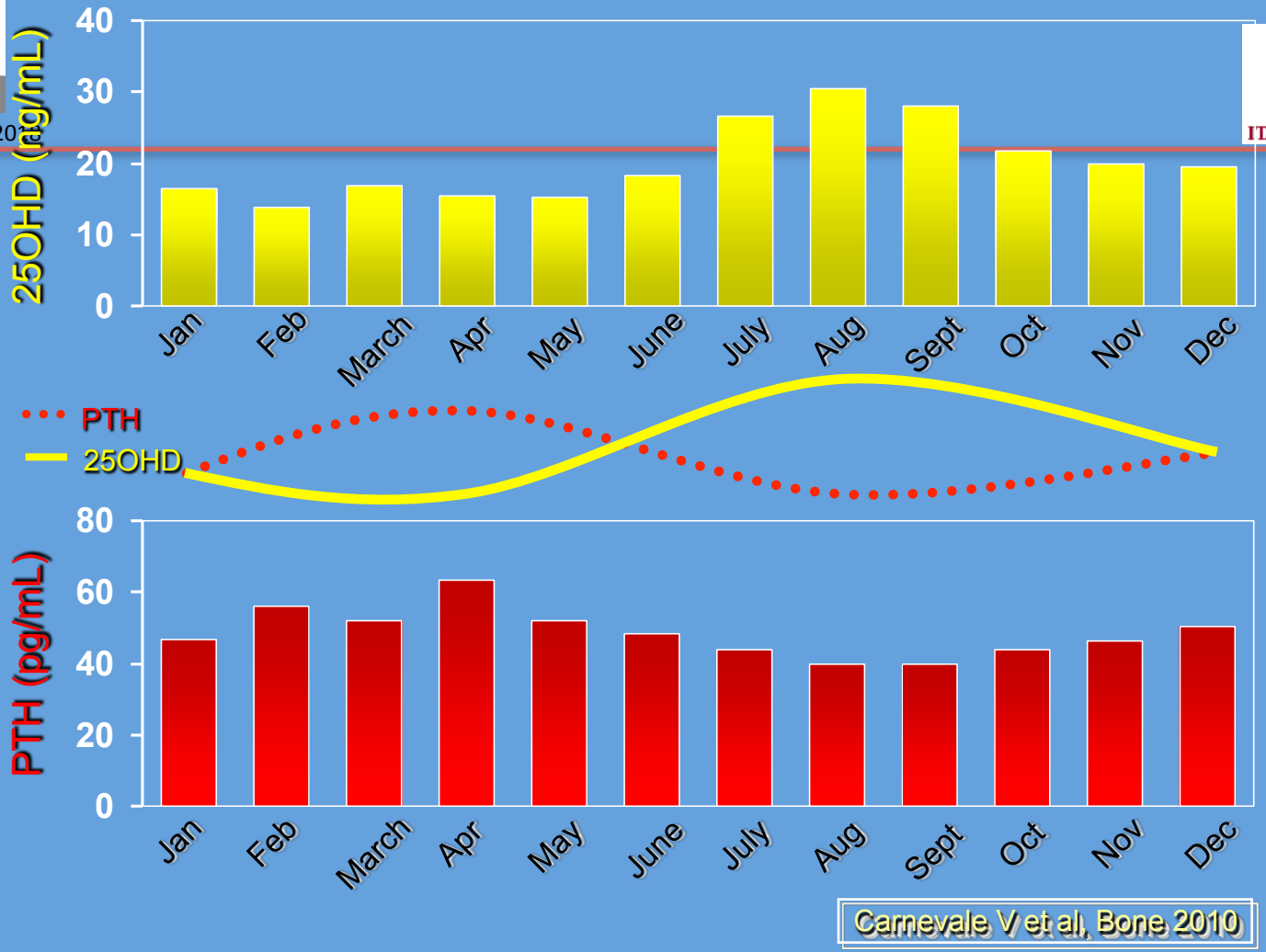
Aging Decreases the Capacity of Human Skin to Produce Vitamin D3

	Epidermis		Dermis		Epidermis and dermis	
Age	7-DHC	$preD_3$	7-DHC	$preD_3$	$preD_3$	% Formation $preD_3$ compared with 8-yr-old
	ng/cm^2	ng/cm^2	ng/cm^2	ng/cm^2	ng/cm^2	
8	1,308	406	1,800	36	442	100
18	1,056	346	1,125	22	368	80
77	605	144	1,630	24	168	37
77	490	141	—	—	—	—
82	659	163	1,040	20	183	40

* In 1 cm^2 of human epidermis and dermis.

