Efectos óseos y otros beneficios de la vitamina D: ¿Cuáles son los niveles óptimos?

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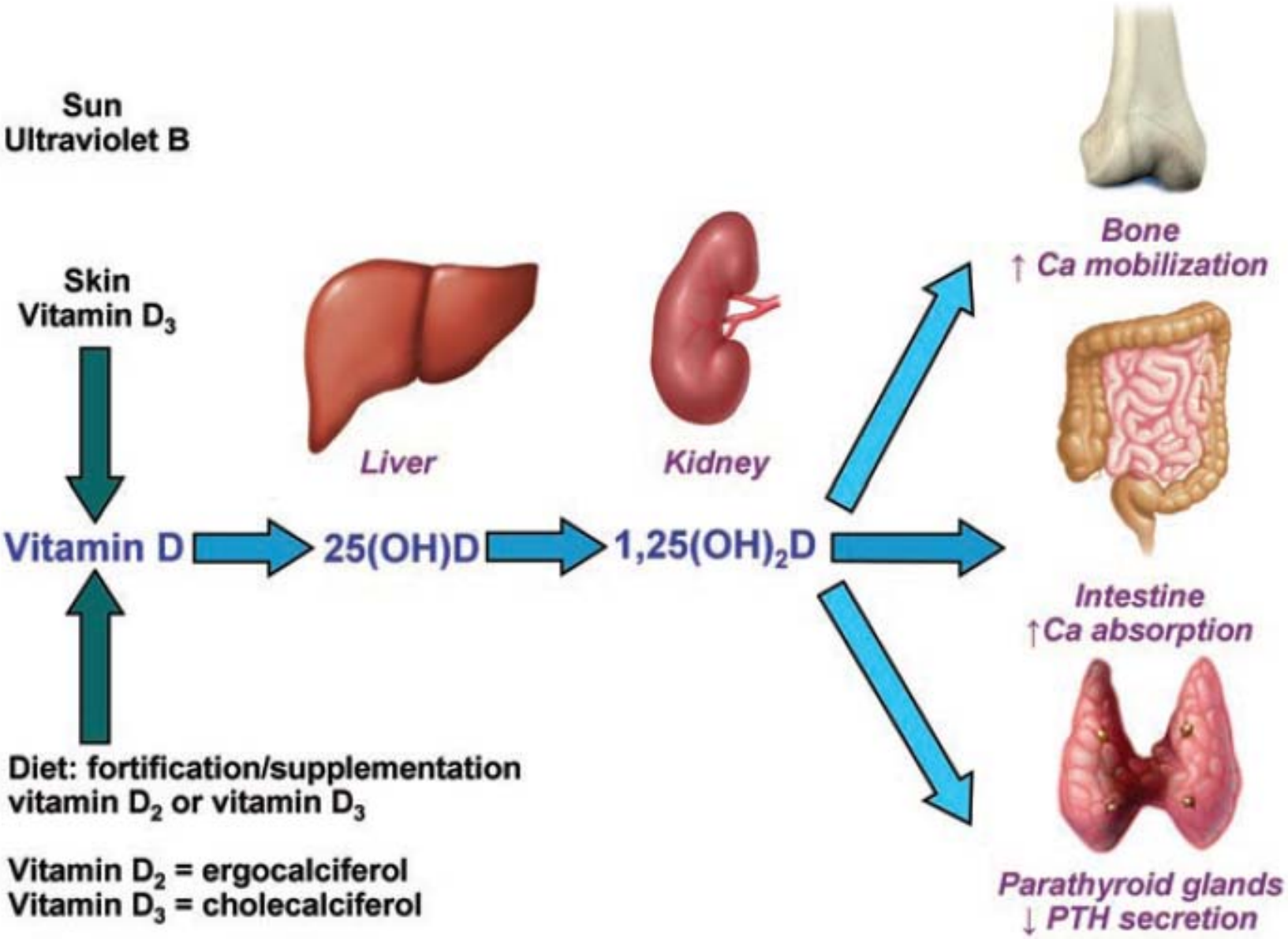
CONSEJERÍA DE SALUD

14 Encuentro Nacional de Salud y Medicina de la Mujer
SAMEM
19-21 de Febrero, 2014
COLEGIO OFICIAL DE MEDICOS DE MADRID

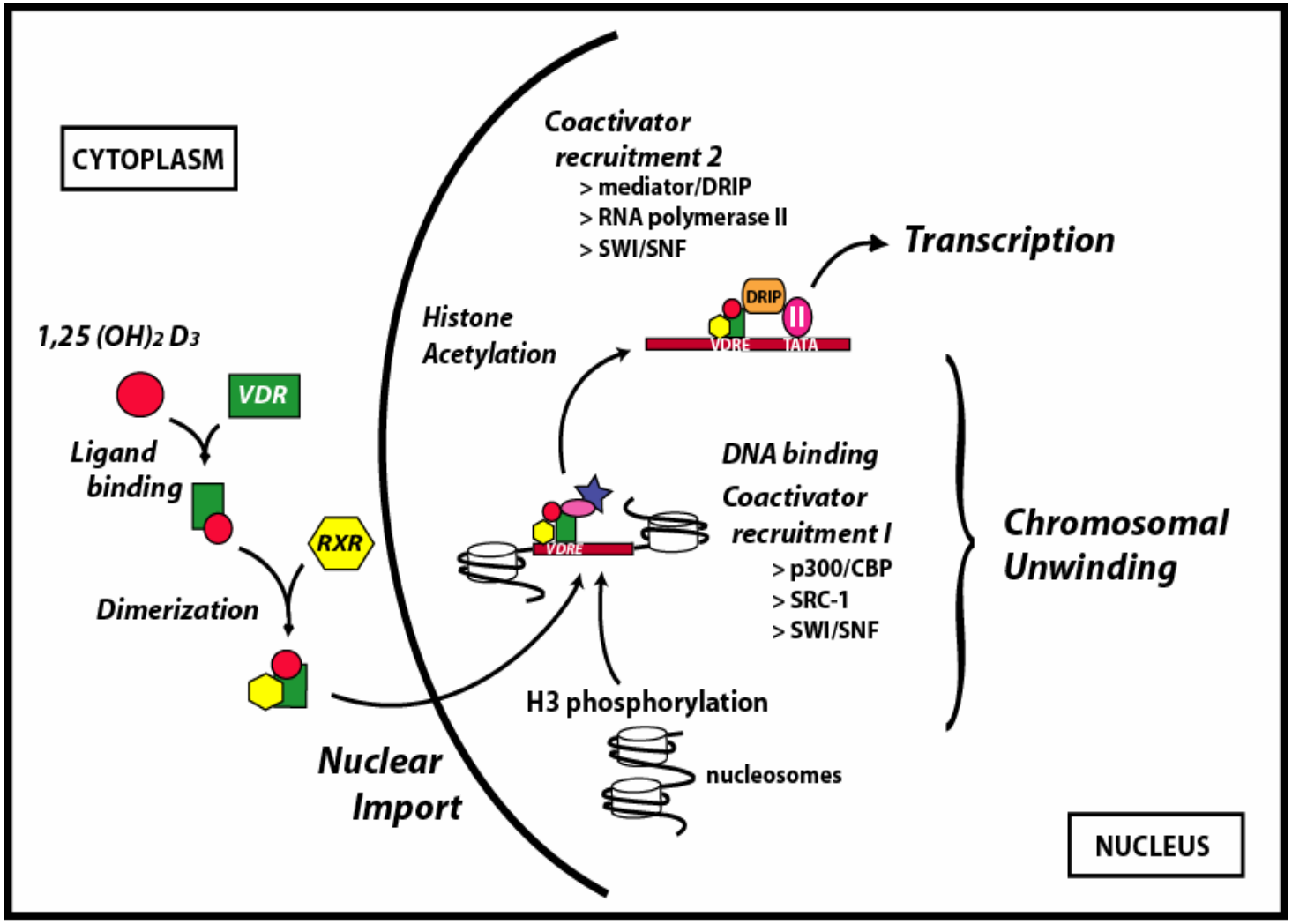
Agenda

1. Metabolismo vitamina D
2. Vitamina D y fragilidad ósea
3. Efectos extraóseos de vitamina D
4. Niveles óptimos, requerimientos & fuentes de vitamina D
5. Resultados preliminares de un estudio de intervención nutricional

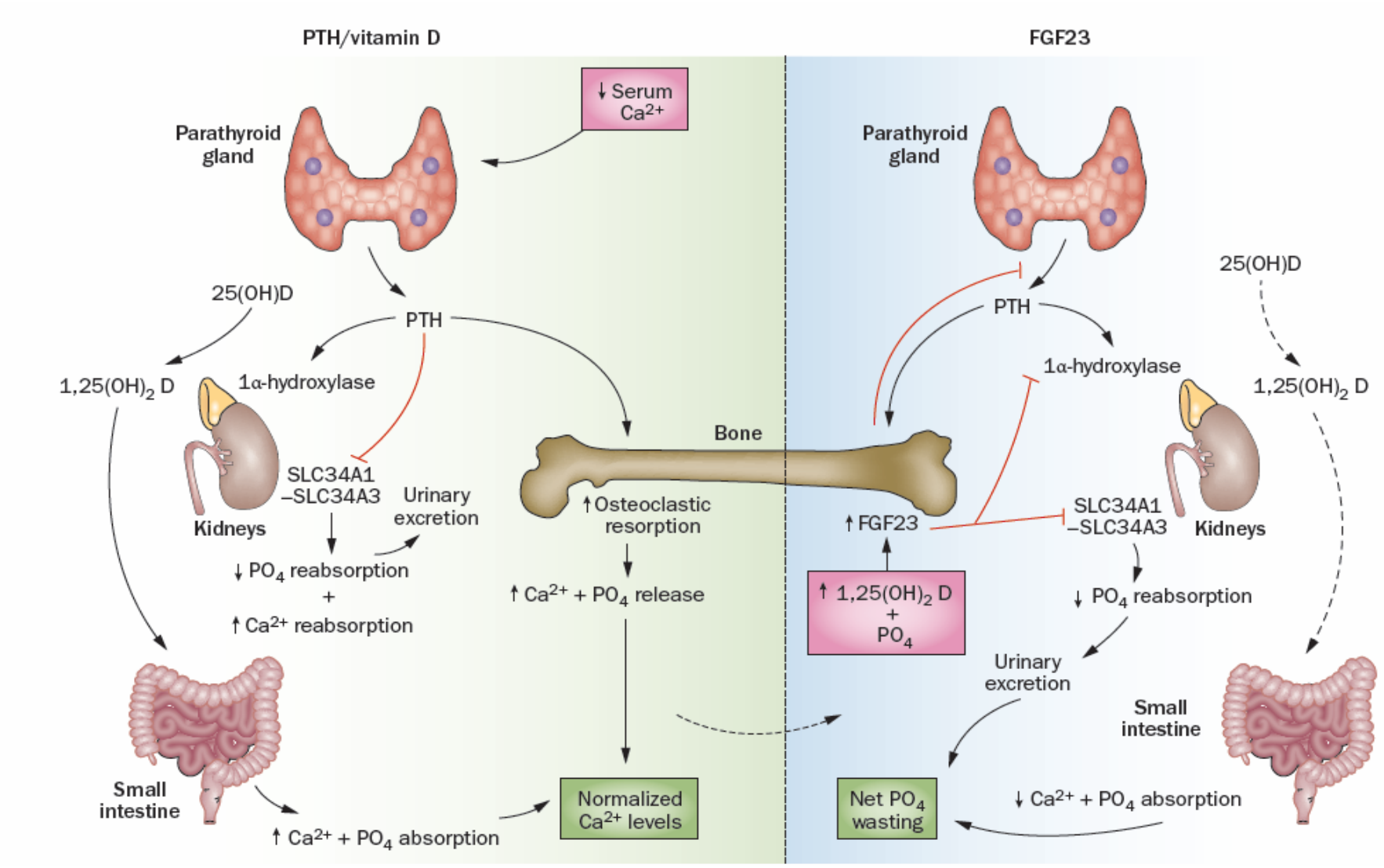
El sístema hormonal de la vitamina D



El receptor de 1,25(OH)2 D (VDR)



