Vitamina D – Calciferol
Antirraquítica

La luz del sol, la vitamina D y la salud: Una historia llena de luz, Holick, 2008
www.dnva.no/geomed/solarpdf/Nr_12_Holick.pdf

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Dpto de Nutrición y Ciencia de los Alimentos. Facultad de Farmacia. UCM.
https://www.ucm.es/nutricioncarbajal/ - https://www.ucm.es/innovadieta/ - https://www.ucm.es/innovadieta/v

Vídeos del Mooc de la Universidad de Wageningen (Holanda)
Nutrition and Health: Micronutrients and Malnutrition
https://courses.edx.org/courses/course-v1:WageningenX+NUTR102x+2T2017/course/

Animation: Absorption and metabolism of (pro)vitamin D
https://youtu.be/iyLfKNuG8Q8

Bibliografía

Resurrection of vitamin D deficiency and rickets, 2006 - https://www.jci.org/articles/view/29449
Vitamin D Is Not as Toxic as Was Once Thought: A Historical and an Up-to-Date Perspective, 2015 – https://www.mayoclinicproceedings.org/article/S0025-6196(15)00244-X/fulltext
Vitamin D: An overview of vitamin D status and intake in Europe, 2014 - https://onlinelibrary.wiley.com/doi/full/10.1111/nbu.12108
Comparative analysis of nutritional guidelines for vitamin D – www.sisdca.it/public/pdf/Guidelines-for-vit-D---Bouillon-2017.pdf
Dietary reference values for vitamin D -EFSA Journal 2016;14(10):4547 - https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4547
Nutripedia, Vitamina D - https://www.ucm.es/innovadieta/v

Vitamina D. Un poco de historia

siglo II aC - raquitismo

1650 - WHISTLER, GLISSON, De BOOT - descripción del raquitismo

siglo XIX - problema de salud pública (80-90% de los niños) Revolución industrial

RAQUITISMO Y EL NUTRIENTE		RAQUITISMO Y MEDIO AMBIENTE
PERCIVAL - aceite de hígado de bacalao	1782	
TROUSSEAU - raquitismo y osteomalacia	1865	
	1890	PALM - papel protector del sol
MELLANBY - raquitismo experimental carencia en la dieta = nutriente	1919	HULDSCHINSKY - fototerapia curativa "no es nutriente"
McCOLLUM - Descubre la vitamina D	1922	

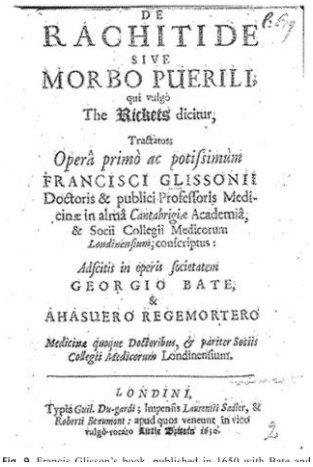
1918-19, Sir Edward Mellanby reproduce experimentalmente el raquitismo en perros por deficiencia nutricional alimentándolos con avena (vivían recluidos en el interior y, por tanto, no estaban expuestos al sol). Posteriormente curó la enfermedad añadiendo aceite de hígado de bacalao a la dieta. Estableció inequívocamente que el raquitismo estaba causado por la deficiencia de un componente traza presente en la dieta. En 1921 escribió: ***"la acción de las grasas en el raquitismo es debida a una vitamina u otro factor del alimento, probablemente idéntico a la vitamina soluble en grasa".***

History of the discovery of vitamin D and its active metabolites, 2014 - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3899558/
Vitamin D and health - a historical overview, 2011 - http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S1681-150X2011000200007

Vitamina D. Un poco de historia

1650 - WHISTLER, GLISSON, De BOOT - descripción del raquitismo

DISPUTATIO MEDICA
INAUGVRALIS,
DE
Morbo puerili Anglorum,
quem patrio idiômate indigenæ
vocant
The Rickets,
QVAM
Deo suppetias ferente,
Ex authoritate Nobilissimi Domini Rectoris Magnifici,
D. JOHANNIS POLYANDRI à KERCHOVEN
SS. Theologiæ Doctoris, ejusdemque Facultatis in Illustrissimâ Acad. Lugd. Bat. Professoris primarii,
Decreto Illustrissimæ Facultatis Medicæ, & Amplissimi Senatûs Academici consensu,
Pro Gradu Doctoratûs, summisque in Medicinâ Privilegiis
consequendis,
Discutiendam proponit
DANIEL WHISTLER, Anglo-Saxonicus-Orientalis.
Ad diem 18. *Octob. Horis & loco consuetis.*
LVGDVNI BATAVORUM,
Ex Officinâ
WILHEMI CHRISTIANI BOXII. 1643.