7-Dehydrocholesterol (7-DHC) Content Before Exposure to Ultraviolet Radiation and Previtamin D3 (preD3) Content After Exposure to Ultraviolet Radiation * and the Percentage ofPreD3 Formed in the Epidermis and Dermis Relative to the 8-yr-old Subject

MacLaughlin J et al, JCI 1985



Carnevale V et al, Bone 2010

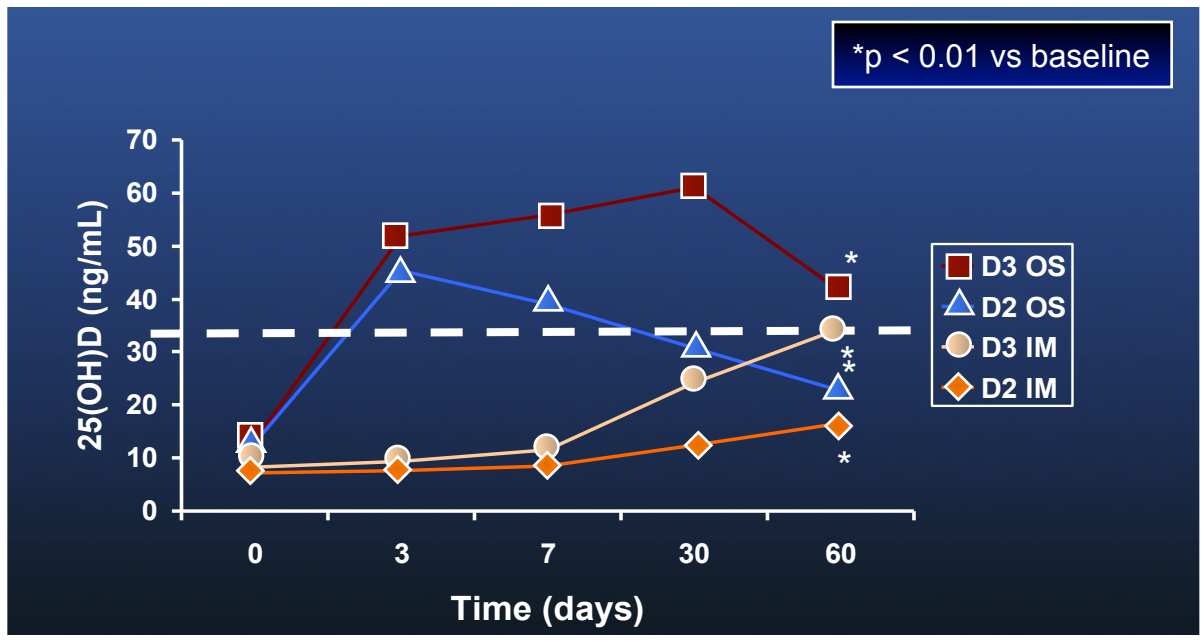
- 4.2. What about the Sun Exposure for the Treatment of Vitamin D Deficiency?

- **We suggest not to consider sun exposure as adequate for the achievement of an optimal vitamin D status in Italy**

- 4.3. How to Supply Vitamin D?

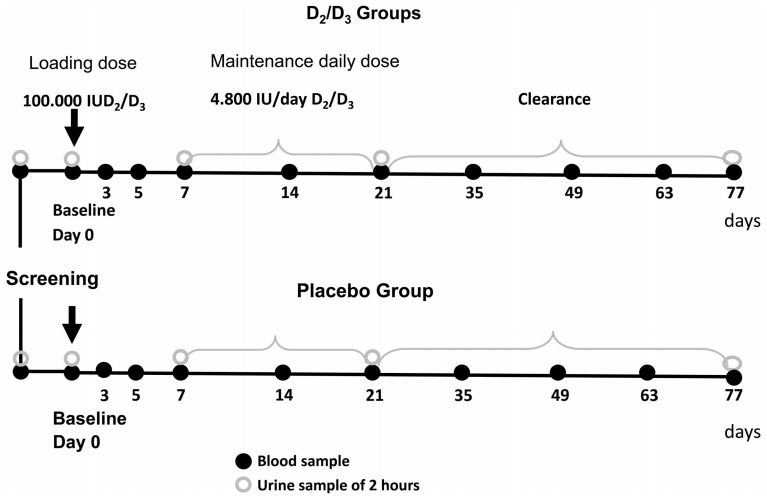
Effect of a single large dose of cholecalciferol and ergocalciferol (300,000 IU) on 25(OH)D serum changes

