Associazione Medici Endocrinologi

Primo Congresso Interregionale AME Sud - Italia

Primo Congresso Interregionale ANIED Sud - Italia

Responsabile Scientifico Vincenzo Triggiani

Matera, 9-10 Maggio 2014 - HILTON GARDEN INN

2ª SESSIONE: OSTEOPOROSI

(in parallelo alla sessione infermieri)

Moderatori: Guido Perrella, Nicola Tota

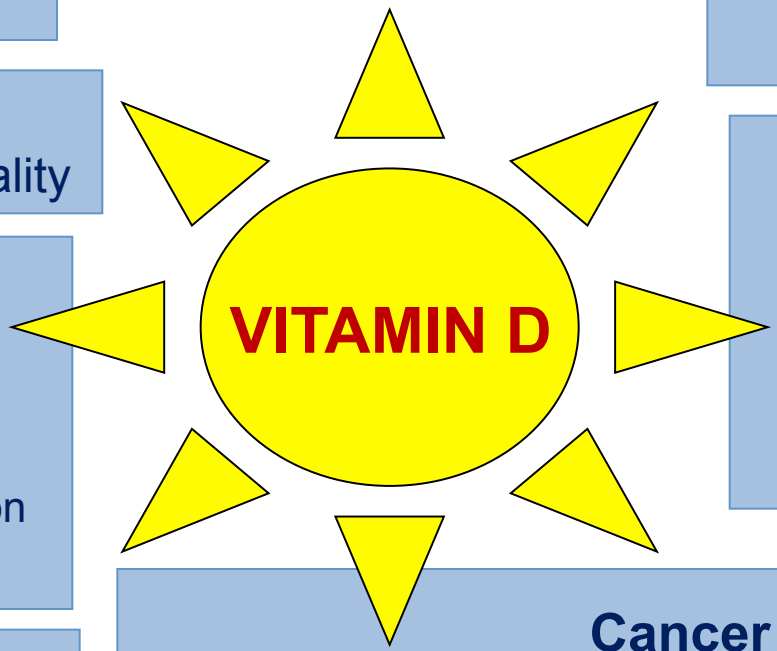
FORMULAZIONI DI VITAMINA D A CONFRONTO

Laura Gianotti , Giorgio Borretta

SC ENDOCRINOLOGIA , DIABETOLOGIA E METABOLISMO

A.S.O. S.Croce e Carle, Cuneo

ACTUAL AND POTENTIAL ROLES OF VITAMIN D



Bone
Decreases the risk of osteoporotic fractures

Falls
May retard sarcopenia and decreases the risk of falls

Pain
Decreases neuropathic pain in type 2 DM

Mortality
Decreases total mortality

Autoimmune disease
Decreases the risk of multiple sclerosis, rheumatoid arthritis, and type 1 DM

Heart disease
Decreases the risk of myocardial infarction
Decreases vascular calcification

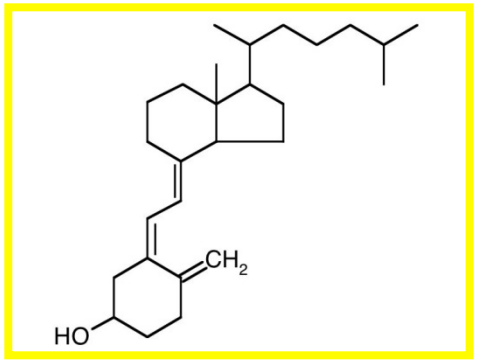
Cognitive function
Improves cognitive function, depression and seasonal affective disorder

Cancer
Decreases the risk of colorectal cancer and leukemia, total cancer incidence and mortality, digestive system cancer incidence and mortality, incidence of breast cancer