DE
RACHITIDE
SIVE
MORBO PUERILI
qui vulgò
The Rickets dicitur,
Tractatus
Operâ primò ac potissimùm
FRANCISCI GLISSONII
Doctoris & publici Professoris Medicinæ in almâ *Cantabrigiæ* Academiâ,
& Socii Collegii Medicorum
Londinensium; conscriptus:
Adscitis in operis societatem
GEORGIO BATE,
&
AHASUERO REGEMORTERO
Medicinæ quoque Doctoribus, & pariter Sociis Collegii Medicorum Londinensium.
LONDINI,
Typis *Guil. Du-gardi*; Impensis *Laurentii Sadler*, & *Roberti Beaumont*: apud quos venenunt in vico vulgò vocato Little Britain 1650.

Vitamina D. Un poco de historia

1925

alimentos irradiados ← HESS y WEINSTOCK → endógena = no esencial

PROVITAMINA (piel y alimentos) —luz UV→ VITAMINA

WINDAUS 1930 – se aísla 1959 – se sintetiza

ergosterol → ERGOCALCIFEROL – **1932**

D_2 (vegetal)

1936 – COLECALCIFEROL ← 7-dehidrocolesterol

D_3 (animal)

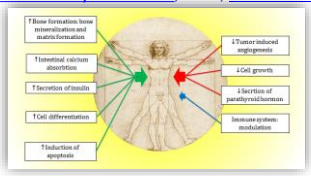
1964 - NORMAN - 3 metabolitos activos

1970 - HAUSSLER et al; FRASER y KODICEK - mecanismo de acción como hormona

1980 - receptores en numerosos órganos

2000s – se "redescubre": deficiencia y papel en la enfermedad crónica

Resurrection of vitamin D deficiency and rickets, 2006; The renaissance of vitamin D, 2014



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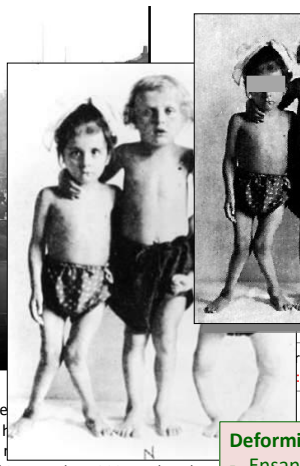
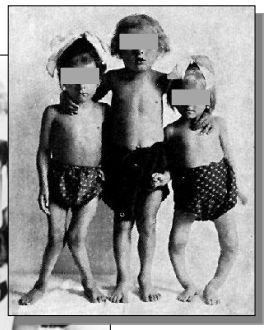
Vitamina D - antirraquítica





Knightsbridge, Westminster London 1870-1900

In **1890, Palm** concluded that rickets was cause
sunlight, because even though children in Britain h
sanitary conditions, they were more susceptible to r
because children in the tropics got plenty of sunshine. In the 1800s and early 1900s, children in smog-filled, crowded urban areas suffered from the 'rickets'.

>90% of children in larger European cities and
~80% of children in Boston suffered from the disease.

http://viewfinder.english-heritage.org.uk

David A Bender 2002 Taylor & Francis Ltd

rmineralization of bone
demineralization of bone

Deformidades óseas características:

- Ensanchamiento de las epífisis de los huesos largos y de las costillas (rosario raquítico costal)
- Curvatura de la columna, de huesos largos
- Debilidad y falta de tono muscular en extremidades