Vitamina D: homeostasis del calcio y fósforo



DiGirolamo, D. J. *et al. Nat. Rev. Rheumatol. 8, 674–683 (2012)*

Acciones clásicas de la vitamina D

Absorción de calcio y fósforo a nivel intestinal

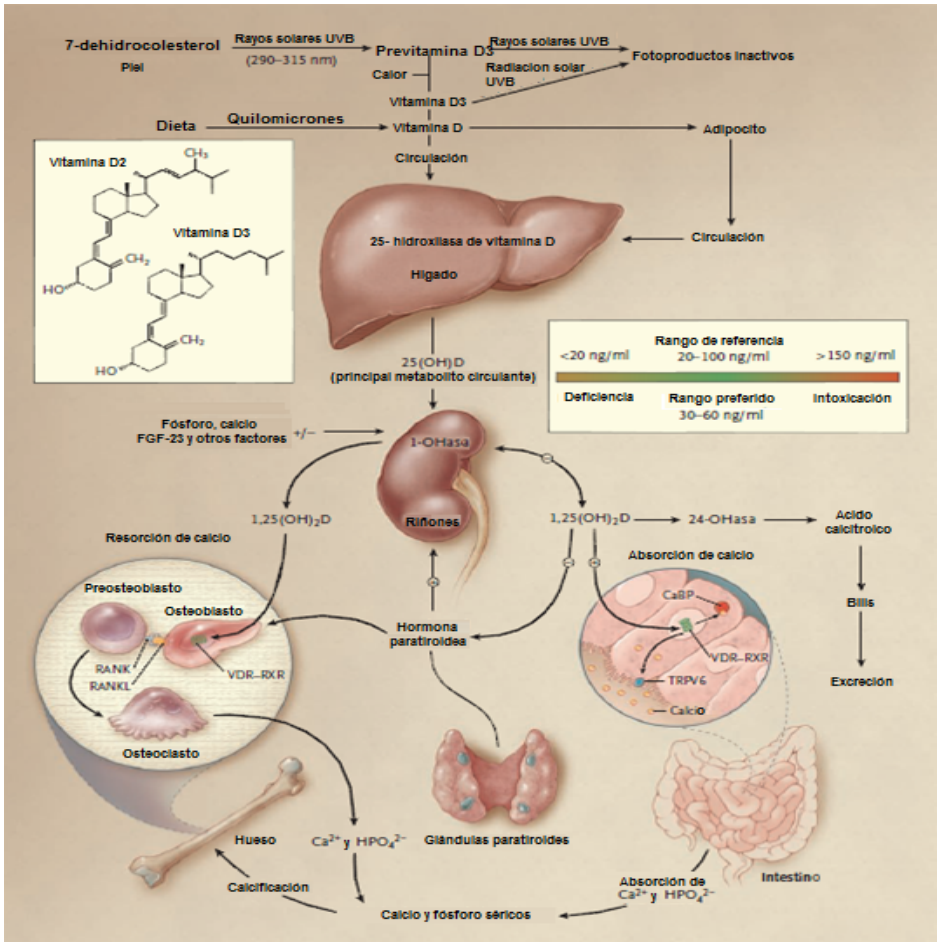
- Expresión de calbindina y TRPV6

Promover la mineralización ósea

- Estimulación osteoclastogénesis
- Diferenciación de osteoblastos

Aumentar la reabsorción renal de calcio

- Aumentar la expresión del receptor de PTH

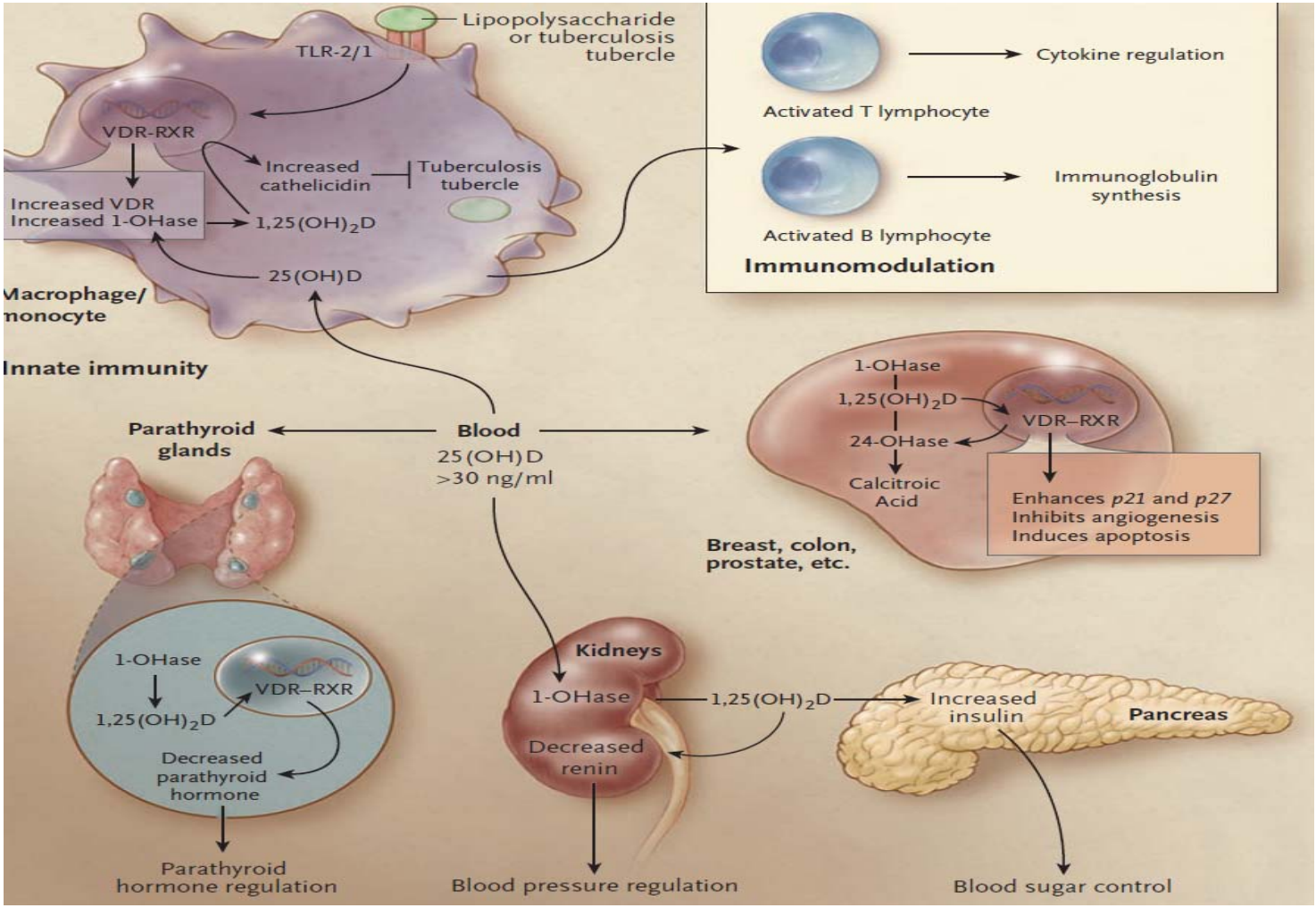


Holick M. N Engl J Med 2007

Células y tejidos que producen 1,25(OH)D y/o poseen receptores para vitamina D (RVD)

Célula /Tejido	VDR	1,25OHD
Endocrino		
Celulas B pancreáticas	+	+
Paratiroides	+	+
Parotidas	+	-
Células C tiroideas	+	-
Hipófisis	+	-
Adrenales	+	-
Musculoesquelético		
Cartílago/Condrocitos	+	+
Osteoblastos	+	+
Fibras musculares	+	-
Cardiovascular		
Miocitos	+	+
Músculo liso vascular	+	-
Endotelio	+	+
Células parénquima hepático	+	-
Túbulos renales	+	+
Tejido adiposo	+	-
Células tumorales	+	-

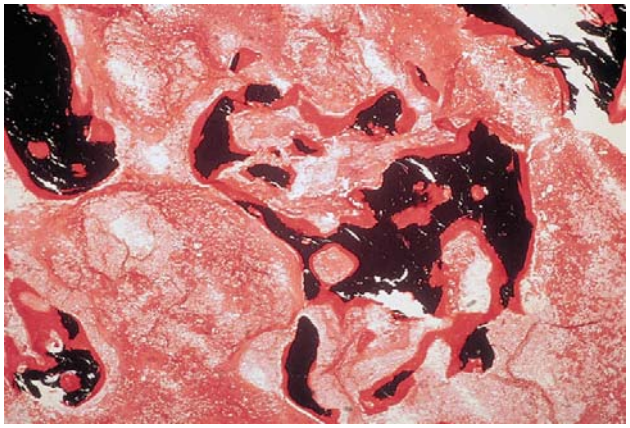
Acciones no clásicas de la vitamina D



Holick M. N Engl J Med 2007

Vitamina D & salud ósea

Deficiencia severa de vitamina D



Raquitismo & Osteomalacia

Hipovitaminosis D y fragilidad ósea

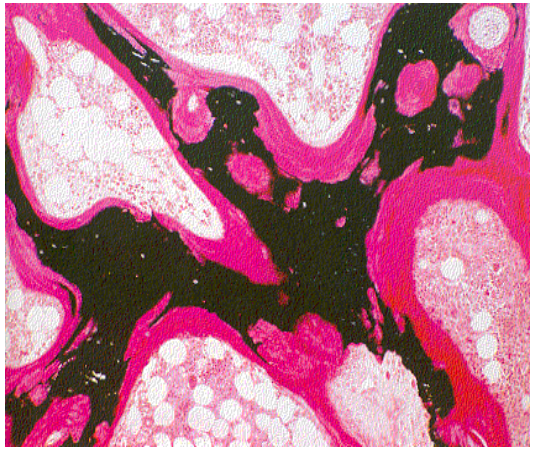
INSUFICIENCIA EN VITAMINA D

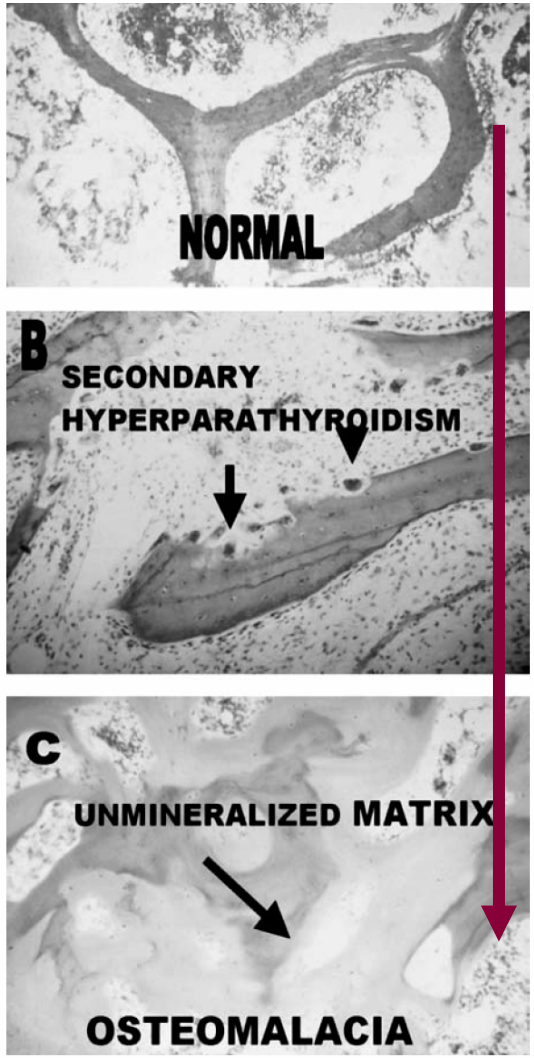
<30 ng/ml

DEPLECCIÓN O DEFICIENCIA GRAVE EN VITAMINA D

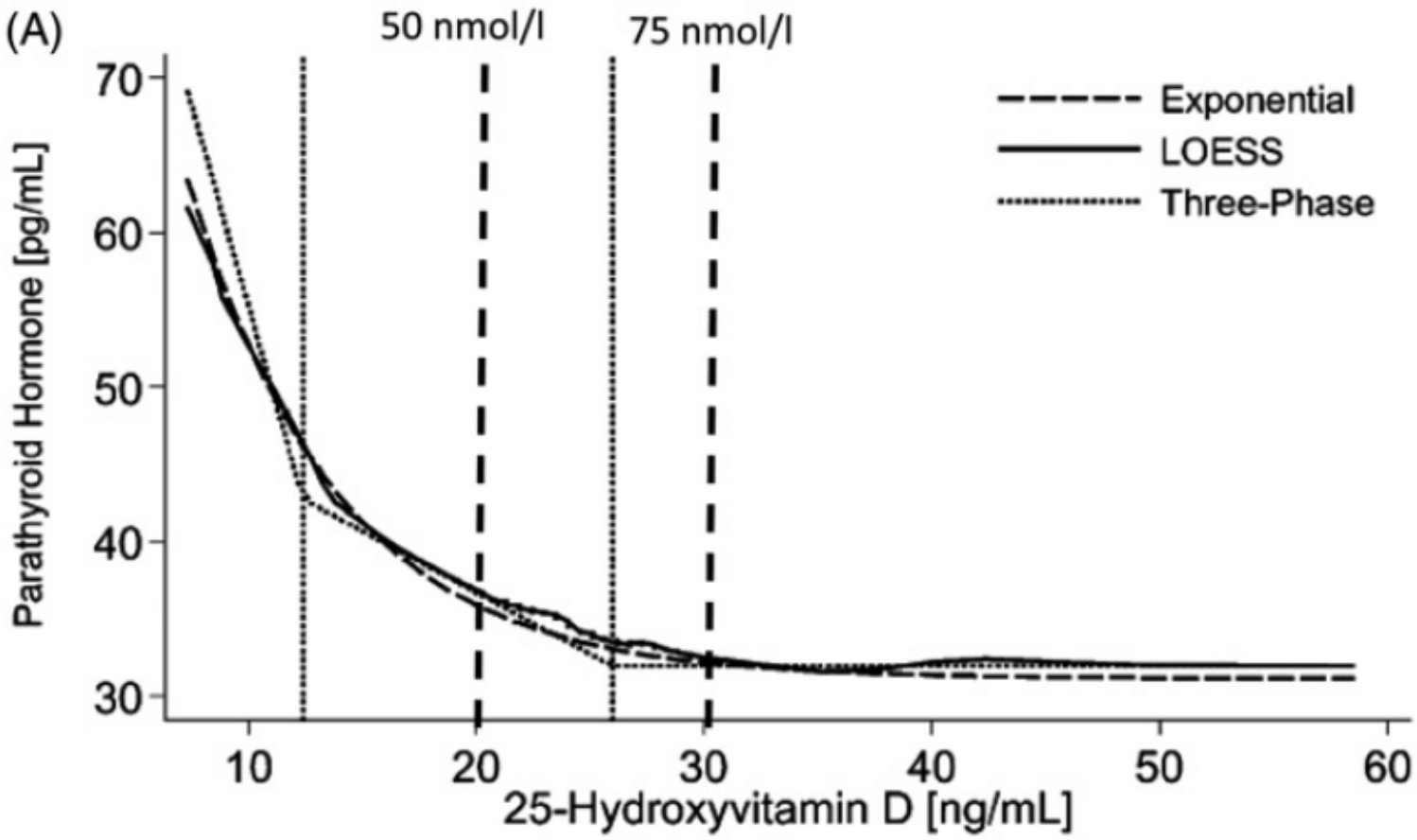
<10 ng/ml

(Consecuencia clínica: raquitismo/osteomalacia)