Courtesy of Dr. M. Procopio

Stechschulte S.A. et al. Am J Med.122, 793-802, 2009

OSTEOMALACIA



OSTEOPOROSI

Incremento della fosfatasi alcalina nel 95 - 100 %

Ca e P sierici ridotti nel 27-38 %

Ipocalciuria nell’ 87 %

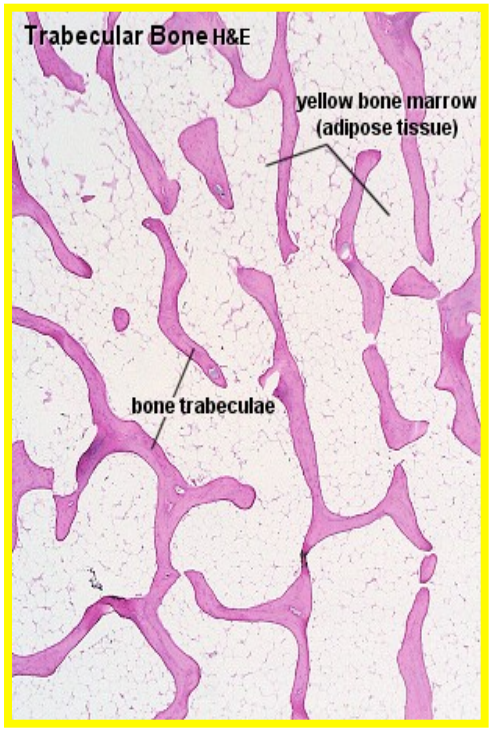
25-OH vitamina D <15 ng/mL nel 100 %

PTH elevato nel 100 %

No segni biochimici

25-OH vitamina D <

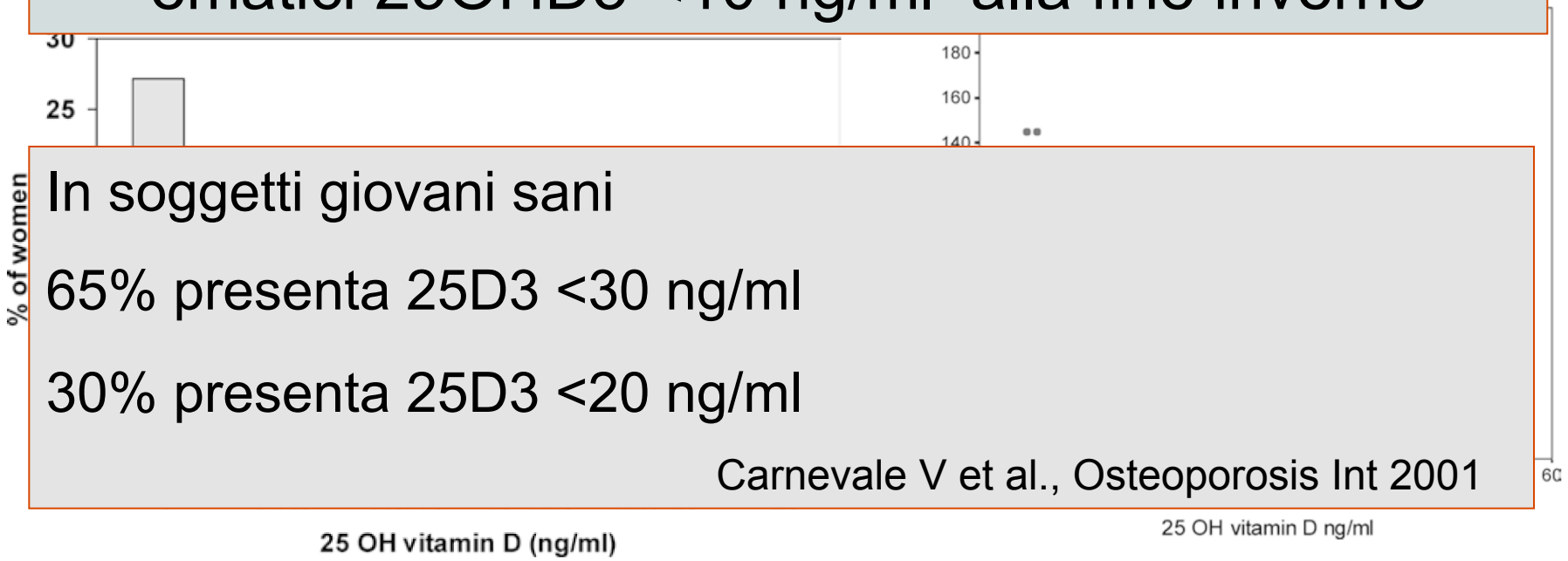
PTH >



Ipovitaminosi D nella popolazione italiana

Studio multicentrico (43 centri in tutta Italia): 700 F di età tra 60 e 80 anni
Dosaggio di 25 OH vitD e PTH.

86% delle donne italiane > 70 anni presenta livelli ematici 25OHD3 <10 ng/ml alla fine inverno



In soggetti giovani sani

65% presenta 25D3 <30 ng/ml

30% presenta 25D3 <20 ng/ml

Carnevale V et al., Osteoporosis Int 2001

Isaia G et al Osteoporos Int (2003) 14: 577–582

Worldwide status of vitamin D nutrition☆

P. Lips*

VU University Medical Center, Department of Internal Medicine, Section Endocrinology, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands

Journal of Steroid Biochemistry & Molecular Biology xxx (2010) xxx–xxx

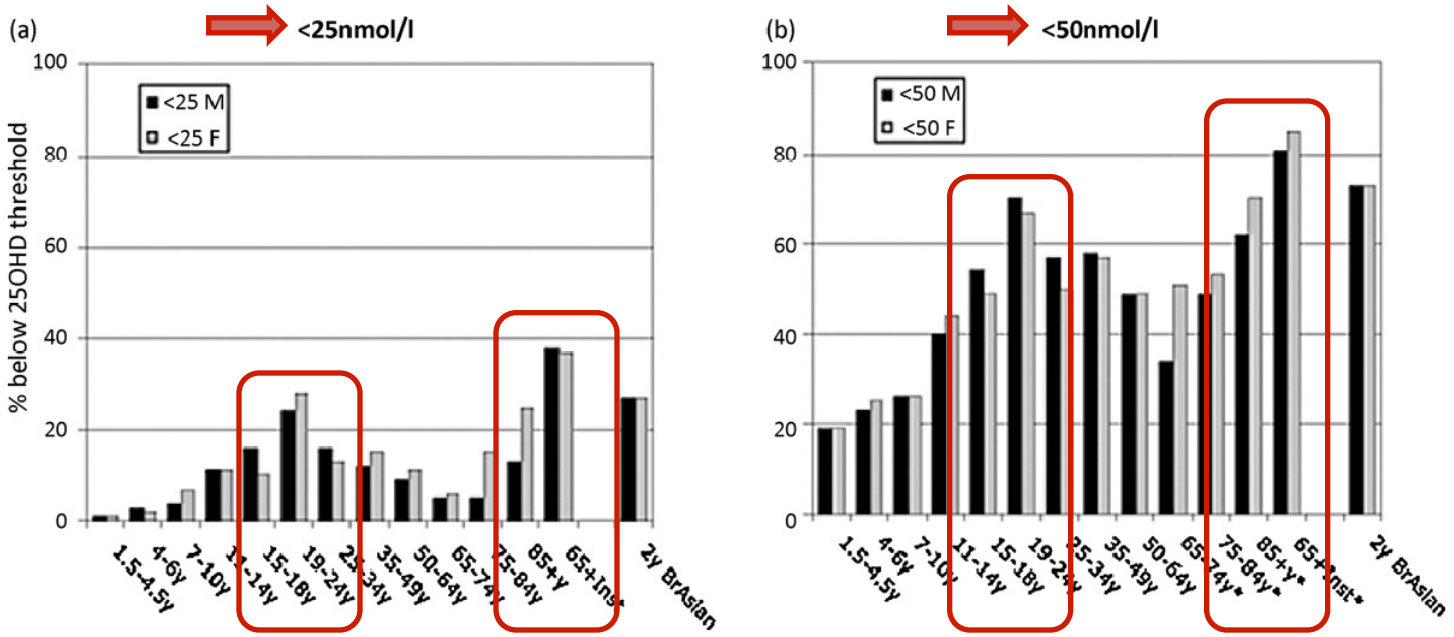


Fig. 1. Vitamin D status in the United Kingdom. Serum 25(OH)D according to sex and age groups showing the lowest levels in young adults, subjects older than 85 years, the institutionalized and British Asian children. Data from a national survey. Reproduced from Prentice A. et al., Nutr Rev 2008;66(Suppl. 2):S153–S164.

In conclusion, vitamin D deficiency and insufficiency are globally still very common especially in risk groups such as young children, pregnant women, elderly and immigrants.