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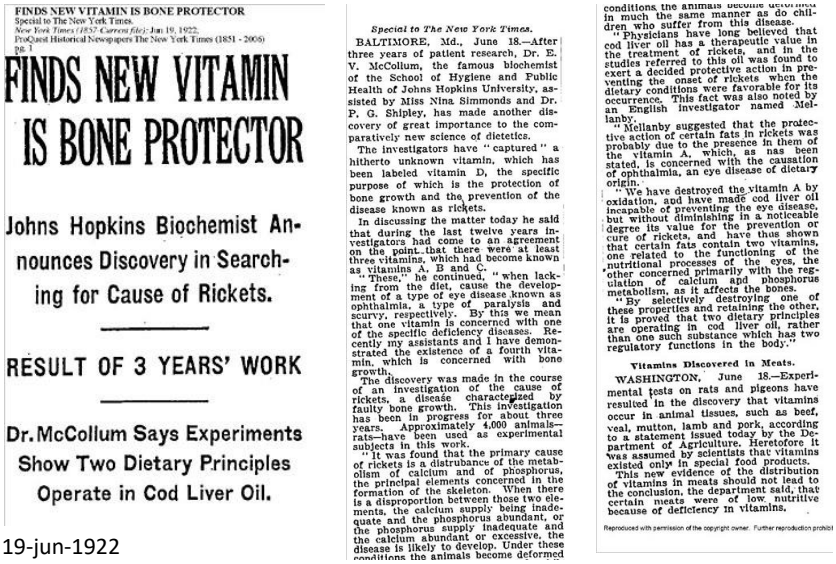
Vitamina D. Un poco de historia



FINDS NEW VITAMIN IS BONE PROTECTOR

Special to The New York Times.
New York Times (1857-Current file): Jun 19, 1922.
ProQuest Historical Newspapers The New York Times (1851 - 2006)
pg. 1

FINDS NEW VITAMIN IS BONE PROTECTOR

Johns Hopkins Biochemist Announces Discovery in Searching for Cause of Rickets.

RESULT OF 3 YEARS' WORK

Dr. McCollum Says Experiments Show Two Dietary Principles Operate in Cod Liver Oil.

Special to The New York Times.

BALTIMORE, Md., June 18.—After three years of patient research, Dr. E. V. McCollum, the famous biochemist of the School of Hygiene and Public Health of Johns Hopkins University, assisted by Miss Nina Simmonds and Dr. P. G. Shipley, has made another discovery of great importance to the comparatively new science of dietetics.

The investigators have "captured" a hitherto unknown vitamin, which has been labeled vitamin D, the specific purpose of which is the protection of bone growth and the prevention of the disease known as rickets.

In discussing the matter today he said that during the last twelve years investigators had come to an agreement on the point that there were at least three vitamins, which had become known as vitamins A, B and C.

"These," he continued, "when lacking from the diet, cause the development of a type of eye disease known as ophthalmia, a type of paralysis and scurvy, respectively. By this we mean that one vitamin is concerned with one of the specific deficiency diseases. Recently my assistants and I have demonstrated the existence of a fourth vitamin, which is concerned with bone growth.

"The discovery was made in the course of an investigation of the cause of rickets, a disease characterized by faulty bone growth. This investigation has been in progress for about three years. Approximately 4,000 animals—rats—have been used as experimental subjects in this work.

"It was found that the primary cause of rickets is a distrubance of the metabolism of calcium and of phosphorus, the principal elements concerned in the formation of the skeleton. When there is a disproportion between those two elements, the calcium supply being inadequate and the phosphorus abundant, or the phosphorus supply inadequate and the calcium abundant or excessive, the disease is likely to develop. Under these conditions the animals become deformed in much the same manner as do children who suffer from this disease.

"Physicians have long believed that cod liver oil has a therapeutic value in the treatment of rickets, and in the studies referred to this oil was found to exert a decided protective action in preventing the onset of rickets when the dietary conditions were favorable for its occurrence. This fact was also noted by an English investigator named Mellanby.

"Mellanby suggested that the protective action of certain fats in rickets was probably due to the presence in them of the vitamin A, which, as has been stated, is concerned with the causation of ophthalmia, an eye disease of dietary origin.

"We have destroyed the vitamin A by oxidation, and have made cod liver oil incapable of preventing the eye disease, but without diminishing in a noticeable degree its value for the prevention or cure of rickets, and have thus shown that certain fats contain two vitamins, one related to the functioning of the nutritional processes of the eyes, the other concerned primarily with the regulation of calcium and phosphorus metabolism, as it affects the bones.

"By selectively destroying one of these properties and retaining the other, it is proved that two dietary principles are operating in cod liver oil, rather than one such substance which has two regulatory functions in the body."

Vitamins Discovered in Meats.

WASHINGTON, June 18.—Experimental tests on rats and pigeons have resulted in the discovery that vitamins occur in animal tissues, such as beef, veal, mutton, lamb and pork, according to a statement issued today by the Department of Agriculture. Heretofore it was assumed by scientists that vitamins existed only in special food products.