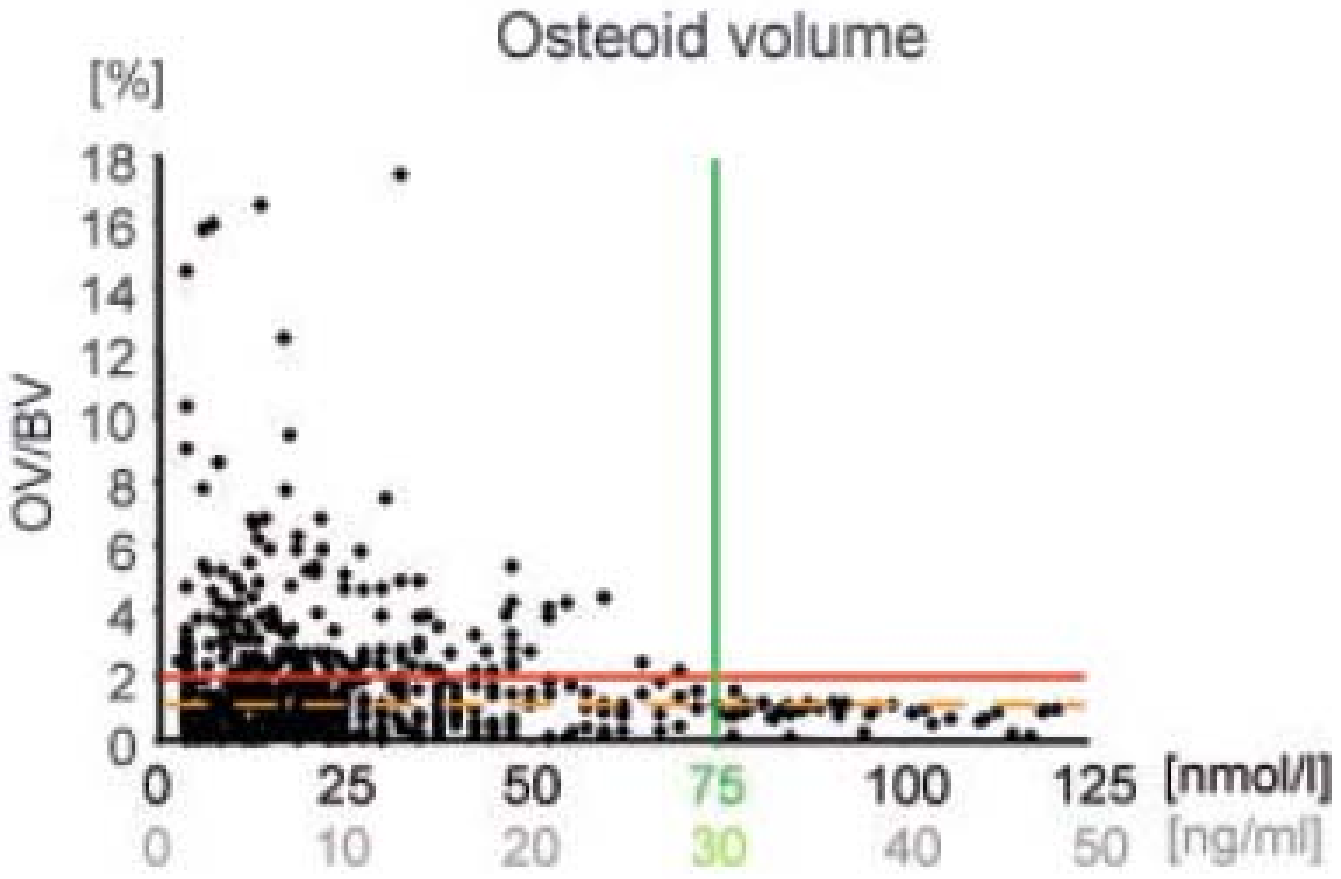


Hipovitaminosis D e hiperparatiroidismo



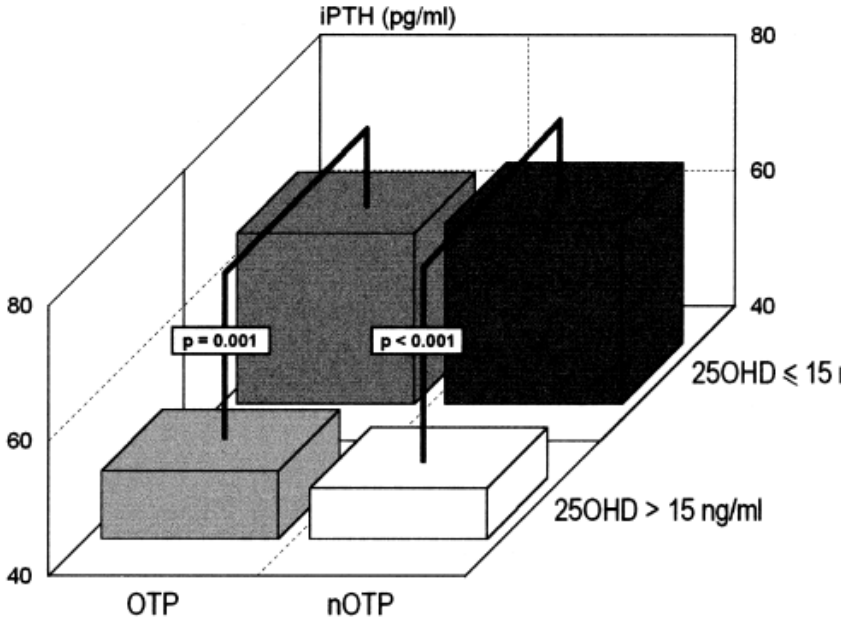
Durazo-Arvizu RA, J Nutr 2010

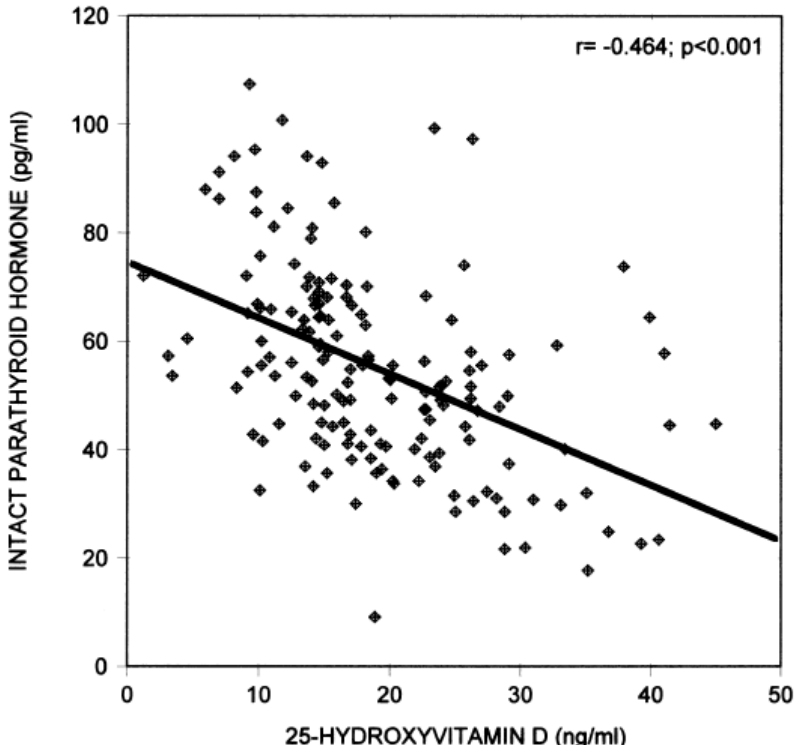
Relación 25OH vitamina D y osteoide no mineralizado



Priemel M JBMR 2010

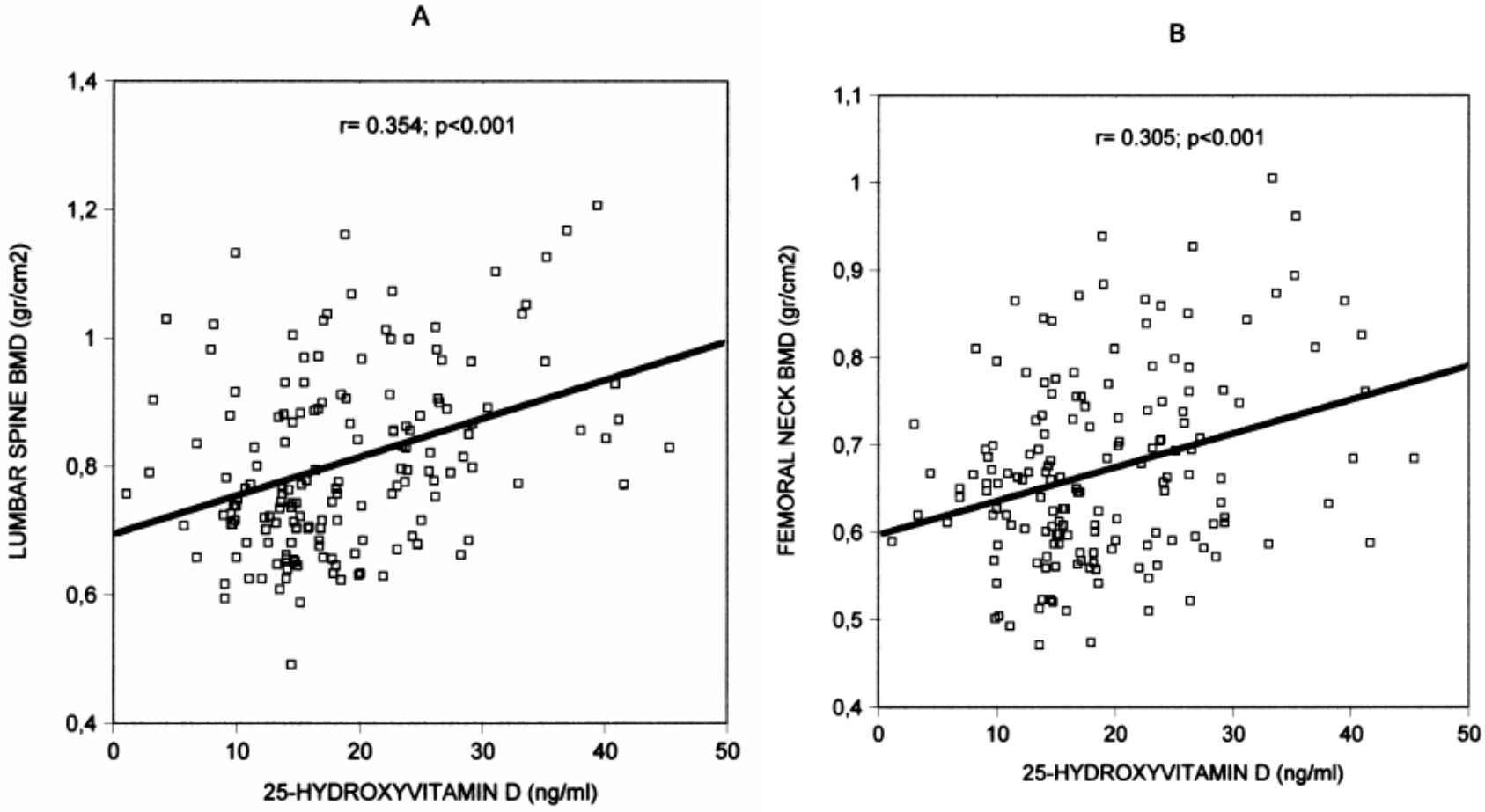
Relation Between Vitamin D Insufficiency, Bone Density, and Bone Metabolism in Healthy Postmenopausal Women