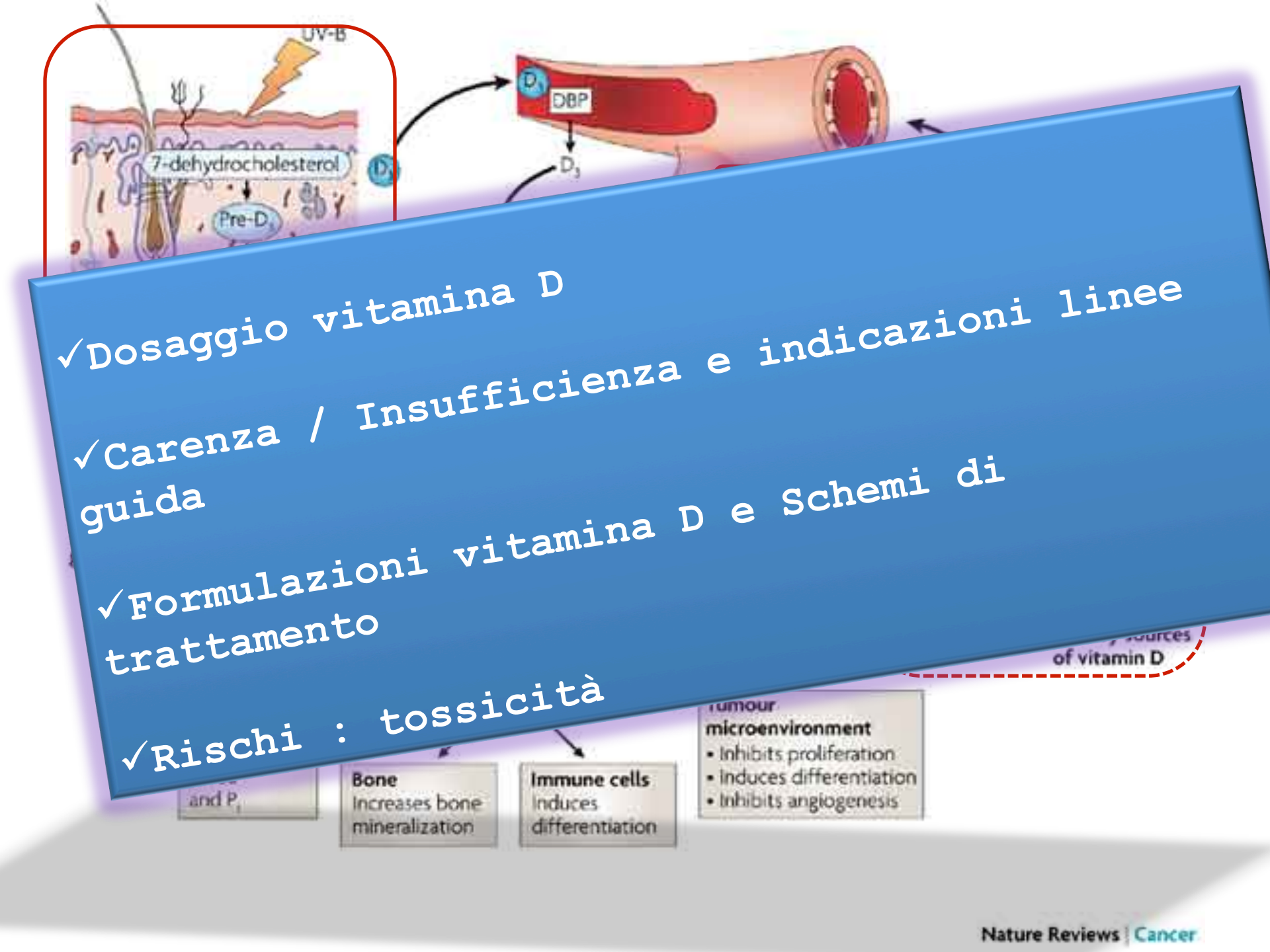
Fattori di rischio per il deficit di vit D

Table 3: Risk Factors for Vitamin D Deficiency

Risk factors for vitamin D deficiency
Factors related to sunlight exposure
▪ Darker skin pigmentation
▪ Season (winter)
▪ Higher latitude
▪ Skin coverage for instance the use of veil
▪ Cloud cover
▪ Use of sunscreen
Factors related to dietary intake
▪ Exclusive breastfeeding (risk for the infant)
Factors related to age and disease conditions
▪ Obesity
▪ Older age worsened by immobility and aging kidneys
▪ Kidney disease
▪ Malabsorption syndromes/other conditions : Crohn's disease, cystic fibrosis, severe liver disease
▪ Drug interactions: anticonvulsants, cimetidine, thiazides, corticosteroids
▪ Drugs that decrease absorption: mineral oil, laxatives orlistat, cholestiramine etc.
▪ Genetics: Indo-Asians

Sources: Schwalfenberg (23), United States Office of Dietary Supplements (5)

From clinical utility of vit D testing, OHTAS 2011



✓Dosaggio vitamina D

✓Carenza / Insufficienza e indicazioni linee guida

✓Formulazioni vitamina D e Schemi di trattamento

✓Rischi : tossicità

Forme di vitamina D e metaboliti

Vitamin D type	Description
Vitamin D_2	Also known as ergocalciferol. It is present in plants (e.g., mushrooms).
Vitamin D_3	Also known as cholecalciferol. Animal origin (such as some fishes) or produced by cutaneous synthesis.
Calcidiol	Also known as 25-hydroxyvitamin D or 25(OH)D Vitamin D metabolite produced by hydroxylation of vitamin D_2 or D_3 in the liver.
Calcitriol	1,25-dihydroxyvitamin D Hormonal form of vitamin D. Active metabolite produced by hydroxylation of calcidiol in the kidneys. Hydroxylation can also occur in other tissues.

Source: Johnson and Kimlin. (19)

Dosaggio vitamina D

Il dosaggio della 25-idrossi-vitamina D [25(OH)D] sierica rappresenta il metodo piu accurato per stimare lo stato di insufficienza/carenza e replezione vitaminica D, sebbene le tecniche di dosaggio non siano tuttora adeguatamente standardizzate.

Different assays for measuring 25(OH)D are available including radioimmunoassays, competitive protein-binding assays (CPBA), high pressure liquid chromatography (HPLC), and liquid

1 Metodica di dosaggio

CROMATOGRAFIA LIQUIDA CON SPETTROMETRIA DI MASSA

2. RIA
3. CPBA
4. HPLC
5. LC-MS/MS

6. ELEVATA VARIABILITA' INTRA- E INTER-ASSAY
7. DIFFERENTE AFFINITA' PER D2 - D3

OHTAS 2011

Esiste un valore ottimale di 25(OH) D?

Figure 1: Relationship between Intact Parathyroid Hormone (IPTH) and Serum Vitamin D

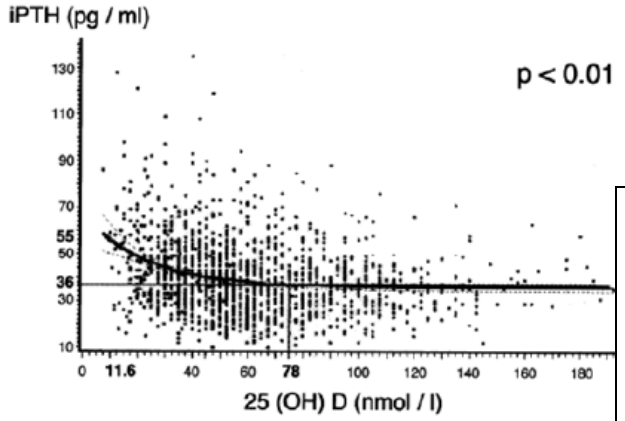


Fig. 1. Relationship between serum intact parathyroid hormone (iPTH) and 25-hydroxyvitamin D (25(OH)D) values in the w studied. For a 25(OH)D concentration higher than 78 nmol/l (31 ng/ml), there is a plateau level at 36 pg/ml for iPTH. When 25(lower than 78 nmol/l (31 ng/ml), the serum iPTH values begin to increase.

Source: Springer/Osteoporosis International 1997, 7(5):439-443. Prevalence of Vitamin D Insufficiency in a Population. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S et al. Figure 1. With kind p Springer Science and Business Media.