This new evidence of the distribution of vitamins in meats should not lead to the conclusion, the department said, that certain meats were of low nutritive because of deficiency in vitamins.

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NYT, 19-jun-1922
https://www.nytimes.com/2009/09/15/health/15first.html

Vitamina D. Un poco de historia

1890 – **Theobald Adrian PALM** (1848-1928) – Papel protector del sol.
Theobald Palm and his remarkable observation: how the sunshine vitamin came to be recognized.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3277100/

1919 – **Sir Edward MELLANBY** (1884-1955) reproduce experimentalmente el raquitismo en perros por deficiencia nutricional.
https://www.annualreviews.org/doi/abs/10.1146/annurev.bi.25.070156.000245
https://royalsocietypublishing.org/doi/10.1098/rsbm.1955.0015

1922 – **Elmer V. McCOLLUM** (1879-1967) descubre la vitamina D.
http://www.nasonline.org/publications/biographical-memoirs/memoir-pdfs/mccollum-elmer.pdf

History of the discovery of vitamin D and its active metabolites
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3899558/

Brief history of rickets and of the discovery of vitamin D
https://www.ncbi.nlm.nih.gov/pubmed/17940496
http://repositorio.ul.pt/bitstream/10451/17693/1/Historia_Raquitismo.pdf

Vitamin D: part I; from plankton and calcified skeletons (500 million years ago) to rickets
https://www.ncbi.nlm.nih.gov/pubmed/29504055
Vitamin D: part II; cod liver oil, ultraviolet radiation, and eradication of rickets
https://www.ncbi.nlm.nih.gov/pubmed/30627846

Vitamina D. Un poco de historia

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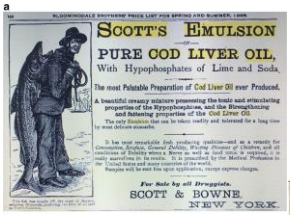

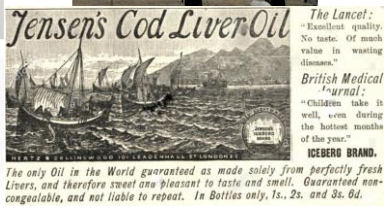

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1: Am J Clin Nutr 2008 Apr;87(4):1080S-6S.

https://www.ncbi.nlm.nih.gov/pubmed/18400738

Vitamin D deficiency: a worldwide problem with health consequences.

Holick MF, **Chen TC**.

Department of Medicine, Boston University School of Medicine, 715 Albany Street, M-1013, Boston, MA 02118, USA. mfholick@bu.edu

Vitamin D deficiency is now recognized as a pandemic. The major cause of vitamin D deficiency is the lack of appreciation that sun exposure in moderation is the major source of vitamin D for most humans. Very few foods naturally contain vitamin D, and foods that are fortified with vitamin D are often inadequate to satisfy either a child's or an adult's vitamin D requirement. Vitamin D deficiency causes rickets in children and will precipitate and exacerbate osteopenia, osteoporosis, and fractures in adults. Vitamin D deficiency has been associated with increased risk of common cancers, autoimmune diseases, hypertension, and infectious diseases. A circulating level of 25-hydroxyvitamin D of >75 nmol/L, or 30 ng/mL, is required to maximize vitamin D's beneficial effects for health. In the absence of adequate sun exposure, at least 800-1000 IU vitamin D3/d may be needed to achieve this in children and adults. Vitamin D2 may be equally effective for maintaining circulating concentrations of 25-hydroxyvitamin D when given in physiologic concentrations.

1 UI = 0,025 µg
800 – 1000 UI = 20-25 µg

Vitamina D
•The influence of dietary intake and sunlight exposure on the vitamin D status in an elderly Spanish group, SENECA, 1992

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Atherosclerosis. 2009 Jul;205(1):255-60. doi: 10.1016/j.atherosclerosis.2008.10.033. Epub 2008 Nov 11.

25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey

Jessica Kendrick[a], Giovanni Targher[b], Gerard Smits

[a] Division of Renal Diseases and Hypertension, University of Colorado Health Sciences Ce
[b] Section of Endocrinology, Department of Biomedical and Surgical Sciences, University o

25-Hydroxyvitamin D deficiency has been identified as a potential novel cardiovascular disease risk factor

ABSTRACT

Objective: Serum 25-hydroxyvitamin D [25(OH)D] levels are inversely as vascular disease (CVD) risk factors. However, the association between 25 has not been extensively examined in the general population.