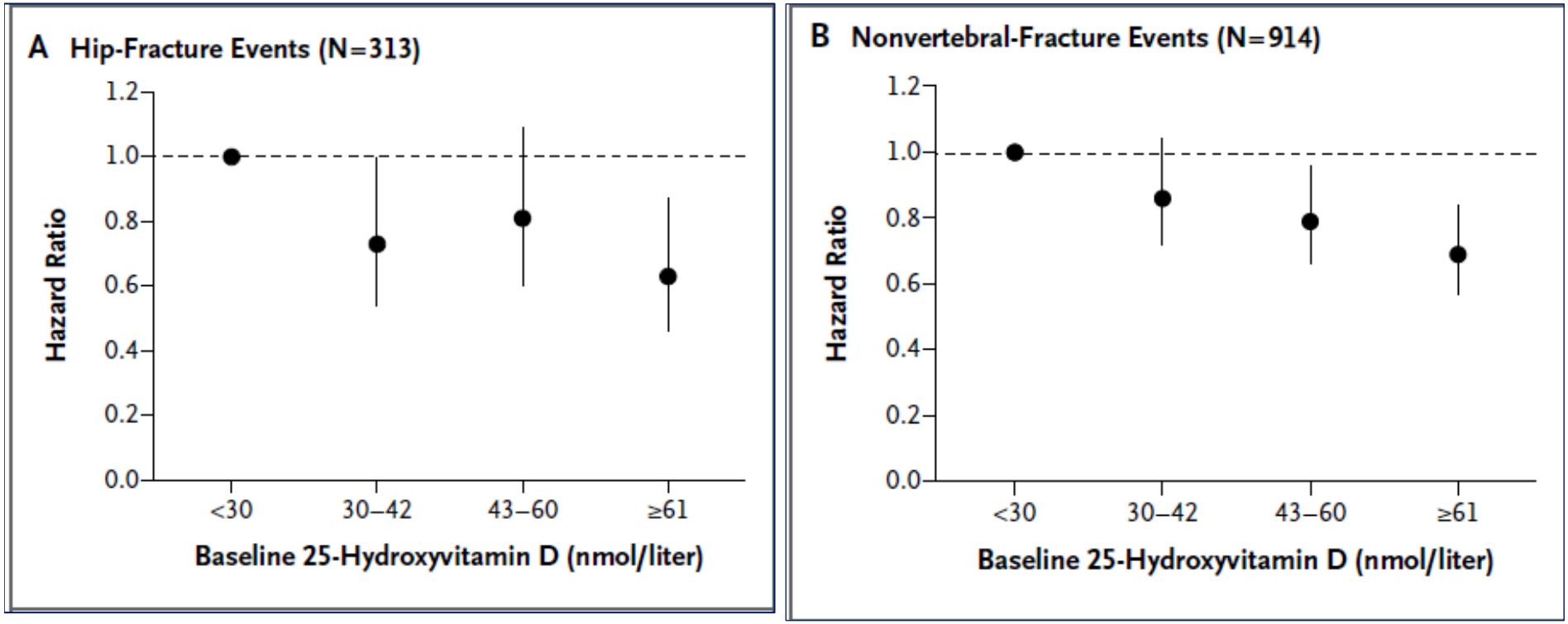
Mezquita Raya P & Muñoz Torres M, JBMR 2001

Relation Between Vitamin D Insufficiency, Bone Density, and Bone Metabolism in Healthy Postmenopausal Women



Mezquita Raya P & Muñoz Torres M, JBMR 2001

Vitamina D y fracturas por fragilidad



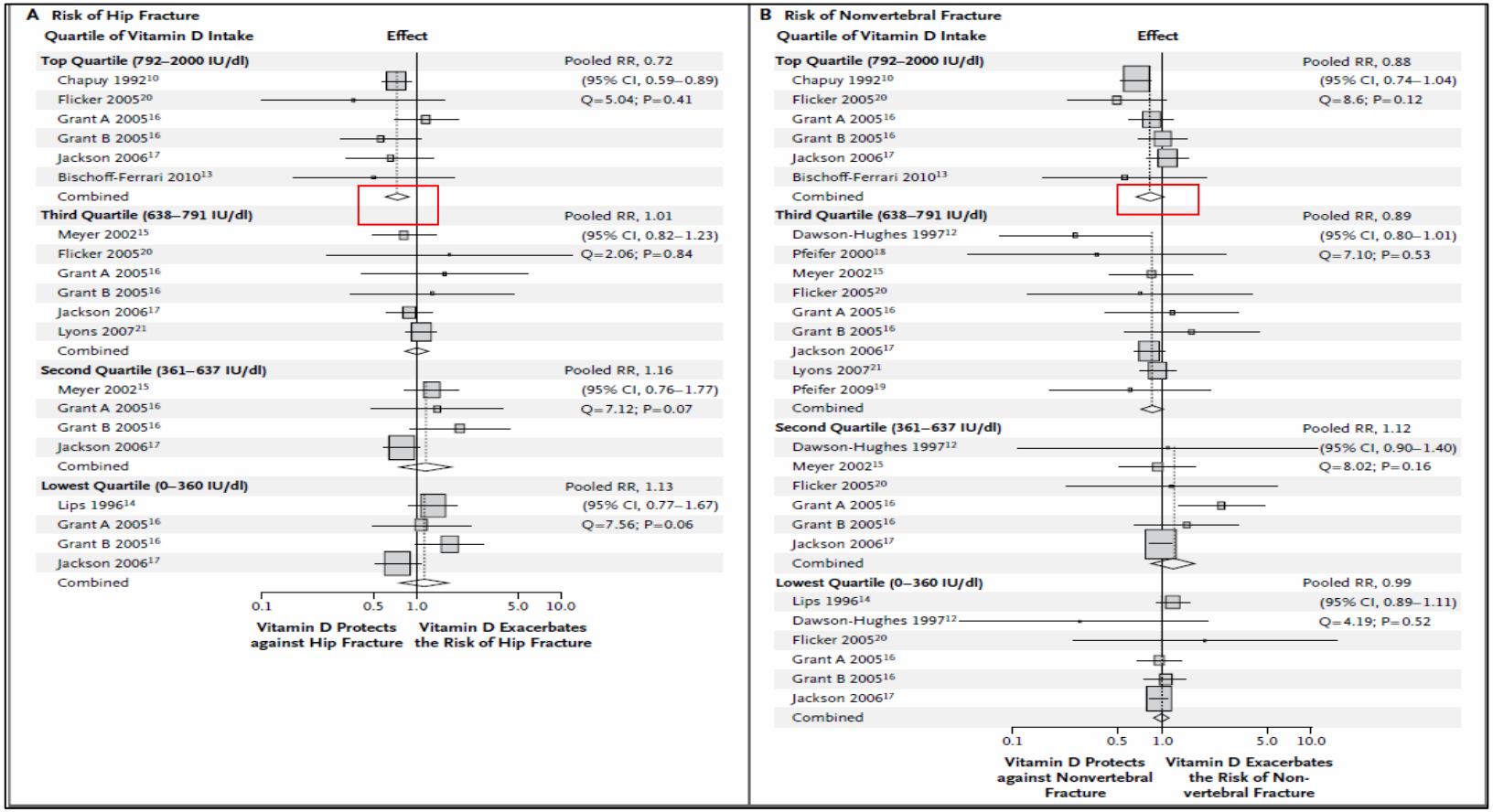
Niveles de 25OHD > de 25 ng/ml disminuyen el riesgo de Fxs de cadera y no vertebrales entre un 37%-31%

Bishoff-Ferrari HA, NEJM 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Pooled Analysis of Vitamin D Dose Requirements for Fracture Prevention



Bishoff-Ferrari HA, NEJM 2012

ORIGINAL ARTICLE

JBMR

Risk Factors for Prediction of Inadequate Response to Antiresorptives

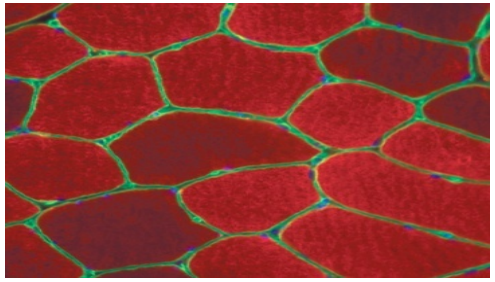
Adolfo Díez-Pérez,[1,2] Jose M Olmos,[2,3] Xavier Nogués,[1,2] Manuel Sosa,[4] Manuel Díaz-Curiel,[2,5] Jose Luis Pérez-Castrillón,[2,6] Ramon Pérez-Cano,[2,7] Manuel Muñoz-Torres,[2,8] Antonio Torrijos,[2,9] Esteban Jodar,[2,10] Luis Del Rio,[2,11] Jose R Caeiro-Rey,[2,12] Jordi Farrerons,[13] Joan Vila,[1] Claude Arnaud,[14] and Jesus González-Macías[2,3]

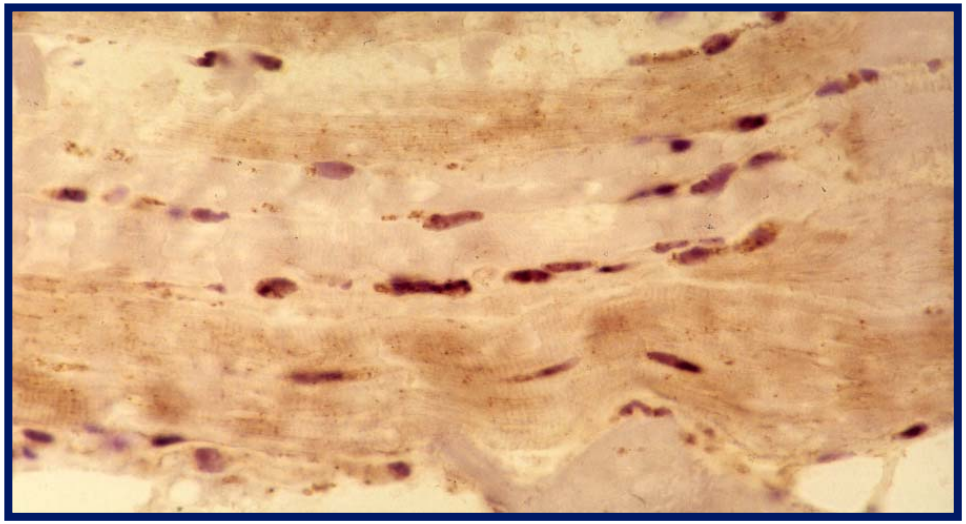
Table 2. Predictive Variables of IR in the Logistic Regression Analysis

Variable in the model	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95%CI)	p	OR (95% CI)	p
Prior fragility fracture	–	–	3.60 (1.47–8.82)	0.005	3.56 (1.28–9.93)	0.015	–	–	3.03 (1.20–7.68)	0.019	3.05 (1.07–8.73)	0.038
Fracture load[a]	0.96 (0.93–0.99)	0.006	–	–	0.097 (0.93–1.01)	0.162	0.96 (0.93–0.99)	0.007			0.97 (0.93–1.01)	0.183
25 Vitamin D[b]	0.58 (0.29–1.13)	0.109	0.43 (0.17–1.10)	0.080	0.39 (0.14–1.07)	0.068	–	–	–	–	–	–
25 Vitamin D > 20 ng/mL	–	–	–	–	–	–	3.25 (1.51–7.00)	0.003	3.89 (1.55–9.77)	0.004	3.29 (1.18–9.21)	0.023