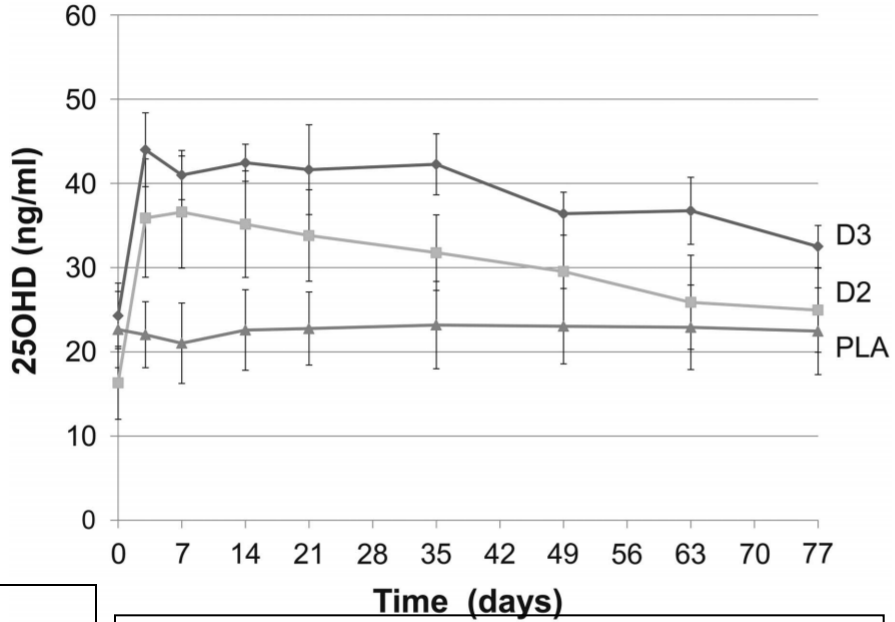
(the dashed line represents the threshold level for vitamin D sufficiency, settled at 32 ng/mL)



Romagnoli E et al, JCEM 2008

Vitamin D3 seems more appropriate than D2 to sustain adequate levels of 25OHD: a pharmacokinetic approach





Design of the study
Three groups of healthy subjects received a loading dose of vitamin D (D2 or D3) or placebo, followed by a maintenance dose for 2 weeks and a periodic control until d77 of follow-up

Time course of 25-hydroxy vitamin D (25OHD) levels (geometric mean) during the protocol (from baseline to day 77)

Olivieri B et al, Eur J Clin Nutr 2015

- 4.3. How to Supply Vitamin D?

We recommend treatment with cholecalciferol by mouth as the first line therapy in most patients.

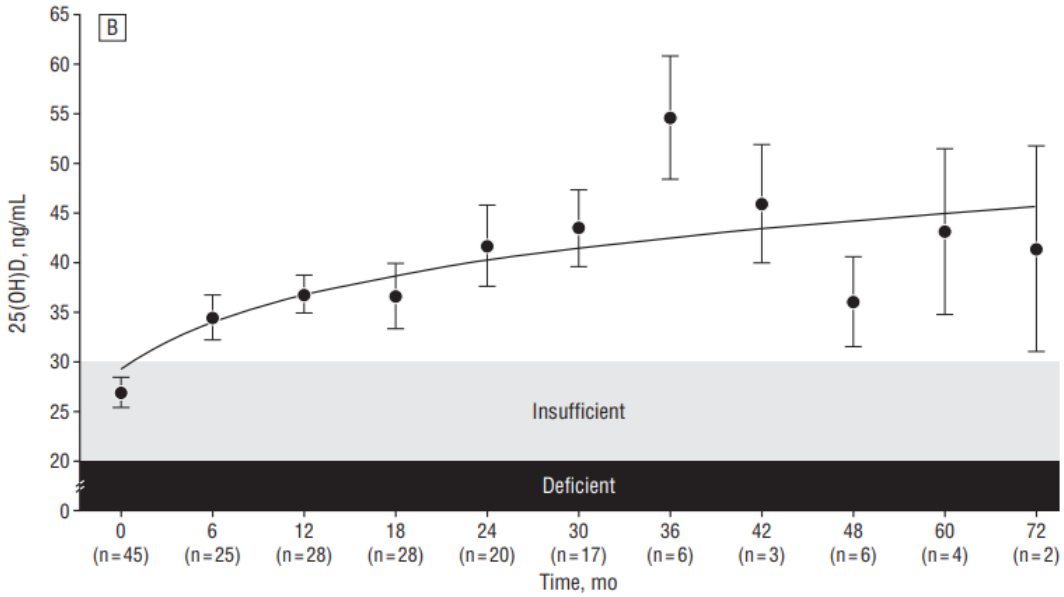
- 4.4. What Is the Appropriate Dosage of Vitamin D Supplementation?