The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know

A. Catharine Ross, JoAnn E. Manson, Steven A. Abrams, John F. Aloia, Patsy M. Brannon, Steven K. Clinton, Ramon A. Durazo-Arvizu, J. Christopher Gallagher, Richard L. Gallo, Glenville Jones, Christopher S. Kovacs, Susan T. Mayne, Clifford J. Rosen, and Sue A. Shapses

(J Clin Endocrinol Metab 96: 53–58, 2011)

Sufficienza 25OHD3 = 20 ng/ml

Sufficienza 25OHD3 = 30 ng/ml
Valore ottimale 30-80 ng/ml

Linee guida su prevenzione e trattamento ipovitaminosi D con colecalciferolo

Adami et al, Reumatismo 2011

Tabella I - Interpretazione dei livelli ematici di 25(OH)D.

Definizione	nmol/L	ng/ml
Carenza	<50	<20
Insufficienza	50-75	20-30
Eccesso	>250	>100
Intossicazione	>375	>150

- **INSUFFICIENZA** → 21-29 ng/ml
- **DEFICIENZA** → <20 ng/ml (<50 nmol/L)

Linee guida End Soc , JCEM 2011,96:1911

Come supplementare ?

- ✓Prevenzione
- ✓Trattamento
- ✓Effetto della vitamina D su outcomes clinici
  - effetti scheletrici (Cadute , Fratture)
  - effetti extra-scheletrici (?)

Quale vitamina D e quale schema terapeutico?

- ✓ colecalciferolo (D3) o ergocalciferolo (D2) o calcifediolo (25OHD)?
- ✓ Im vs Os
- ✓ Carico periodico
- ✓ Carico+giornaliero/settimanale/mensile
- ✓ No carico

PREVENZIONE

- APPORTO MINIMO QUOTIDIANO :
- 400 U/DIE sino a 1 anno
- 600 U/DIE sino a 70 anni
- 800 U/DIE > 70 anni

IOM 2011 ….. Si applica su popolazione americana …

In soggetti sani

<60 anni non necessario misurare 25OHD3 ne' supplementare se adeguata esposizione solare

Soggetti 60-70 anni giustificato misurare 25OHD3 e supplementare se D3 <30 ng/ml

Soggetti>70 anni giustificato il trattamento in cieco

SIOMMMS, 2011

Trattamento

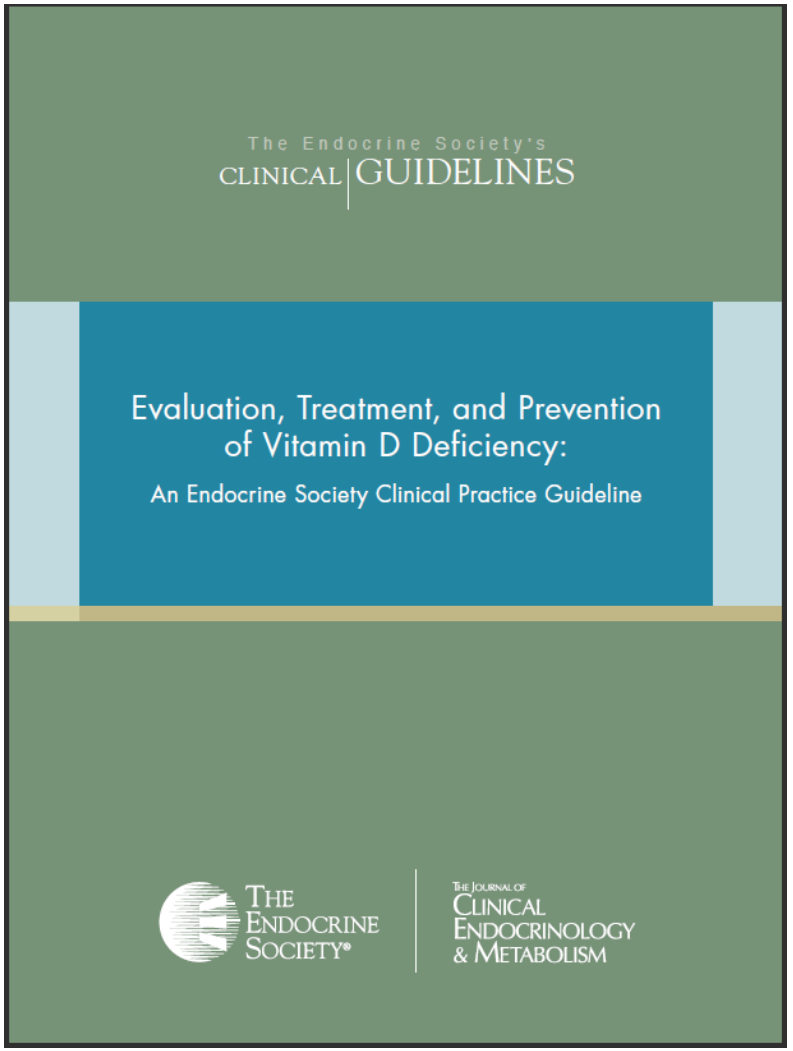
3.0. Treatment and prevention strategies

3.1. We suggest using either vitamin D_2 or vitamin D_3 for the treatment and prevention of vitamin D deficiency (2 | ⊕⊕⊕⊕).

3.4. We suggest that all adults who are vitamin D deficient be treated with 50,000 IU of vitamin D_2 or vitamin D_3 once a week for 8 wk or its equivalent of 6000 IU of vitamin D_2 or vitamin D_3 daily to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1500–2000 IU/d (2 | ⊕⊕⊕⊕).

3.5. In obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism, we suggest a higher dose (two to three times higher; at least 6000–10,000 IU/d) of vitamin D to treat vitamin D deficiency to maintain a 25(OH)D level above 30 ng/ml, followed by maintenance therapy of 3000–6000 IU/d (2 | ⊕⊕⊕⊕).

3.6. In patients with extrarenal production of $1,25(OH)_2D$, we suggest serial monitoring of 25(OH)D levels and serum calcium levels during treatment with vitamin D to prevent hypercalcemia (2 | ⊕⊕⊕⊕).