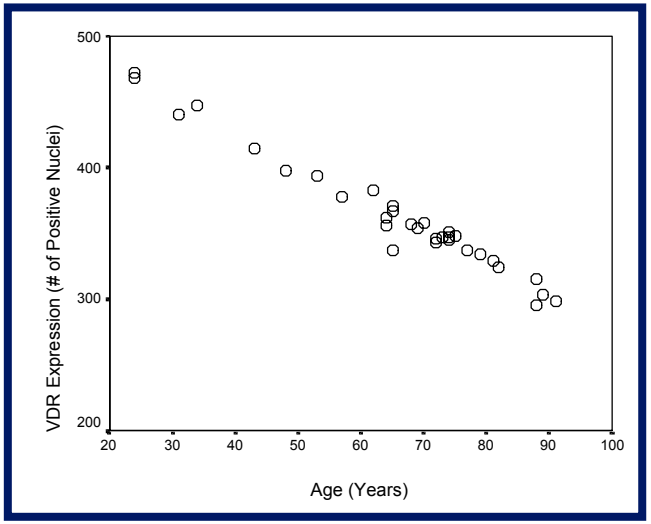
JBMR 2012

Receptor VD en músculo





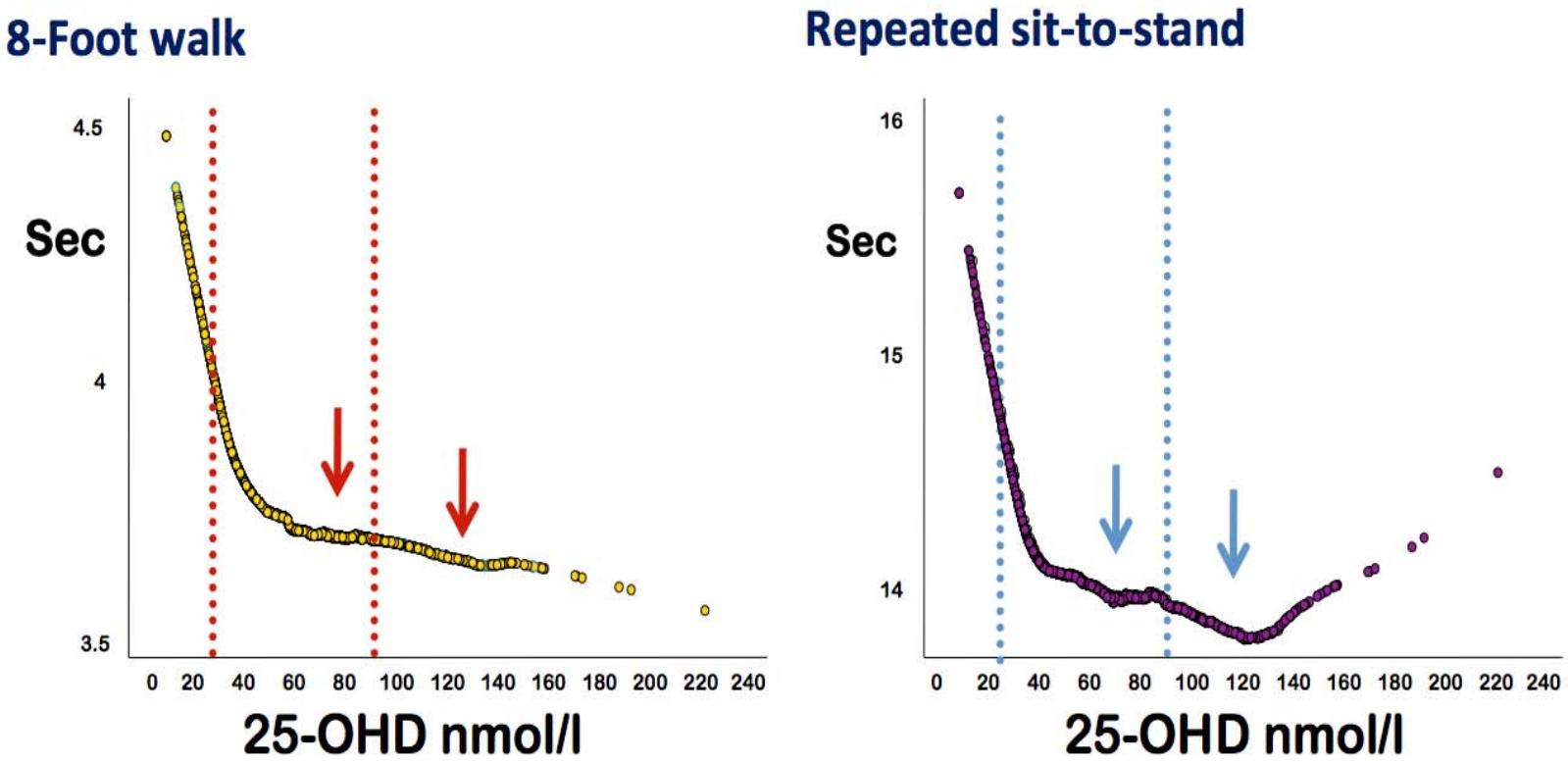
Human muscle – immunohistochemistry
(Bischoff-Ferrari HA et al. JBMR 2004)



Nº of VDRs in muscle < with age among 32 women 21 – 91 yrs with hip or spine surgery (p = .047)

Muscle biopsies in adults with profound vitamin D deficiency show atrophy of type II (fast-twitch) muscle fibers, --- first fibers to be recruited when preventing a fall *(McComas 1996)*

25OHD y función de MMII

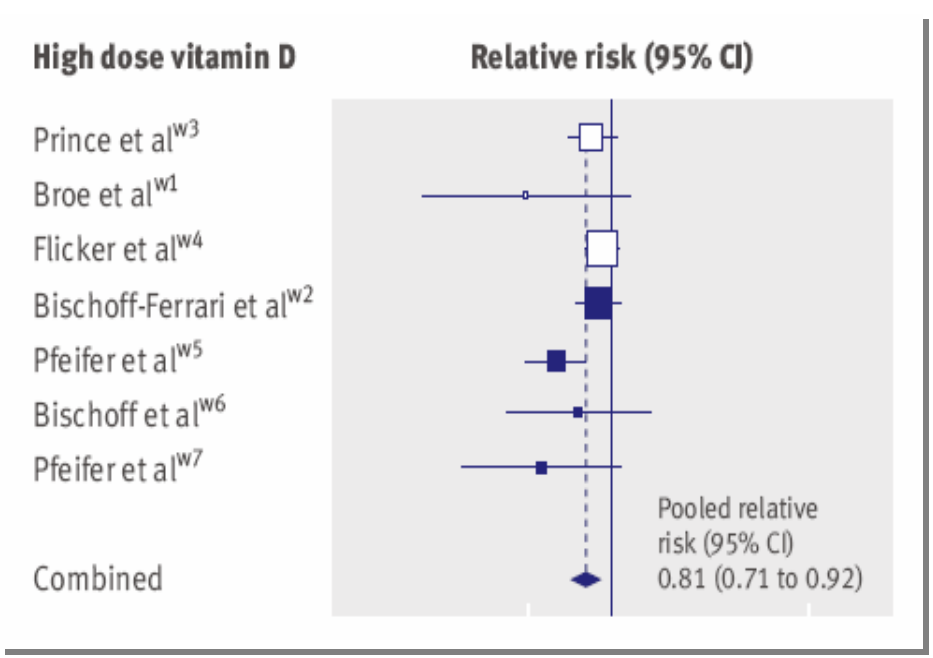


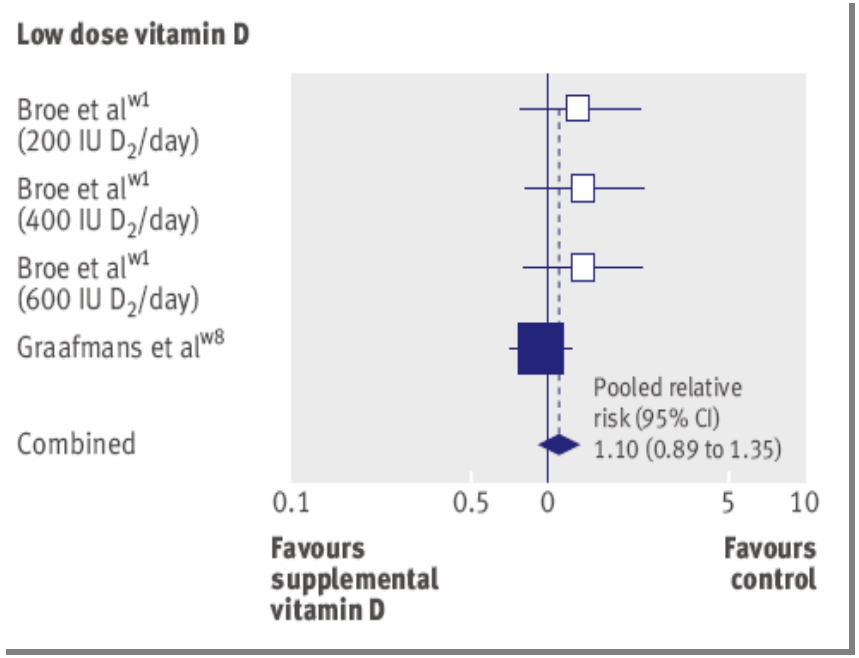
Bischoff-Ferrari HA, Dawson-Hughes B et al. Am J Clin Nutr. 2004;80:752–758.

BMJ

RESEARCH

Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials





700-1000 UI/d

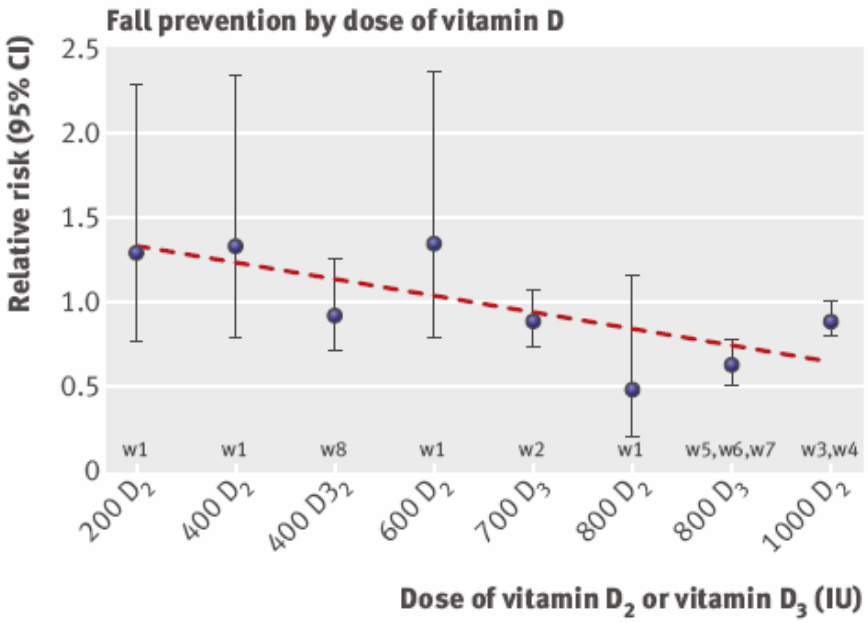
200-600 UI/d

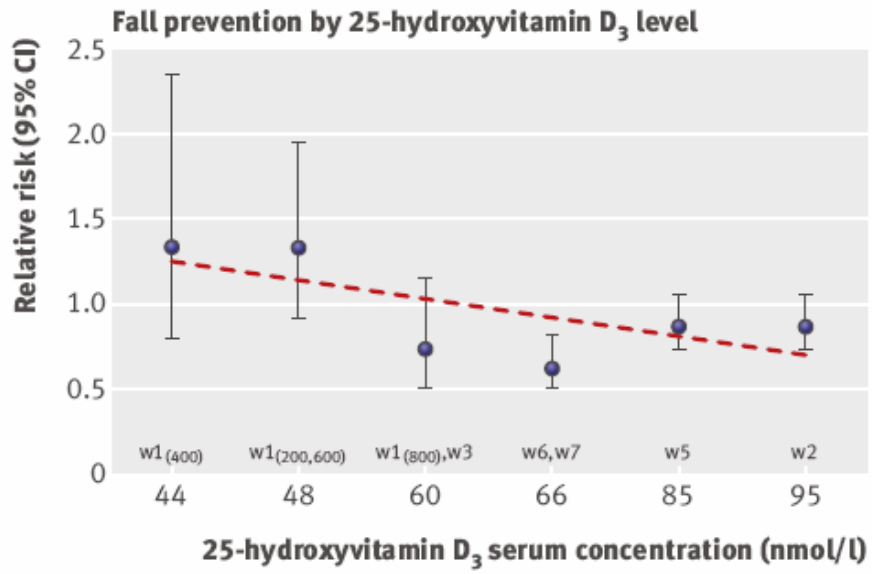
Bishoff-Ferrari et al, BMJ 2009

BMJ

RESEARCH

Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials





Bishoff-Ferrari et al, BMJ 2009

Recommendations Abstracted from the American Geriatrics Society Consensus Statement on Vitamin D for Prevention of Falls and Their Consequences

American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults[1]

"The workgroup concluded that a serum 25 hydroxyvitamin D (25(OH)D) concentration of 30 ng/mL (75 nmol/L) should be a minimum goal to achieve in older adults, particularly in frail adults, who are at higher risk of falls, injuries, and fractures."