Methods: We performed a cross-sectional analysis of data from the Thir Examination Survey (1988–1994) and examined the association between s lence of CVD in a representative population-based sample of 16,603 m older. Prevalence of CVD was defined as a composite measure inclusive of infarction or stroke.

Results: In the whole population, there were 1308 (8%) subjects with self- CVD had a greater frequency of 25(OH)D deficiency [defined as serum those without (29.3% vs. 21.4%; $p < 0.0001$). After adjustment for age, g measurement, physical activity, body mass index, smoking status, hyper density lipoprotein cholesterol, hypertriglyceridemia, low high-density kidney disease and vitamin D use, participants with 25(OH)D deficiency h CVD (odds ratio 1.20 [95% confidence interval (CI) 1.01–1.36; $p = 0.03$]).

Conclusions: These results indicate a strong and independent relationship of 25(OH)D deficiency with prevalent CVD in a large sample representative of the US adult population.

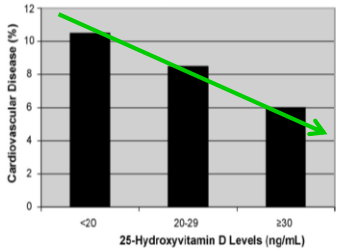


Fig. 1. Age-adjusted prevalence of clinical cardiovascular disease by levels of 25-hydroxyvitamin D.

https://www.ncbi.nlm.nih.gov/pubmed/19091317

Vitamina D – Calciferol
Antirraquítica

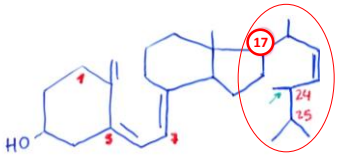
- Síntesis endógena
- "no nutriente" en algunas personas/circunstancias
- Esencial en la dieta si la exposición al sol es limitada o la capacidad de síntesis endógena está reducida.
- Pro-hormona
- Regula la expresión genética
- Necesidad de activación en hígado y riñón

Vitamina D

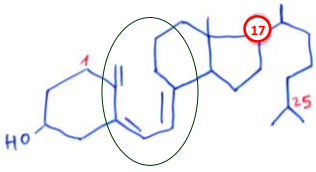
For most people, vitamin D is more correctly viewed as a hormone rather than a vitamin because sufficient amounts of it can be produced by the body. Provitamin D is synthesized in the skin from a derivative of cholesterol in a process that depends on ultraviolet light. With adequate sun exposure, no dietary intake of vitamin D is needed. The provitamin, whether produced in the skin or obtained from the diet, is metabolized in the liver and kidneys to yield 1,25(OH)2D (or calcitriol), the active hormonal form of vitamin D. 1,25(OH)2D is important for calcium absorption from the intestine and, with other hormones, it helps regulate bone metabolism. Vitamin D is found in fish oils and fortified milk. Vitamin D can be very toxic when taken in supplement form, especially in infancy, when an intake just three times or more than the Adequate Intake can be toxic. Anyone who feels a need to use a vitamin D supplement containing more than two times the Adequate Intake, such as an older person, should consult a physician first.

http://highered.mheducation.com/sites/0072287845/student_view0/chapter9/chapter_summary.html

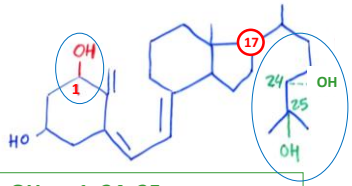
Vitamina D – Calciferol – vitámeros activos



Vitamina D2-Ergocalciferol
(vegetal)
Actividad vitamínica (AV): 50



Vitamina D3-Colecalciferol
(síntesis cutánea / animal)
(AV): 100



25(OH)D3-Calcidiol
(AV): 200-500

1,25(OH)$_2$D3-Calcitritol
(AV): 500-1.000

24,25(OH)$_2$D3
(AV): 200-500

OH en 1, 24, 25
Reconocimiento por receptores nucleares

Fuentes de vitamina D

Exógena

Alimentos
Alimentos fortificados
Suplementos

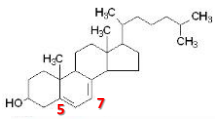
D_2 (Ergocalciferol) (vegetal)
D_3 (Colecalciferol) (animal)