J Clin Endocrinol Metab, 2011, 96(7) 1911–1930

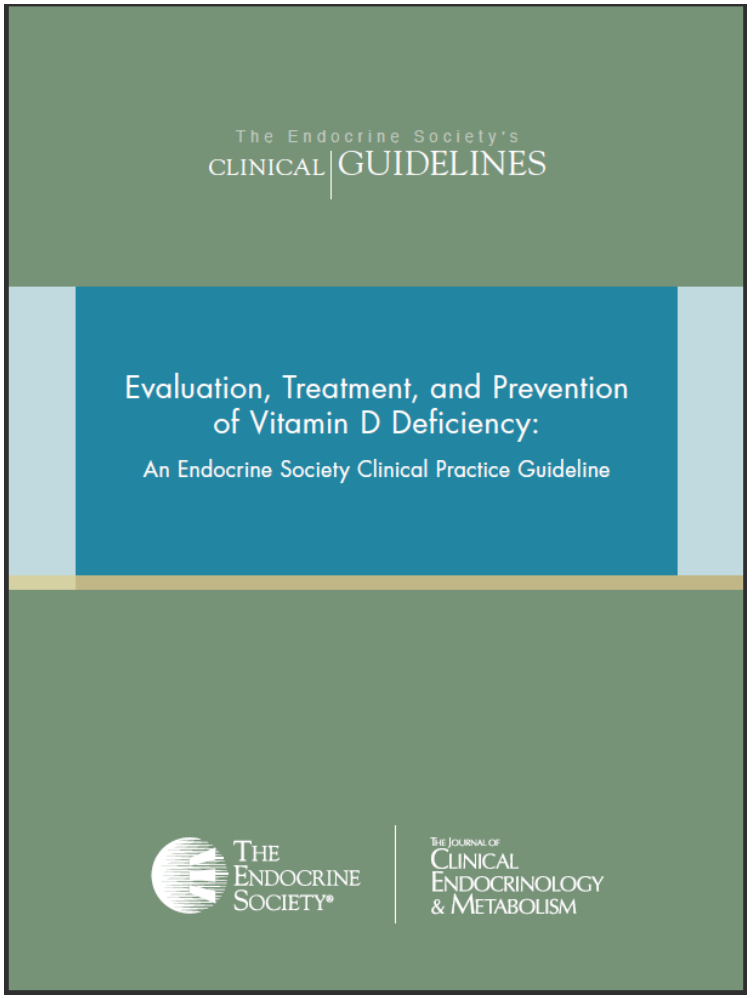
4.0. NONCALCEMIC BENEFITS OF VITAMIN D

Recommendation

4.1. We recommend prescribing vitamin D supplementation for fall prevention. We do not recommend prescribing vitamin D supplementation beyond recommended daily needs for the purpose of preventing cardiovascular disease or death or improving quality of life (21⊕⊕⊕⊕).

4.1. Evidence

Because most tissues and cells in the body have a vitamin D receptor and 1,25$(OH)_2$D influences the expression levels along with other factors of up to one third of the human genome, it is not at all unexpected that a numerous of studies has demonstrated an association of vitamin D deficiency with increased risk of more than a dozen cancers, including colon, prostate, breast, and pancreas; autoimmune diseases, including both type 1 and type 2 diabetes, rheumatoid arthritis, Crohn's disease, and multiple sclerosis; infectious diseases; and cardiovascular disease. There are, however, very few RCT with a dosing range adequate to provide level I evidence for the benefit of vitamin D in reducing the risk of these chronic diseases (20).



***J Clin Endocrinol Metab,* 2011, 96(7) 1911–1930**

Trattamento : confronto vitamina D2 vs D3

a systematic review and meta-analysis

Supplemento con bolo+daily

	D3			D2				Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Biancuzzo 2010-1 (7)	23.3	17.8	20	27	14.8	16	11.2%	-3.70 [-14.35, 6.95]
Biancuzzo 2010-2 (7)	32	25.3	18	26.5	18	17	9.9%	5.50 [-8.99, 19.99]
Binkley 2011-1 (15)	23	33.8	16	15.3	16.5	16	8.6%	7.70 [-10.73, 26.13]
Binkley 2011-2 (15)	22.3	18.3	15	9	14.3	16	10.9%	13.30 [1.69, 24.91]
Glendenning 2009 (16)	40	24.7	17	26	11.2	20	10.5%	14.00 [1.27, 26.73]
Heaney 2011 (17)	98.4	29.1	17	57.4	22	16	8.9%	41.00 [23.46, 58.54]
Holick 2008 (6)	23.3	17.8	20	24.8	8	16	11.8%	-1.50 [-10.23, 7.23]
Romagnoli 2008-1 (5)	70.2	20.8	8	25.5	16.9	8	8.6%	44.70 [26.13, 63.27]
Romagnoli 2008-2 (5)	65.4	30.3	8	23.1	13.8	8	7.2%	42.30 [19.23, 65.37]
Trang 1998 (4)	23.3	15.7	55	13.7	11.4	17	12.3%	9.60 [2.77, 16.43]
Total (95% CI)			**194**			**150**	**100.0%**	**15.23 [6.12, 24.34]**

Heterogeneity: Tau² = 162.74; Chi² = 47.10, df = 9 (P < 0.00001); I² = 81%

Test for overall effect: Z = 3.28 (P = 0.001)