J Am Geriatr Soc 62:147–152, 2014

Vitamina D & efectos extraóseos

Efectos pleiotrópicos de la vitamina D

Regulación del sistema inmunológico

- Inmunidad innata y adaptativa
- inmunoregulación

Regulación del crecimiento celular

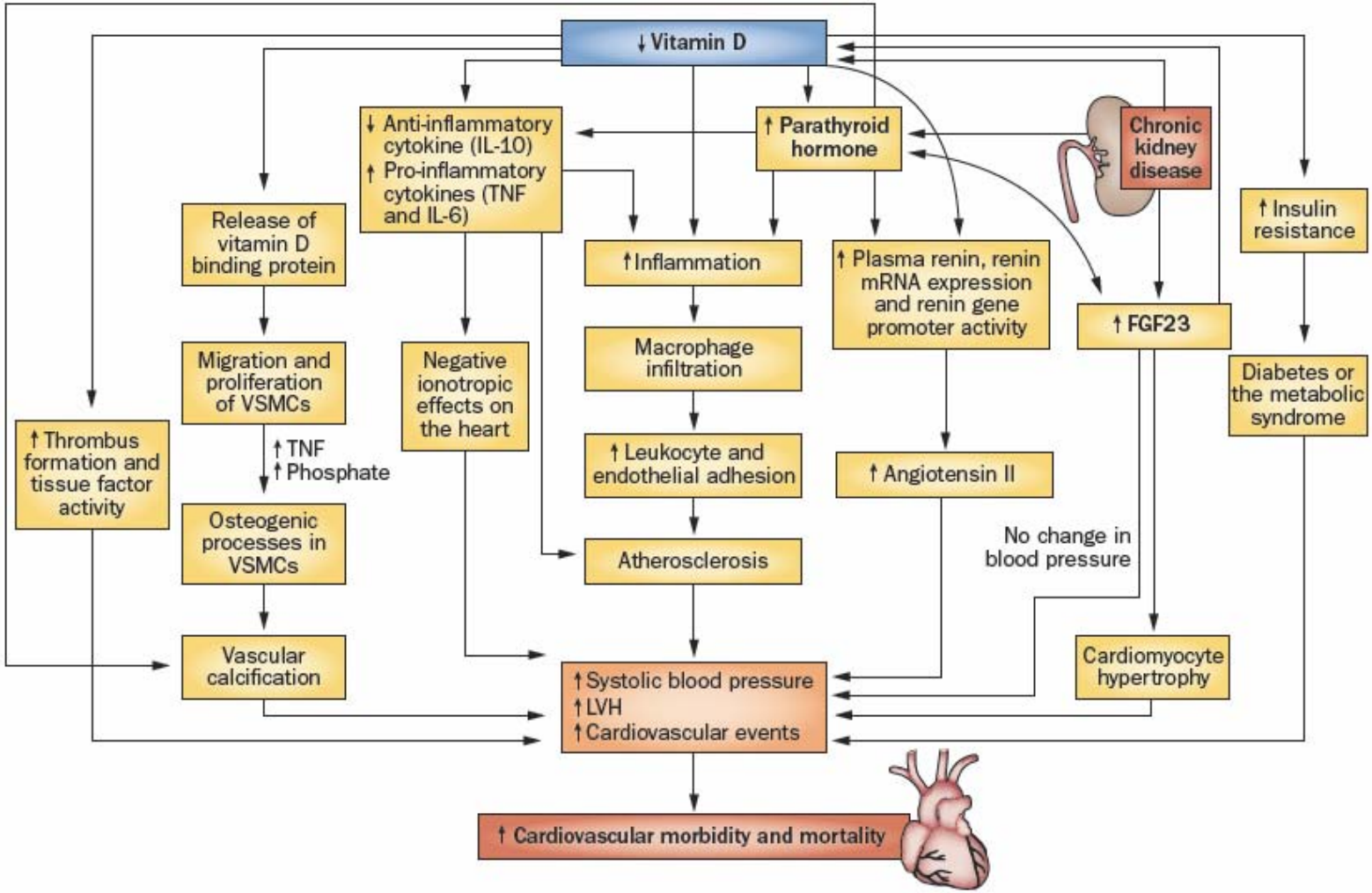
- Inhibición proliferación
- Inducción de diferenciación celular
- Inhibición de angiogénesis
- Aumento de apoptosis

Regulación de la secreción y acción hormonal

- Aumenta producción de insulina en cel β
- Aumenta sensibilidad a la insulina
- Inhibe producción de renina a nivel renal
- Inhibe secreción de PTH

- Enfermedades infecciosas
- Enfermedades autoinmunes
- Cáncer
- Diabetes & síndrome metabólico
- Enfermedades cardiovasculares

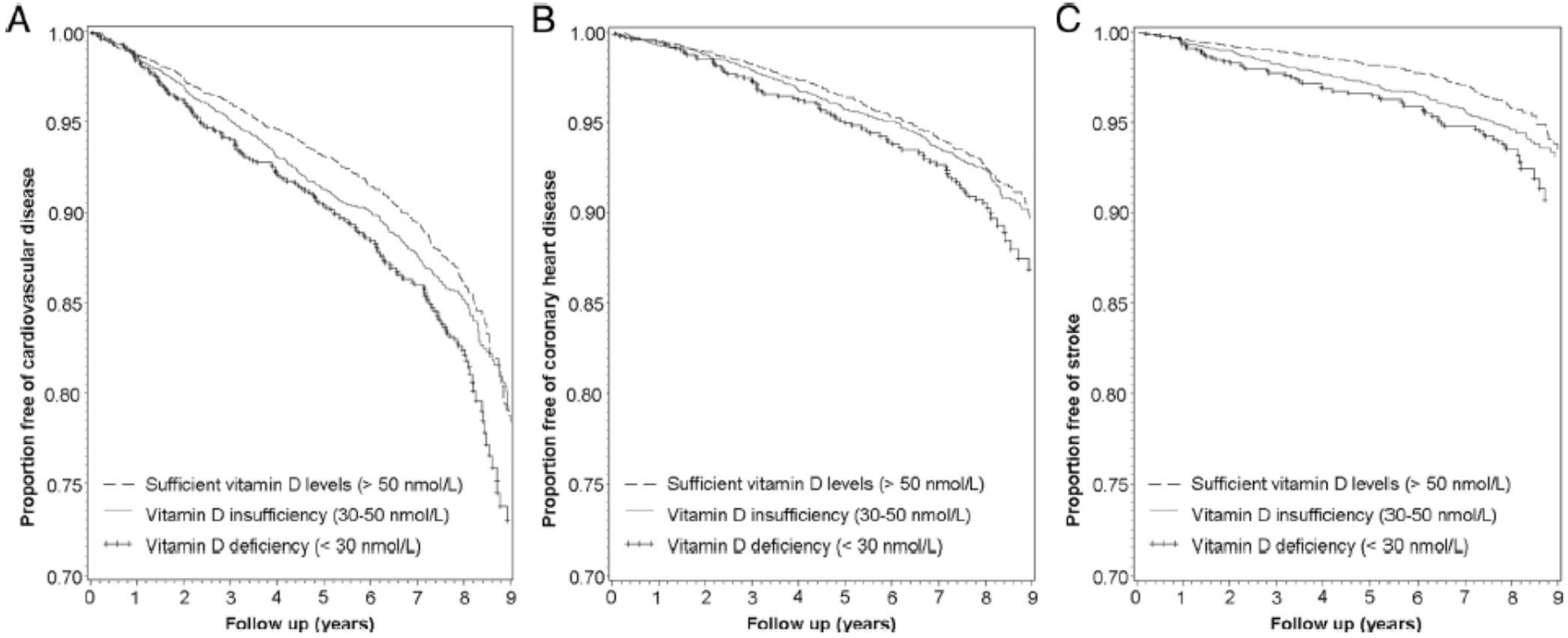
The effect of vitamin D status on risk factors for cardiovascular disease



Gunta, S. S. *et al. Nat. Rev. Nephrol*, 2013

Serum 25-Hydroxyvitamin D and Incidence of Fatal and Nonfatal Cardiovascular Events: A Prospective Study With Repeated Measurements

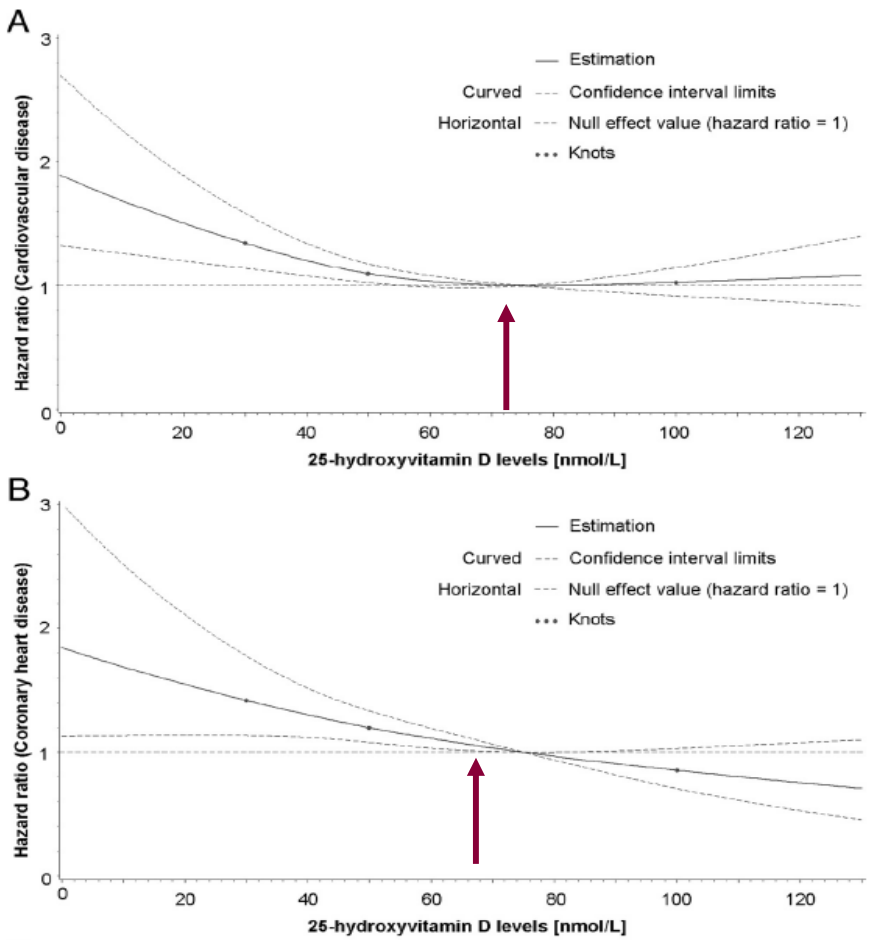
9949 personas (50-74 años, 59% mujeres) seguidos durante 8 años



Supervivencia libre de ECV, ECC o ictus en funcion del status de vitamina D

Perna et al, JCEM 2013

Serum 25-Hydroxyvitamin D and Incidence of Fatal and Nonfatal Cardiovascular Events: A Prospective Study With Repeated Measurements



ECV

ECC

Relación dosis-respuesta entre 25OHD y ECV o ECC incidente

Perna et al, JCEM 2013

Niveles óptimos, requerimientos y fuentes de vitamina D

Publicaciones de sociedades científicas sobre vitamina D

NATIONAL OSTEOPOROSIS FOUNDATION

Clinician's Guide to Prevention and Treatment of Osteoporosis

01/2010

IOM

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)

International Osteoporosis Foundation

IOF position statement: vitamin D recommendations for older adults

B. Dawson-Hughes · A. Mithal · J.-P. Bonjour · S. Boonen · P. Burckhardt · G. E.-H. Fuleihan · R. G. Josse · P. Lips · J. Morales-Torres · N. Yoshimura

Osteoporos Int 2010;21:1151-4.

THE ENDOCRINE SOCIETY®

Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

Michael F. Holick, Neil C. Binkley, Heike A. Bischoff-Ferrari, Catherine M. Gordon, David A. Hanley, Robert P. Heaney, M. Hassan Murad, and Connie M. Weaver

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

Commenting on Task Force **Draft** Recommendations

U.S. Preventive Services TASK FORCE

This fact sheet explains the Task Force's draft recommendation statement on vitamin D and calcium supplements to prevent cancer and fractures related to osteoporosis. It also tells you how you can send comments about the draft recommendation statement to the Task Force. Comments may be submitted from June 12 to July 10, 2012. The Task Force welcomes your comments.

iomm

Documento de posición sobre las necesidades y niveles óptimos de vitamina D

Sociedad Española de Investigación Ósea y del Metabolismo Mineral (SEIOMM) y Sociedades afines

Gómez de Tejada Romero MJ[1], Sosa Henríquez M[2], Del Pino Montes J[3], Jódar Gimeno E[4], Quesada Gómez JM[5], Cancelo Hidalgo MJ[6], Díaz Curiel M[7], Mesa Ramos M[8], Muñoz Torres M[9], Carpintero Benítez P[10], Navarro Ceballos C[11], Valdés y Llorca C[12], Giner Ruíz V[13], Blázquez Cabrera JA[14], García Vadillo JA[15], Martínez Rodríguez ME[16], Peña Arrebola A[16], Palacios Gil-Antuñano S[17]

Rev Osteoporos Metab Miner 2011 3;1:53-64

ESCEO

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)

Current Medical Research & Opinion Volume 29, Number 4 2013

Publicaciones de sociedades internacionales sobre vitamina D

IOM

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)

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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)

Current Medical Research & Opinion Volume 29, Number 4 2013

INSTITUTE OF MEDICINE

OF THE NATIONAL ACADEMIES

Advising the nation / Improving health

Dietary Reference Intakes for Calcium and Vitamin D

For more information visit www.iom.edu/vitamind

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

TABLE 1. Calcium and vitamin D dietary reference intakes by life stage

Life-stage group (age and gender)	Calcium: RDA (mg/d) (intake that covers needs of ≥97.5% of population)	Calcium: UL (mg/d)[a]	Vitamin D: RDA (IU/d) (intake that covers needs of ≥97.5% of population)	Vitamin D: Serum 25OHD level (ng/ml) (corresponding to the RDA)[b]	Vitamin D: UL (IU/d)[a]
1–3 yr (M+F)	700	2500	600	20	2500
4–8 yr (M+F)	1000	2500	600	20	3000
9–13 yr (M+F)	1300	3000	600	20	4000
14–18 yr (M+F)	1300	3000	600	20	4000
19–30 yr (M+F)	1000	2500	600	20	4000
31–50 yr (M+F)	1000	2500	600	20	4000
51–70 yr (M)	1000	2000	600	20	4000
51–70 yr (F)	1200	2000	600	20	4000
71+ yr (M+F)	1200	2000	800	20	4000
Pregnant or lactating (F)					
14–18 yr	1300	3000	600	20	4000
19–50 yr	1000	2500	600	20	4000
Infants					
0–6 months (M+F)	200[c]	1000	400[c]	20	1000
6–12 months (M+F)	260[c]	1500	400[c]	20	1500

Ross AC et al, JCEM 2011

Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

TABLE 3. Vitamin D intakes recommended by the IOM and the Endocrine Practice Guidelines Committee