Table 3. Strategies to Prevent and Treat Vitamin D Deficiency.*

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Children		
Breast-feeding without vitamin D supplementation[28,33,89,104] — up to 1 yr	400 IU of vitamin D_3/day,[1,28,104] sensible sun exposure,[1] 1000–2000 IU of vitamin D_3/day is safe,[1,2,27,75] maintenance dose is 400–1000 IU of vitamin D_3/day[1,2,104]	200,000 IU of vitamin D_3 every 3 mo,[1,105] 600,000 IU of vitamin D intramuscularly, repeat in 12 wk[106]; 1000–2000 IU of vitamin D_2 or vitamin D_3/day[1,107] with calcium supplementation
Inadequate sun exposure[24,29-31,108] or supplementation,[1,28,104-107] dark skin[23] — 1 through 18 yr	400–1000 IU vitamin D_3/day,[1,104,107] sensible sun exposure, 1000–2000 IU of vitamin D_3/day[1,108] is safe,[1,27,75,104,107] maintenance dose is 400–1000 IU of vitamin D/day[1,75]	50,000 IU of vitamin D_2 every wk for 8 wk[1,9]‡
Adults		
Inadequate sun exposure[7,15] or supplementation,[7-20] decreased 7-dehydrocholesterol in skin because of aging (over 50 yr)[7]	800–1000 IU of vitamin D_3/day,[1-3,8,16,21,42] 50,000 IU of vitamin D_2 every 2 wk or every mo,[7,9] sensible sun exposure[7,15,109,110] or use of tanning bed or other UVB radiation device (e.g., portable Sperti lamp),[111-114] up to 10,000 IU of vitamin D_3/day is safe for 5 mo,[27] maintenance dose is 50,000 IU every 2 wk or every mo[7,9]‡	50,000 IU of vitamin D_2 every wk for 8 weeks[9]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Pregnant or lactating (fetal utilization,[33] inadequate sun exposure[33,89] or supplementation[33,89])	1000–2000 IU of vitamin D_3/day,[33,89] 50,000 IU of vitamin D_2 every 2 wk, up to 4000 IU of vitamin D_3/day is safe for 5 mo,[33,89] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk[9]‡	50,000 IU vitamin D_2 every wk for 8 wk[115]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡

Holick MF 2007

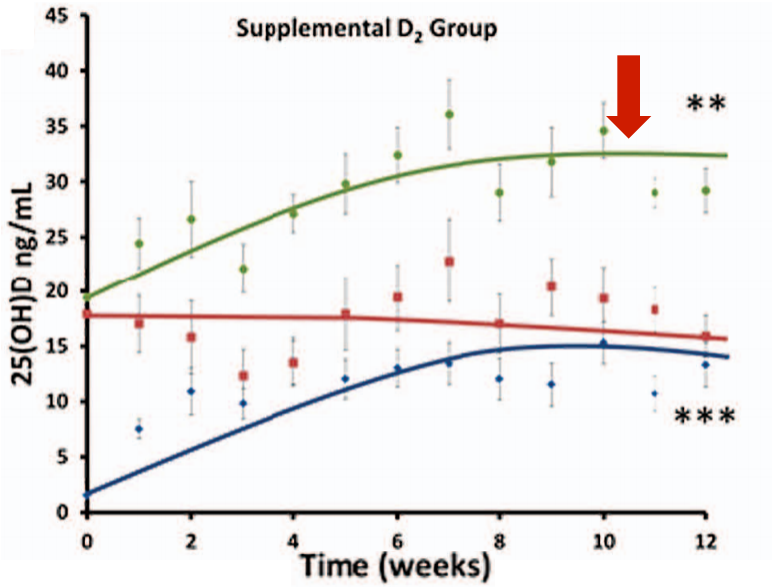
Vitamin D_2 Treatment for Vitamin D Deficiency and Insufficiency for Up to 6 Years