Potencialmente tóxica
Fortificación indiscriminada
1930s

Síntesis endógena

Luz UV-B
290-320 nm

Lámparas



7-dehidrocolesterol

piel
60% epidermis
40% dermis

<20%

colecalciferol (D_3)

Dieta:
Fuente secundaria = 10%

Absorción: 50-80%

Óptimas condiciones
Fuente principal = 90%

Alrededor de un 80-90% de los requerimientos de vit D podrían ser cubiertos por la exposición solar en países soleados (Holick, 1996)

Adecuada exposición solar (≈20 min/día) → 10 µg/día

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Fuentes dietéticas de vitamina D (µg/100 g)

aceite de hígado de bacalao 250 - 750

pescados grasos 20 - 110

huevo (yema) 1 - 20

hígado 0.2 - 2.5

mantequilla 0.3 - 2,5

quesos 0.2 - 0.5

leche entera 0.01 - 0.12

Alimentos fortificados:
Leches, margarinas, zumos, batidos, cereales

Pérdidas cocinado: < 20%

	mcg de vitamina D/ 100g parte comestible
Superior a 100 mcg	
Anguila y angula	110
Entre 20 y 100 mcg	
Atún	25
Arenque	22.5
Congrio	22
Bonito	20
Entre 10 y 20 mcg	
Sardina	17
Caballa	16
Inferior a 10 mcg	
Anchoa	8.0
Yema de huevo	4.9
Bacalao fresco	1.3
Queso emmental	1.1
Mantequilla	0.76
Cordera, pierna y paletilla	0.70
Queso manchego fresco	0.23
Yogurt natural entero	0.07
Leche entera de vaca	0.03
Lomo de cerdo	0.01

Moreiras O, Carbajal A, Cabrera L, Cuadrado C.
Tablas de composición de alimentos. Guía de prácticas
Ed. Pirámide (Grupo Anaya, SA). 19ª edición revisada y ampliada. 2018

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Vitamina D
Dieta: Fuente secundaria

Consumo medio en España (1991)
76 g/día pescado

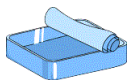
2.6 µg vit D
Pescados: 72% de la ingesta total
Resto: huevos, lácteos, otros.

ESPAÑA (2000)
Ingesta: 3,6 µg/día (36% de IR: 10 µg/día)

Para ingerir 10 µg vit D

Tendríamos que consumir

292 g/día de pescado
(ej. mezcla de
200 g sardinas y
100 g atún)



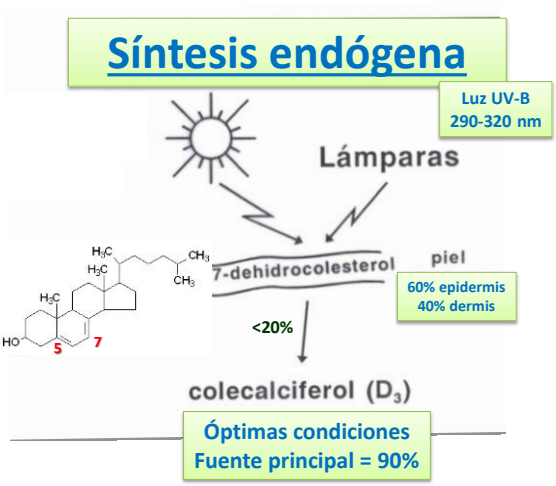
Fuentes de vitamina D

Exógena

Dieta:
Fuente secundaria = 10%

Síntesis endógena

Luz UV-B
290-320 nm

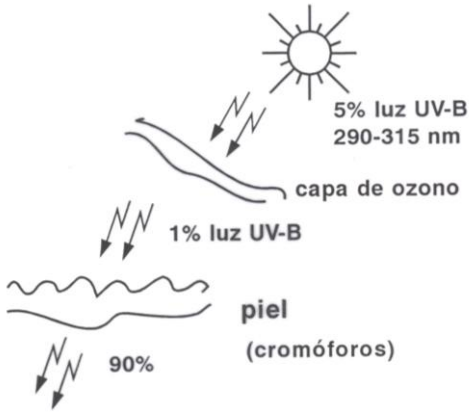


Óptimas condiciones
Fuente principal = 90%

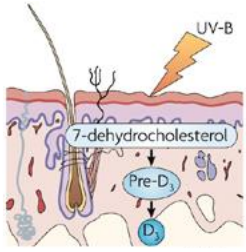
Adecuada exposición solar
(≈20 min/día)→ 10 µg/día