Life stage group	IOM recommendations				Committee recommendations for patients at risk for vitamin D deficiency	
	AI	EAR	RDA	UL	Daily requirement	UL
Infants						
0 to 6 months	400 IU (10 μg)			1,000 IU (25 μg)	400–1,000 IU	2,000 IU
6 to 12 months	400 IU (10 μg)			1,500 IU (38 μg)	400–1,000 IU	2,000 IU
Children						
1–3 yr		400 IU (10 μg)	600 IU (15 μg)	2,500 IU (63 μg)	600–1,000 IU	4,000 IU
4–8 yr		400 IU (10 μg)	600 IU (15 μg)	3,000 IU (75 μg)	600–1,000 IU	4,000 IU
Males						
9–13 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
51–70 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
>70 yr		400 IU (10 μg)	800 IU (20 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
Females						
9–13 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
51–70 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
>70 yr		400 IU (10 μg)	800 IU (20 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
Pregnancy						
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
Lactation[a]						
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU

Holick MF, J Clin Endocrinol Metab, 2011

THE ENDOCRINE SOCIETY®

Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

En base a concentraciones circulantes de 25OHD

- **Deficiencia**: 25OHD ≤ 20 ng/ml
- **Insuficiencia**: 25OHD entre 21-29 ng/ml
- **Suficiencia**: 25OHD entre 30-100 ng/ml

Holick MF, J Clin Endocrinol Metab, 2011

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)

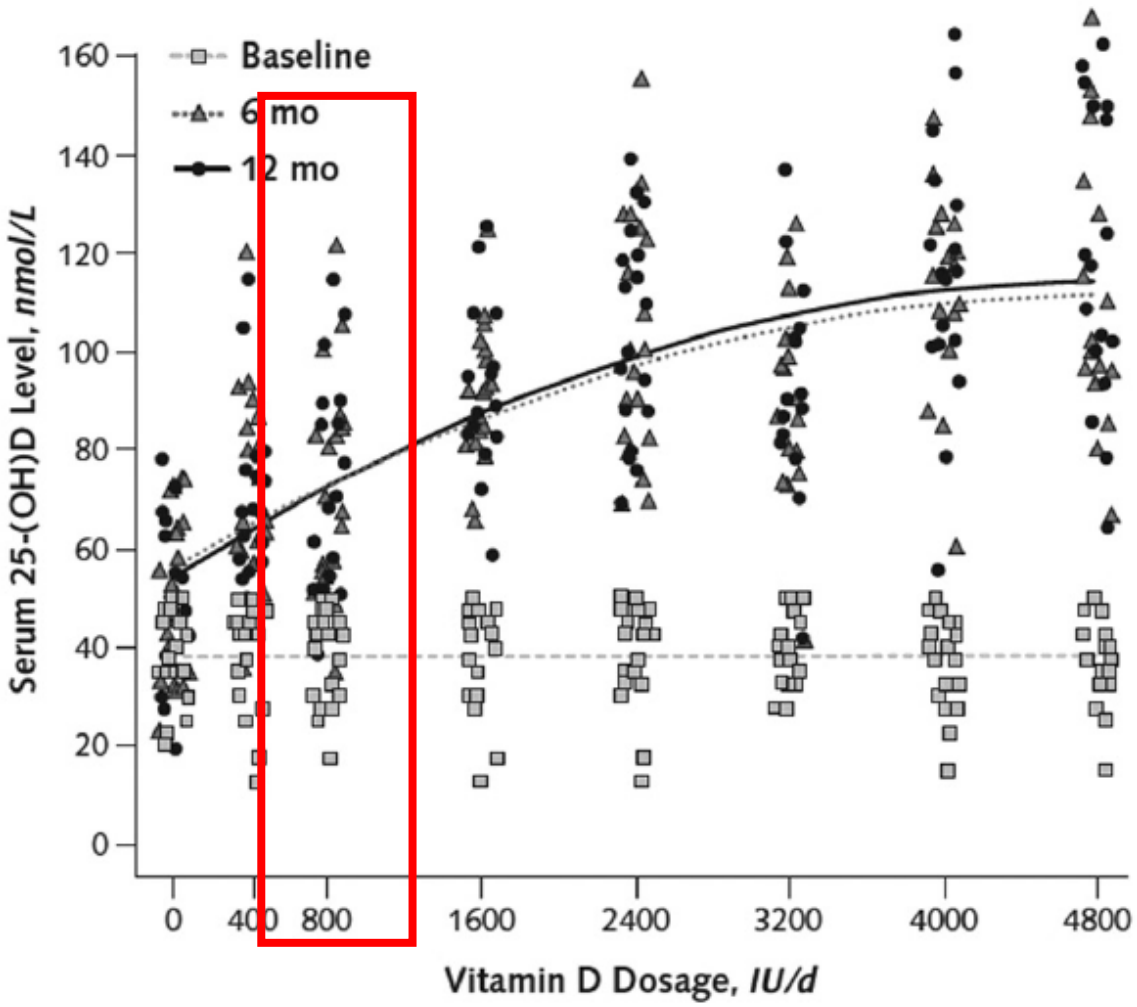
Current Medical Research & Opinion Volume 29, Number 4 2013

Table 2. Vitamin D (25-(OH)D) levels and their impact on bone health.

Definition	Serum 25-(OH) D level*	Impact on bone health
Vitamin D deficiency	<25 nmol/L	Mineralization defect
Vitamin D insufficiency	<50 nmol/L	Increased bone turnover and/or PTH
Vitamin D sufficiency	50 to 75 nmol/L	Neutral effect (bone turnover and PTH normalized), desirable benefits on fracture, falls, and mortality
	≥75 nmol/L	Desirable target in the fragile elderly due to optimal benefits on fracture, falls, and mortality
Upper limit of adequacy	125 nmol/L	Possibility of adverse effects above this level

*25 nmol/L is equivalent to 10 ng/mL, 50 nmol/L to <20 ng/mL, and 75 nmol/L to 30 ng/mL.

Relación entre ingesta de vitamina D3 y concentraciones séricas de de 25OHD



Gallagher JC et al, Ann Intern Med 2012

Fuentes de vitamina D

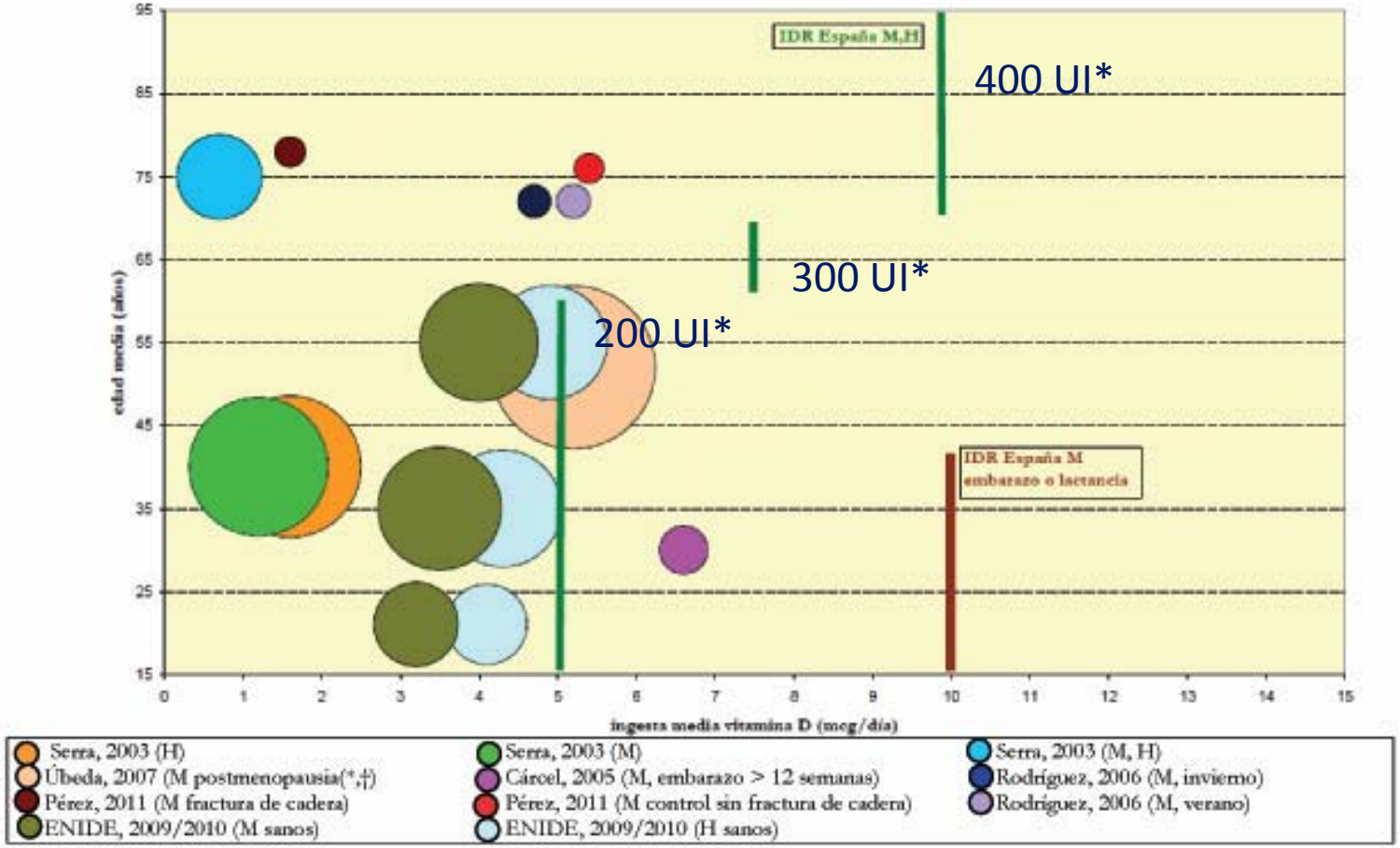
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D_3
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D_3 or D_2
Canned (3.5 oz)	About 300–600 IU of vitamin D_3
Sardines, canned (3.5 oz)	About 300 IU of vitamin D_3
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D_3
Tuna, canned (3.6 oz)	About 230 IU of vitamin D_3
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D_3
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D_2
Sun-dried (3.5 oz)	About 1600 IU of vitamin D_2
Egg yolk	About 20 IU of vitamin D_3 or D_2
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythemal dose)†	About 3000 IU of vitamin D_3

Fortified foods	
Fortified milk	About 100 IU/8 oz, usually vitamin D_3
Fortified orange juice	About 100 IU/8 oz vitamin D_3
Infant formulas	About 100 IU/8 oz vitamin D_3
Fortified yogurts	About 100 IU/8 oz, usually vitamin D_3
Fortified butter	About 50 IU/3.5 oz, usually vitamin D_3
Fortified margarine	About 430 IU/3.5 oz, usually vitamin D_3
Fortified cheeses	About 100 IU/3 oz, usually vitamin D_3
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D_3

Supplements	
Prescription	
Vitamin D_2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D_2) liquid supplements	8000 IU/ml
Over the counter	
Multivitamin	400 IU vitamin D, D_2, or D_3‡
Vitamin D_3	400, 800, 1000, and 2000 IU