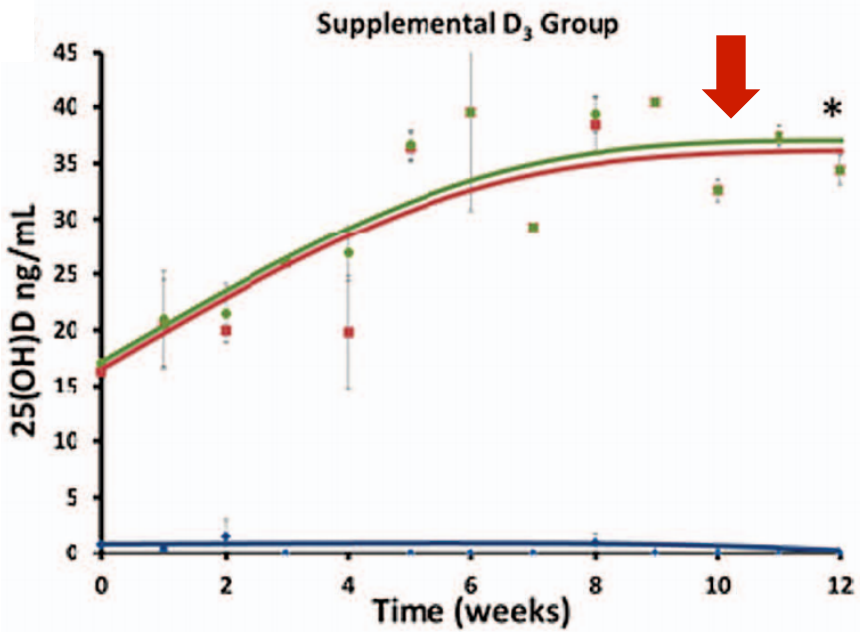
maintenance therapy of 50 000 IU of ergocalciferol every 2 weeks

Pietras SM et al, Arch Intern Med 2009

Position statement AME: deficit di vitamina D nell'adulto



2000 IU of supplemental vitamin D2 in capsules



2000 IU of supplemental vitamin D3 in capsules

Keegan RJ et al, Dermatoendocrinol 2013

• 4.4. What Is the Appropriate Dosage of Vitamin D Supplementation?

Vitamin D dosage and schedule depend on different factors: severity of deficiency, body weight, age of the patient, and need of rapid normalization of blood levels. It is usually appropriate to achieve target levels within 2–3 months and, when the intestinal absorption is normal and baseline 25(OH)D levels are very low, in a healthy adult subject it has been estimated an average 0.7–1.0 ng/mL (1.7–2.5 nmol/L) rise for every 100 IU of daily ingested vitamin D. Subsequently, the increase slows as the 25(OH)D levels rise.

When malabsorption is suspected, the use of hydroxylated metabolites (calcifediol) or injectable formulations of vitamin D may be considered.

Cesareo R et al, Nutrients 2018

• 4.4. What Is the Appropriate Dosage of Vitamin D Supplementation?

We suggest the following schedules for vitamin D supplementation:

- Deficiency and insufficiency: 50,000 IU once a week for 8 weeks; alternatively, a daily dose of 5000 IU for 8 weeks;
- Maintenance of sufficiency: 50,000 IU twice a month; alternatively, a daily dose of 2000 IU.

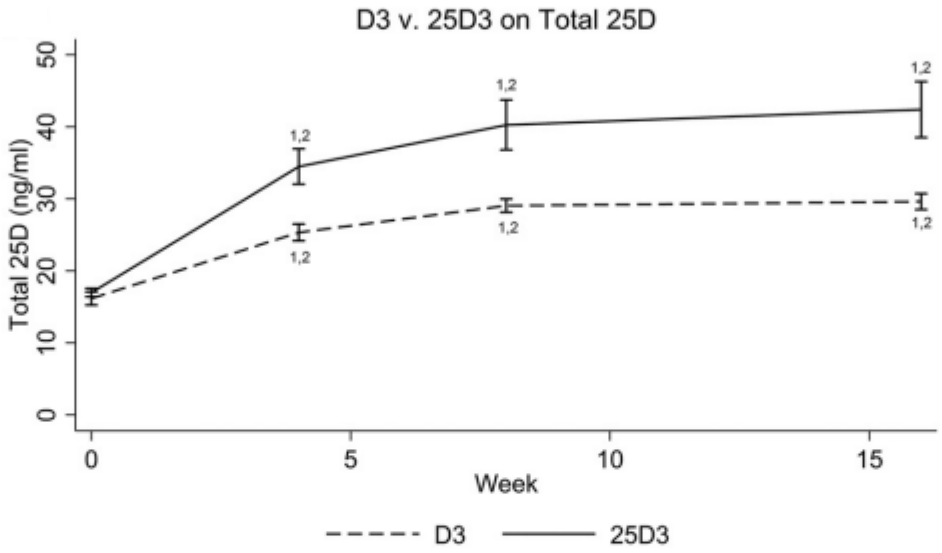
We suggest an individually tailored approach for vitamin D administration, involving the patient's opinion about the schedule (daily, weekly or monthly) that may offer the best adherence.