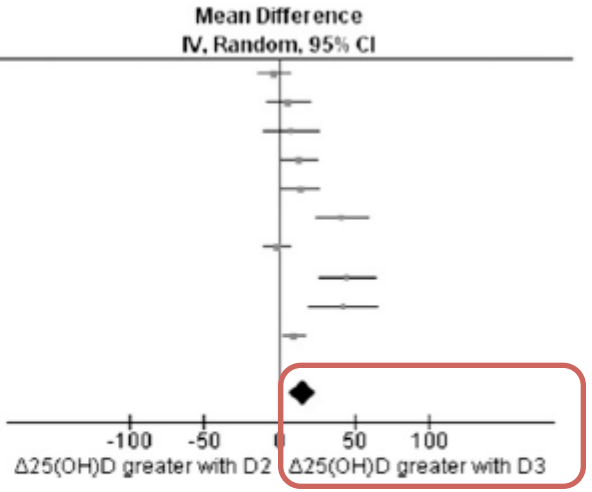


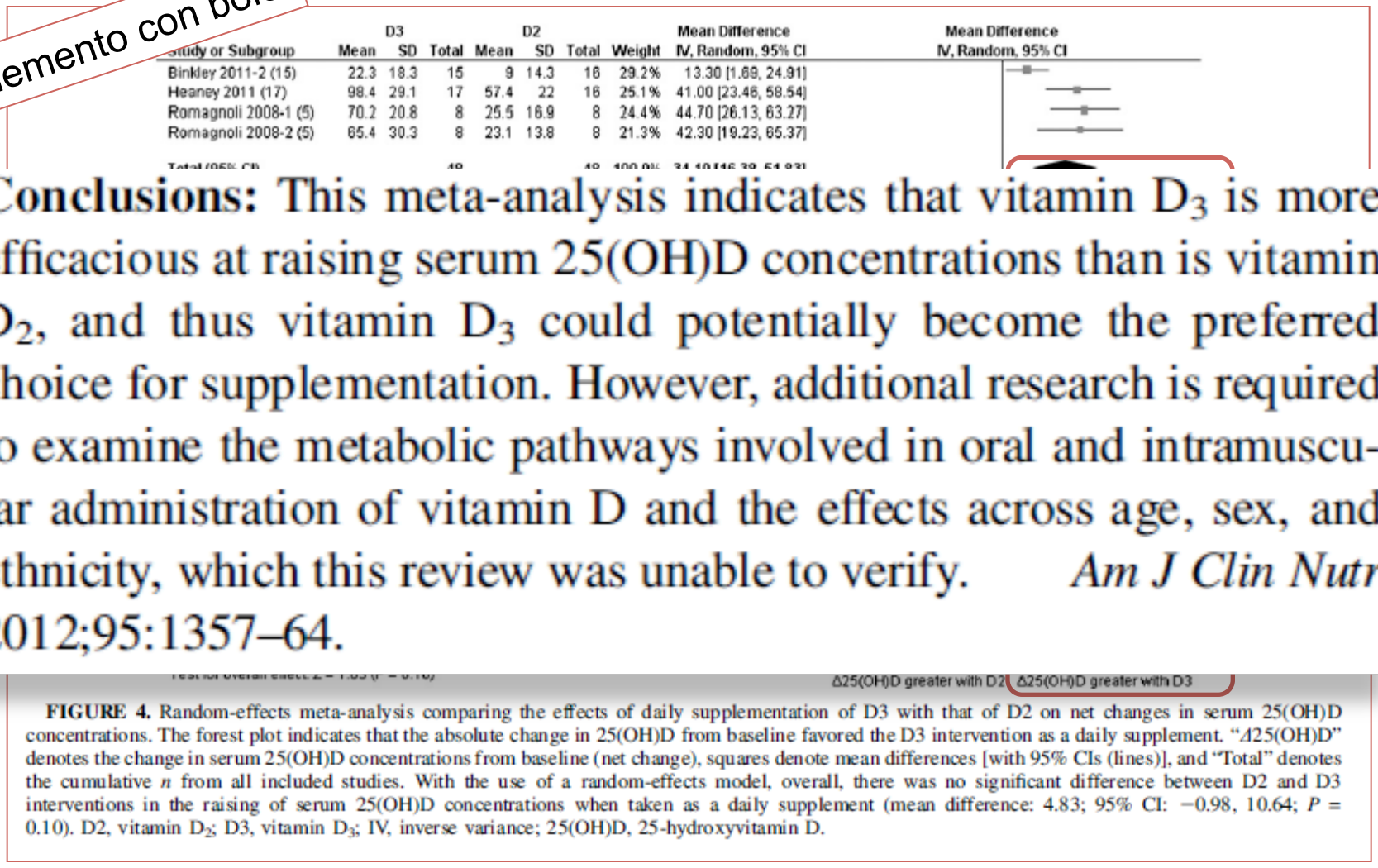
FIGURE 2. Random-effects meta-analysis comparing the effects of daily and bolus supplementation of D3 with that of D2 on net changes in serum 25(OH)D concentrations. The forest plot indicates that the absolute change in 25(OH)D from baseline favored the D3 intervention. In the figure, "Δ25(OH)D" denotes the change in serum 25(OH)D concentrations from baseline (net change), squares denote mean differences [with 95% CIs (lines)], and "Total" denotes the cumulative *n* from all included studies. With the use of a random-effects model, overall, there was a significantly greater effect in the raising of serum 25 (OH)D concentrations over time for D3 supplementation than for D2 supplementation (mean difference: 15.23; 95% CI: 6.12, 24.34; $P = 0.001$). D2, vitamin D_2; D3, vitamin D_3; IV, inverse variance; 25(OH)D, 25-hydroxyvitamin D.

Laura Tripkovic et al. Am J Clin Nutr 2012

Confronto vitamina D2 vs D3 :

a systematic review and meta-analysis

Supplemento con bolo



Conclusions: This meta-analysis indicates that vitamin D_3 is more efficacious at raising serum 25(OH)D concentrations than is vitamin D_2, and thus vitamin D_3 could potentially become the preferred choice for supplementation. However, additional research is required to examine the metabolic pathways involved in oral and intramuscular administration of vitamin D and the effects across age, sex, and ethnicity, which this review was unable to verify. *Am J Clin Nutr* 2012;95:1357–64.

FIGURE 4. Random-effects meta-analysis comparing the effects of daily supplementation of D3 with that of D2 on net changes in serum 25(OH)D concentrations. The forest plot indicates that the absolute change in 25(OH)D from baseline favored the D3 intervention as a daily supplement. "Δ25(OH)D" denotes the change in serum 25(OH)D concentrations from baseline (net change), squares denote mean differences [with 95% CIs (lines)], and "Total" denotes the cumulative *n* from all included studies. With the use of a random-effects model, overall, there was no significant difference between D2 and D3 interventions in the raising of serum 25(OH)D concentrations when taken as a daily supplement (mean difference: 4.83; 95% CI: −0.98, 10.64; P = 0.10). D2, vitamin D_2; D3, vitamin D_3; IV, inverse variance; 25(OH)D, 25-hydroxyvitamin D.

D3 > D2 ?

Meccanismi che contribuiscono a spiegare la maggiore efficacia della D3

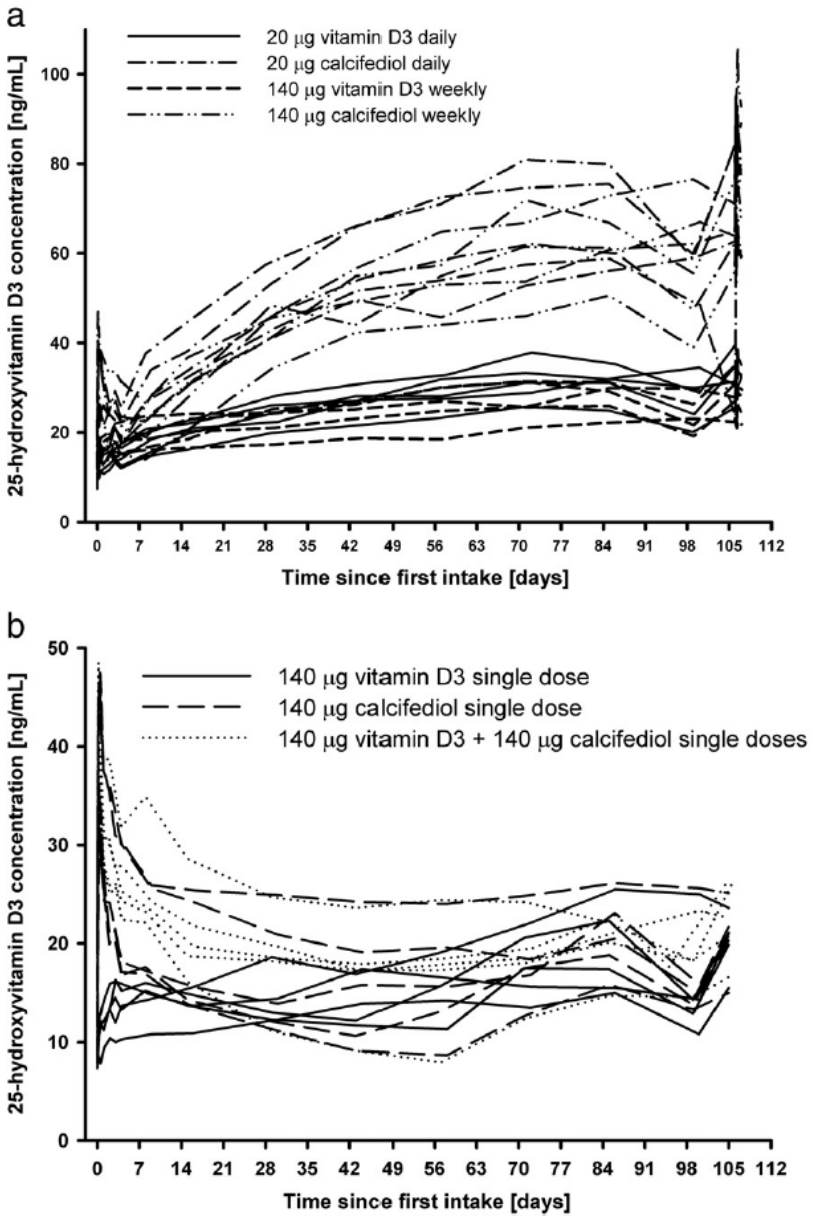
- ✓Minore affinità della D2 e dei suoi metaboliti per la DBP
- ✓D2 ha emivita più breve
- ✓25idrossilasi mitocondriale converte la D3 molto più velocemente rispetto a D2
- ✓25idrossilasi microsomiale non converte la D2
- ✓Affinità diversa per VDR (D3 > D2)