Holick M. N Engl J Med 2007

Ingesta de vitamina D en población Española

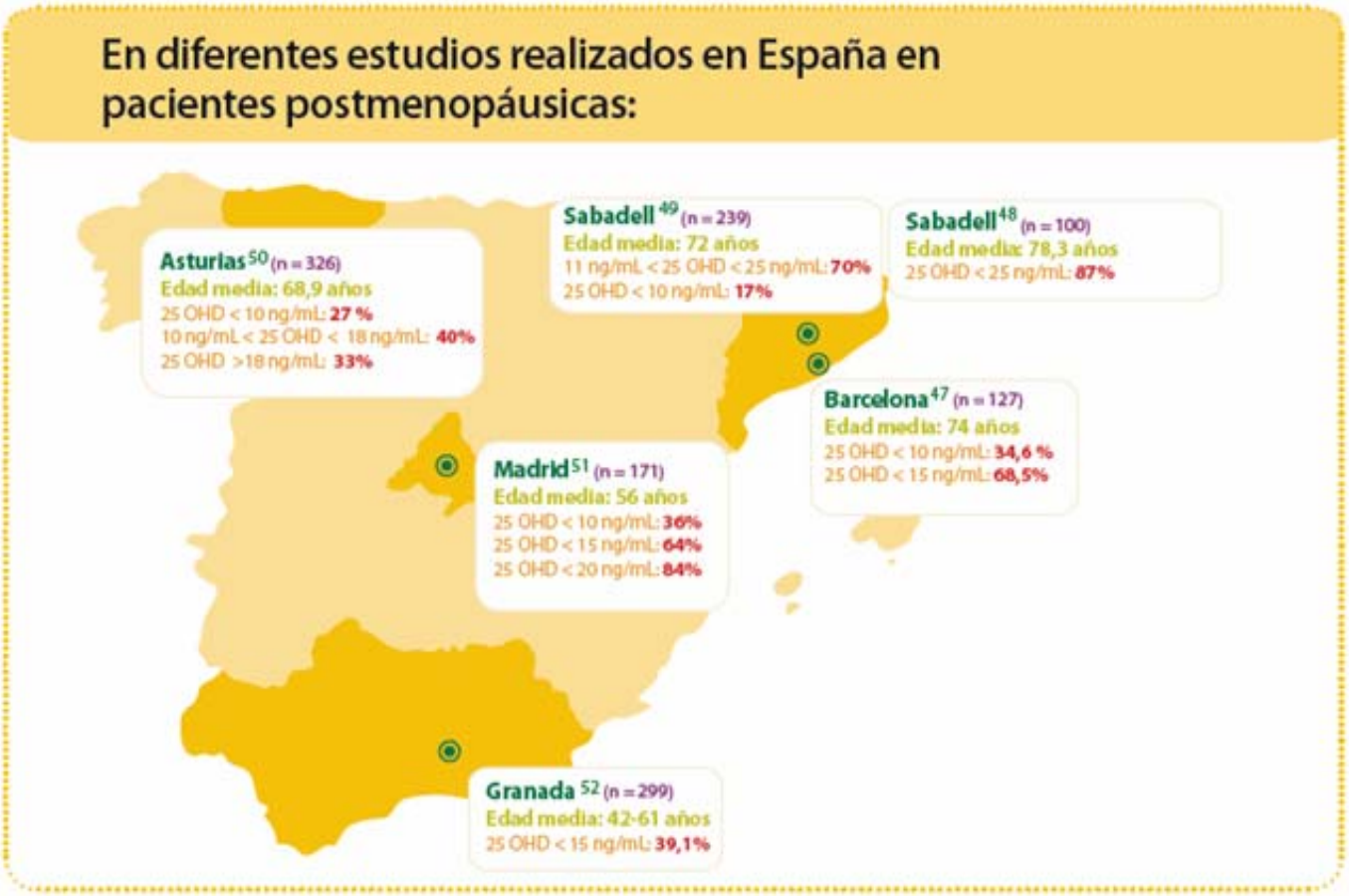


M: mujeres, H: hombres, mcg: microgramos, 1mcg vitamina D: 40 Unidades Internacionales, IDR española según referencia 20 (*): especifica

*IDR vit D, FESNAD 2010

Rev Esp Salud Pública 2012, Vol. 86, N.º 5

Niveles inadecuados de Vitamina D en diferentes estudios realizados en España



*Niveles inadecuados definidos como 25(OH)D sérica <30 ng/ml

47) González-Clemente et al. *Med Clin* 2001;113 (17):641-5. 48) Larrosa et al. *Med Clin* 2001;117:611-4. 49) Vaqueiro et al. *Med Clin* 2006;127(17):648-50. 50) Gómez Alonso et al. *Kidney Int* 2003;63(suppl85):S44-S48. 51) Aguado et al. *Osteoporos Int* 2000;11:739-44. 52) Mezquita-Raya et al. *Med Clin* 2002;119(3):85-9.

¿Como conseguir niveles óptimos de vitamina?

1. Alimentos naturales y exposición solar
2. Alimentos fortificados
3. Suplementos farmacológicos

Effect of daily intake of milk enriched with a high dose of vitamin D in healthy postmenopausal women: Preliminary results from a randomized, controlled and double-blind nutritional trial (The EFICALCIO Study)

Objetivos:

Determinar el efecto de la ingesta regular de una bebida láctea altamente enriquecida en vitamina D3 en mujeres postmenopáusicas sanas

Sujetos y Métodos:

Ensayo clínico con 480 mujeres postmenopáusicas (58.1± 4.8 años) aleatorizadas en 3 grupos que ingirieron 500 ml/día de una bebida láctea y seguidas durante 2 años:

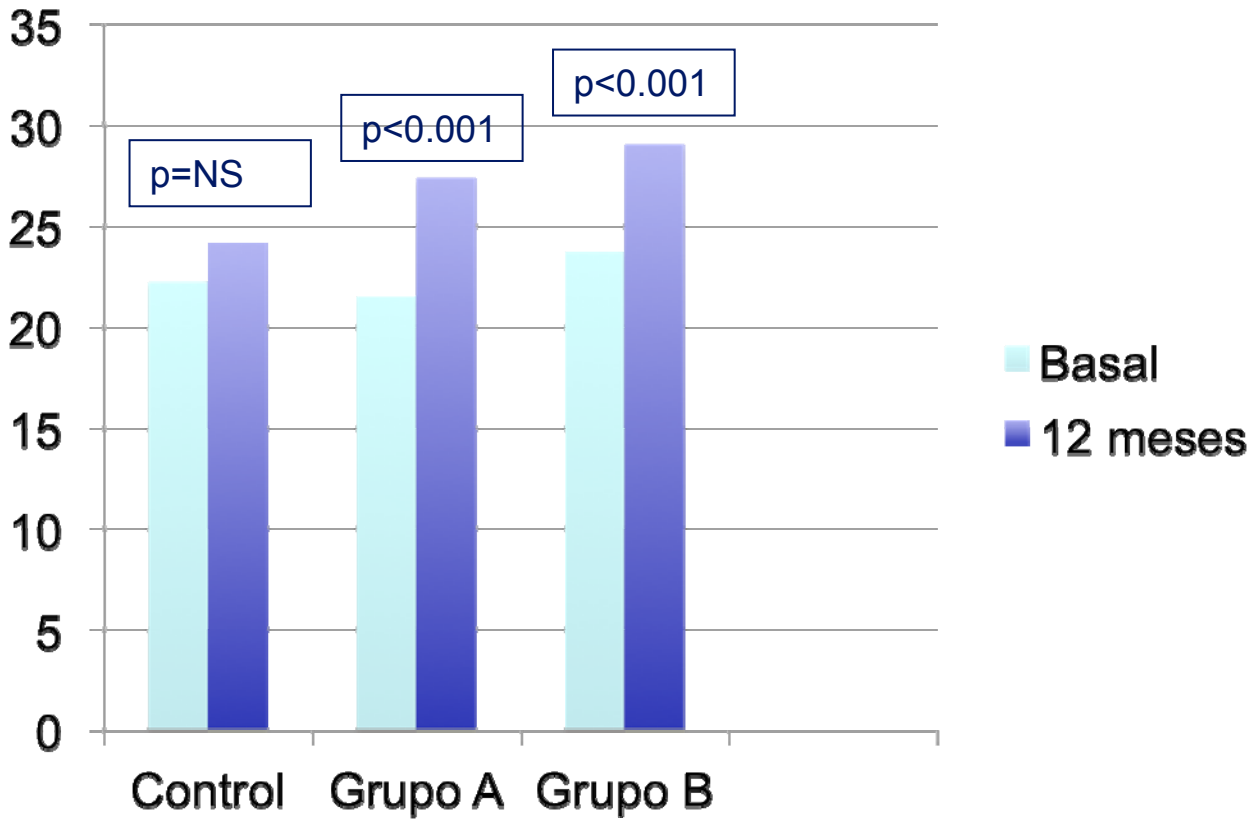
- Grupo Control: 0.75 ug/100 ml de Vitamina D3 (**150 UI/día**)
- Grupo A: 3 ug/100 ml de vitamina D3 (**600 UI/dia**)
- Grupo B: 3 ug/100 ml de vitamina D3 (**600 UI/dia**) + FOS (5 g/l)

biosearch life

Eficalcio Study Group 2014

Effect of daily intake of milk enriched with a high dose of vitamin D in healthy postmenopausal women: Preliminary results from a randomized, controlled and double-blind nutritional trial (The EFICALCIO Study)

Resultados preliminares: cambios en valores de 25OHD a los 12 meses

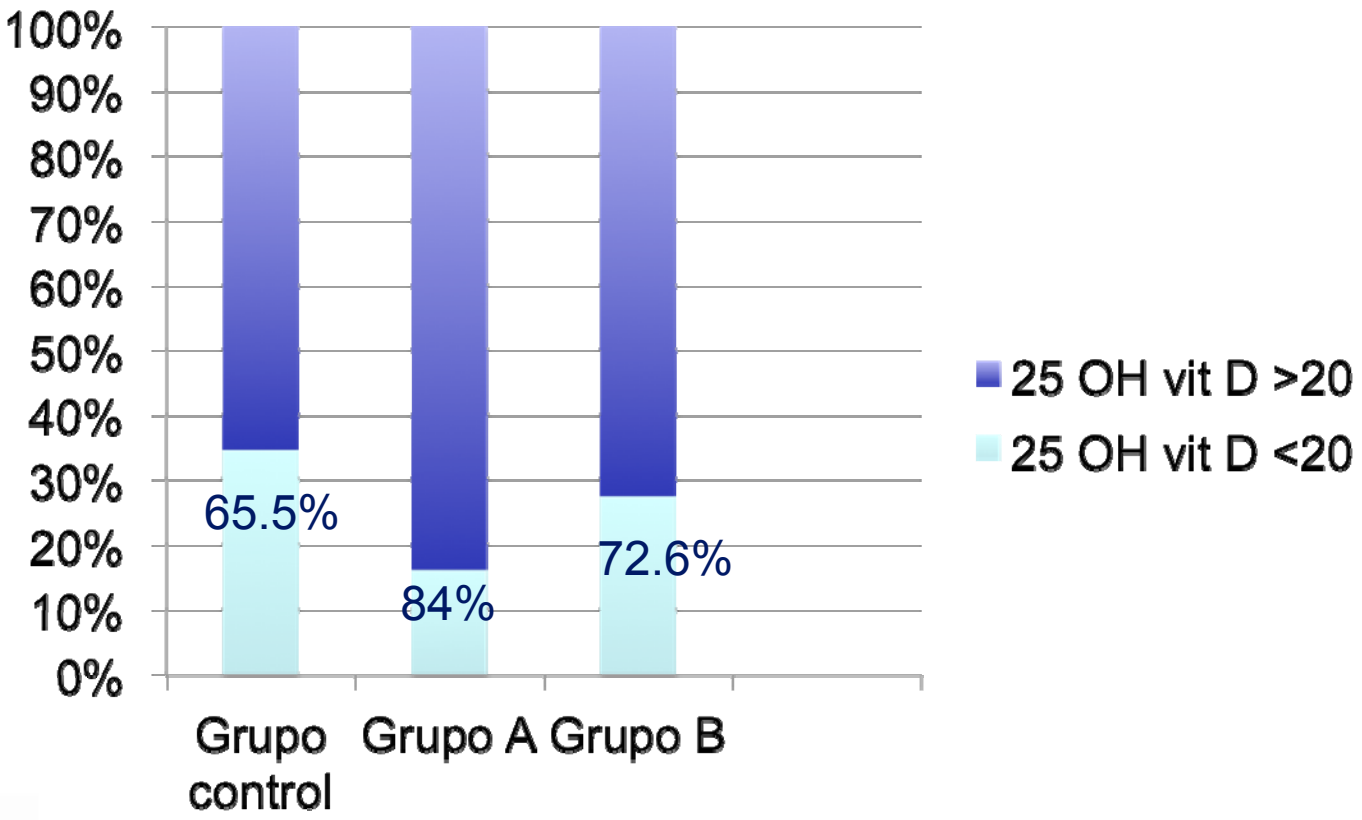


biosearch life

EFICALCIO Study Group 2014

Effect of daily intake of milk enriched with a high dose of vitamin D in healthy postmenopausal women: Preliminary results from a randomized, controlled and double-blind nutritional trial (The EFICALCIO Study)

Resultados preliminares: Porcentaje de mujeres que alcanzan valores de 25OHD > de 20 ng/ml



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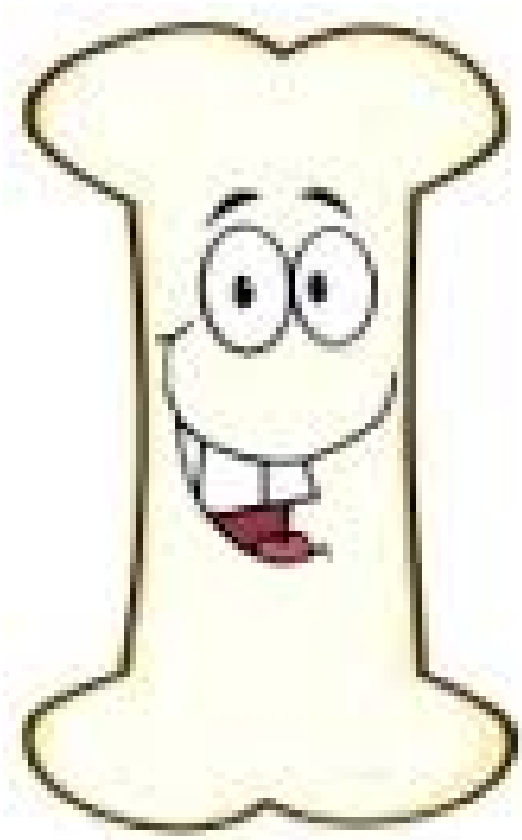
EFICALCIO Study Group 2014

Conclusiones

1. La optimización de los niveles de vitamina D es relevante para prevenir la fragilidad ósea y las caídas

2. Los potenciales beneficios extraóseos de la vitamina D deben ser confirmados mediante estudios apropiados

3. La intervención poblacional fomentando un estilo de vida saludable y el consumo de alimentos fortificados en vitamina D pueden representar una medida costo-efectiva



¡GRACIAS POR VUESTRA ATENCIÓN¡