Cesareo R et al, Nutrients 2018

- 4.5. When Hydroxylated Metabolites of Vitamin D Should Be Prescribed?

Effects of Cholecalciferol vs Calcifediol on 25-Hydroxyvitamin D

20 mcg (2400 IU)/d of D_3 or 20 mcg/d of $25D_3$



1: p<0.05 for within-group change from baseline
2: p<0.05 for between-group difference at given time point

Shieh A et al, JCEM 2017

- # 4.5. When Hydroxylated Metabolites of Vitamin D Should Be Prescribed?

Calcifediol has been reported to restore normal circulating levels of vitamin D more rapidly than cholecalciferol [98–100]. Reliable comparative evaluations of hydroxylated vitamin D metabolites vs. vitamin D-equivalent doses are lacking [101]. Calcifediol can be used in the general population and has an elective indication in congenital abnormalities of hepatic 25-hydroxylase activity [102], intestinal malabsorption and, sometimes, obesity [103].

Calcifediol is available in drops (0.15 mg/mL, where 1 drop contains 5 μg). Due to its potency, 3–4 drops/day or 20–30 drops/week of calcifediol are generally adequate to restore normal 25(OH)D plasma levels [98,99].

Cesareo R et al, Nutrients 2018

4.5. When Hydroxylated Metabolites of Vitamin D Should Be Prescribed?

We suggest the use of calcifediol in case of:

- Hepatic impairment;
- Congenital abnormalities of the hepatic 25-hydroxylase enzyme;
- Malabsorption of cholecalciferol;
- Obesity.

We recommend against routine use of $1.25(OH)_2D$ or alpha-calcidiol for vitamin D deficiency.

We recommend to use $1.25(OH)_2D$ or alpha-calcidiol only when treating:

- Chronic renal failure;
- Hypoparathyroidism.

We suggest to use cholecalciferol as add on to $1.25(OH)_2D$, or alpha-calcidiol, in patients with CRF or hypoparathyroidism associated with demonstrated vitamin D deficiency.

Cesareo R et al, Nutrients 2018

5. Treatment Monitoring

5.1. Vitamin D Assessment during Supplementation: When and How?

Vitamin D pharmacokinetics is complex and serum 25(OH)D level is influenced not only by vitamin D supplement but also by dietary vitamin D intake and exposure to sunlight.

Monitoring of serum 25(OH)D during supplementation is generally unnecessary but is appropriate in patients with symptomatic vitamin D deficiency, malabsorption conditions, and when poor compliance is suspected. In patients at risk of persistent 25(OH)D level below 30 ng/mL (75 nmol/L), retesting after 8–12 weeks may be appropriate. In the other patients, retesting should not be performed before 6 months of vitamin D supplementation.

Cesareo R et al, Nutrients 2018

5.1. Vitamin D Assessment during Supplementation: When and How?

We recommend against routine serum 25(OH)D testing during vitamin D supplementation.

We suggest the assessment of vitamin D levels after at least 6 months of therapy, also if combined with bone active drugs, in patients:

- With previous severe hypovitaminosis D or persistent risk of severe hypovitaminosis because of renal or liver failure, metabolic bone diseases, malabsorption, severe obesity, hypogonadism, glucocorticoid treatment;
- At risk for hypercalcemia due to underlying diseases (i.e., granulomatosis and lymphoproliferative tumors) where $1.25(OH)_2D$ assay is appropriate for monitoring;
- Who assume high doses of vitamin D and present with symptoms of vitamin D toxicity.

Cesareo R et al, Nutrients 2018