With courtesy from E. Romagnoli, GEP 2014

Calcifediolo vs D3

Pharmacokinetics of oral vitamin D_3 and calcifediol☆

Alexander Jetter [a], Andreas Egli [b,c,1], Bess Dawson-Hughes [d], Hannes B. Staehelin [e], Elisabeth Stoecklin [f], Richard Goessl [g], Jana Henschkowski [b,c], Heike A. Bischoff-Ferrari [b,g,*]



Calcifediolo somministrato giornalmente, settimanalmente o come bolo singolo è circa 2-3 volte più potente nell' aumentare i livelli circolanti di 25(OH)D3 rispetto a D3

Bone 59 (2014) 14–19

Somministrazione IM vs Os ?

Più efficace la somministrazione p.o. nell' aumentare i livelli circolanti di 25(OH)D

Short and Long-Term Variations in Serum Calciotropic Hormones after a Single Very Large Dose of Ergocalciferol (Vitamin D_2) or Cholecalciferol (Vitamin D_3) in the Elderly

Elisabetta Romagnoli, Maria Lucia Mascia, Cristiana Cipriani, Valeria Fassino, Franco Mazzei, Emilio D'Erasmo, Vincenzo Carnevale, Alfredo Scillitani, and Salvatore Minisola

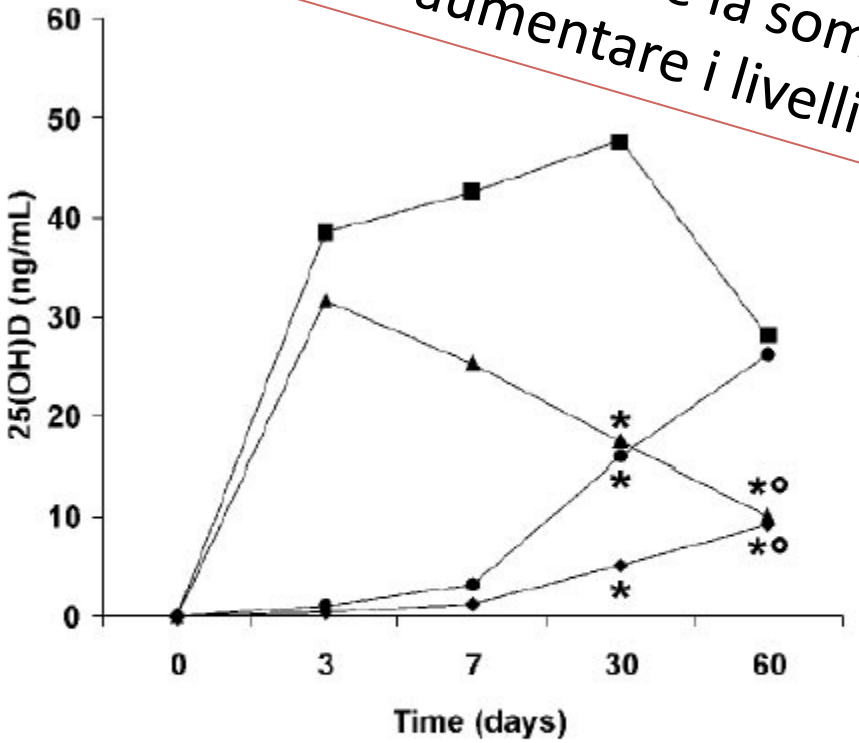


FIG. 2. Effect of vitamin D supplementation on basal difference of serum 25(OH)D at each time point for the four study groups. ■ = D_3 os, ●= D_3 im, ▲ = D_2 os, and ◆ = D_2 im represent mean values at each time point. The 30-d basal difference was significantly greater after cholecalciferol per os compared with other forms ($P < 0.001$). The 60-d basal difference was significantly lower for ergocalciferol compared with cholecalciferol, independently of route of administration (see figure for statistical significance).

(*J Clin Endocrinol Metab* 93: 3015–3020, 2008)

Modalità di somministrazione

Supplemento giornaliero (D3, colecalciferolo)

- ✓Livello 25(OH)D basale (esempio 10 ng/ml)
- ✓Stabilire il livello di 25(OH) da raggiungere (20, 30 o >30 ng/ml)
- ✓Emivita della vitamina D (functional half-life) : 2 mesi

Supplemento giornaliero richiede tempo troppo lungo per raggiungere livelli di adeguatezza ?

Loading dose : dose carico

- ✓La dose carico equivale a circa 60 volte la dose giornaliera di mantenimento
- ✓Nell'esempio 60x 2000 UI = 120.000 UI
- ✓Dopo una settimana dalla dose carico i livelli di 25(OH)D circolanti sovrapponibili a quelli ottenuti dopo 8 mesi con dose giornaliera
- ✓Dopo la dose carico , mantenere un apporto giornaliero di 2000 UI/die o, in alternativa , 14.000 UI/ settimana o 28.000 UI ogni 2 settimane

Tabella V - Stima della dose terapeutica e di quella di mantenimento in funzione dei livelli di 25(OH)D in soggetti che non hanno ricevuto supplementi nell'ultimo anno.

Valore basale di 25(OH)D	Dose terapeutica cumulativa di vitamina D	Dose giornaliera di mantenimento
<10 ng/ml o 25 nmol/l	1.000.000	2.000
10-20 ng/ml o 25- 50 nmol/l	600.000	1.000
20-30 ng/ml o 50-75 nmol/l	300.000	800

Siommms 2011

Bolo annuale ?

Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women

A Randomized Controlled Trial

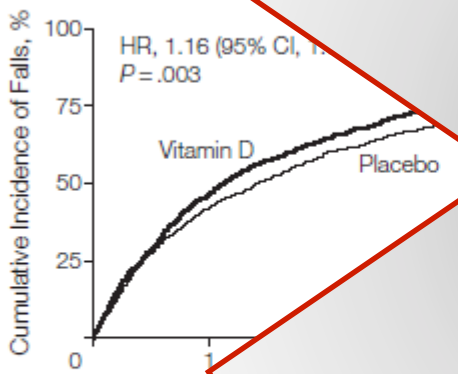
Sanders KM et al., JAMA 2010

NO

ting, and Participants A

bo-controlled trial of 2256
red to be at high risk of
randomly assigned to
o 5 years. The study

Figure 2. Kaplan-Me … e of Time to Firs



No. of women
Vitamin D 1131 588
Placebo 1125 635

This analysis censors data after … ture. Time to fi
portional hazards models. CI indic … idence intervals; H

… s, partici-
pants rece … gh-dose oral
cholecalcifero … ced 15% more
falls and 26% mor … actures than the
placebo group. Women not only expe-

Rischio intossicazione?

Vitamin D Intoxication with Severe Hypercalcemia due to Manufacturing and Labeling Errors of Two Dietary Supplements Made in the United States

Takak… …Gharlap, Carla…

Rischio intossicazione minimo e in letteratura associato a utilizzo di prodotti/integratori non controllati

Caso 1 : **25(…** spectrophotometry and HPLC … **contained a significantly higher amount of …vitamin D3**. In addition, there was an error in labeling recommending 10 capsules instead of one capsule per day. Thus, the patient consumed **1,864,000 IU** of vitamin D3 daily for 2 months, more than 1,000 times what th… manufacturer had led the patient to belie… ingesting.

La dose massima giornaliera oltre cui si ritiene elevato il rischio di intossicazione è stata identificata in 4.000 UI.

Caso 2: **25…** a manufac… …ion the daily dose actual… …**IU** of vitamin D3.

FIG. 1. A, Serum calcium levels and 25(OH)D over time. B, Serum calcium and $1,25(OH)_2D$ over time. *Shaded area* reflects normal range for $1,25(OH)_2D$.

[*J Clin Endocrinol Metab* 96: 3603–3608, 2011]

Over-supplementation of vitamin D in two patients with primary hyperparathyroidism

Claudia Battista,[1] Raffaella Viti,[1] Salvatore Minisola,[2] Iacopo Chiodini,[3]
Vincenzo Frusciante,[4] Alfredo Scillitani,[1] Vincenzo Carnevale[5]

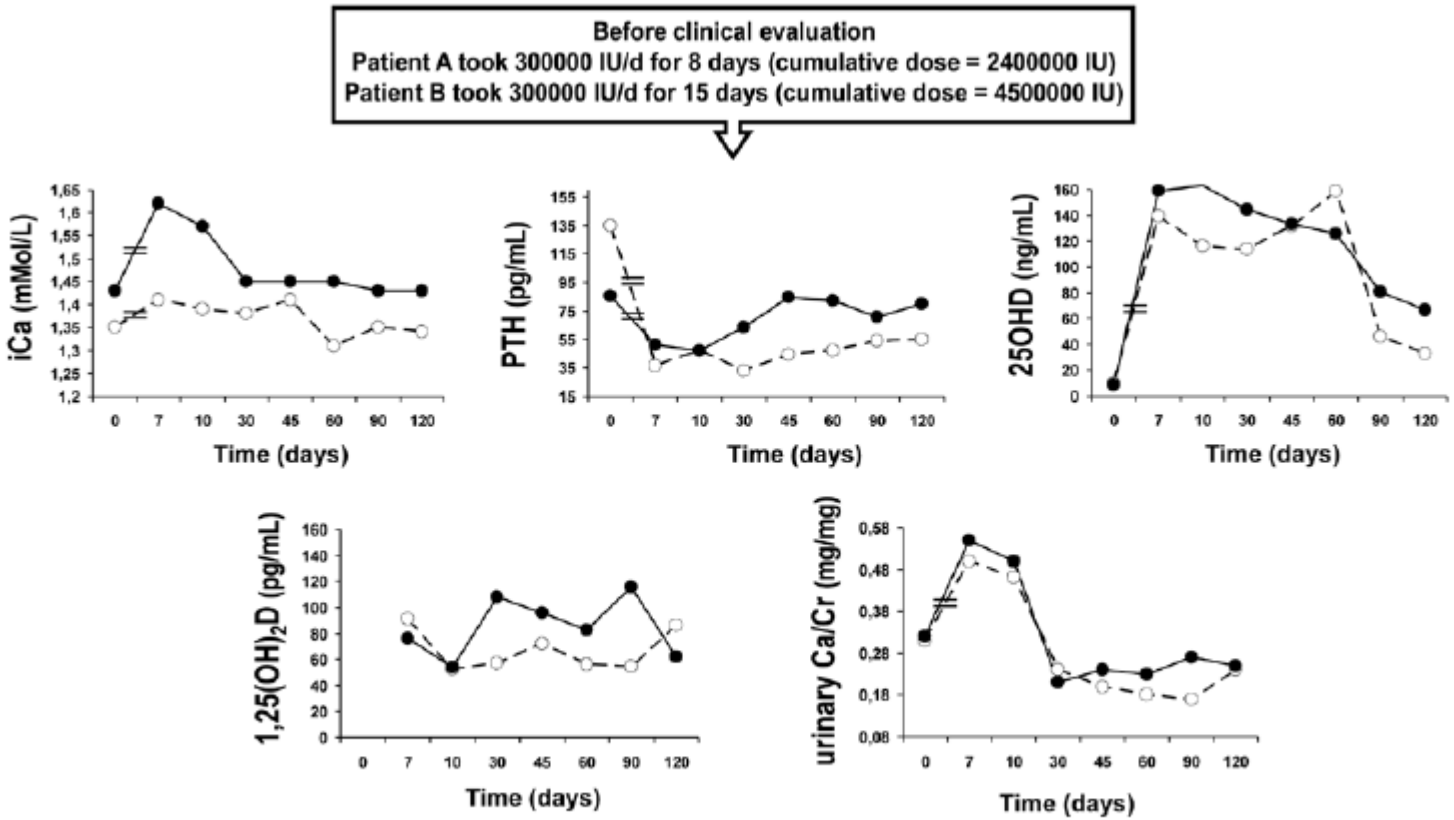


FIGURE 1. Biochemical data of the vitamin D3 over-treatment Variations of the levels of iCa, PTH, 25OHD, $1,25(OH)_2D$ and urinary Ca/Cr during the 4 months after vitamin D loading dose in patient A (○) and B (●).

Conclusioni

✓Le condizioni di "deficienza" e "insufficienza" sono definite da livelli di 25(OH)D: < 20 ng/ml e 20-30 ng/ml, rispettivamente

✓In presenza di una condizione di deficienza, considerare una dose cumulativa nell'arco di 1-4 settimane, seguita da una dose di mantenimento giornaliera o settimanale o bimensile (raccomandazione SIOMMMS 2011)

✓In presenza di osteoporosi considerare sempre supplemento di vitamina D (D3 800-1000 U/die o comunque al fine di garantire 25OHD3>= 30 ng/ml)

✓Colecalciferolo (D3) risulta superiore a ergocalciferolo (D2) nell'incrementare i livelli di 25OHD3

✓Calcifediolo (25OHD3) risulta più veloce nell'incrementare I livelli di 25OHD3

✓Da evitare il bolo annuale

✓Rischio tossicità minimo per D2 e D3.

Grazie