1 µg = 2.5 nmol
1 µg = 40 IU
1 ng/mL = 2.5 nmol/L

Síntesis cutánea



Tipo de luz



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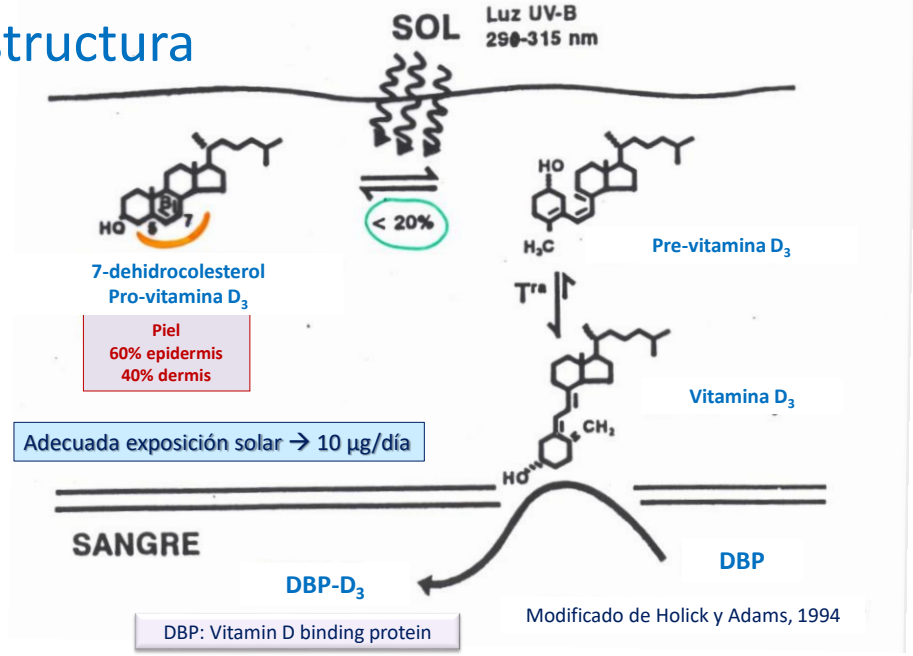
Estructura



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Síntesis cutánea

Ultraviolet Transmission and Vitamin-D Synthesis

In 1958 Beckemeier (*4*) reported that 1 square centimeter of white human skin synthesized up to 18 I.U. of vitamin D in 3 hours. Using this figure, we calculate that an antirachitic preventive dose of 400 I.U. per day can be synthesized by daily exposure of an area of skin approximately equal to that of the nearly transparent pink cheeks of European infants (about 20 square centimeters). Perhaps this explains why mothers in northern climates customarily put their infants out of doors for "some fresh air and sunshine" even in the middle of winter.

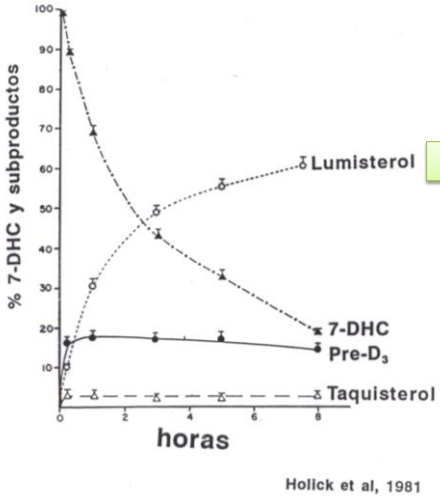
From this high rate of synthesis by only a small area of thin unpigmented skin, one can calculate the daily amount of vitamin D that would be synthesized at the equator by the skin of adults who exposed almost all their 1½ square meters (22,500 square centimeters) of body surface during the whole of a tropical day. Such a calculation shows that the skin of such individuals would synthesize up to 800,000 I.U. of vitamin D in a 6-hour period if the stratum corneum contained no pigment capable of filtering out the intense solar ultraviolet radiation.

Figure 1. An example of the wire cage fixed to the tenement window, so that babies can benefit from sunshine and fresh air. London, 1934 (Copywright 2014, reproduced with permission).

The renaissance of vitamin D, 2014

Loomis, W. F. Skin-pigment regulation of Vitamin-D biosynthesis in man. Science 1967;157, 501-506.
https://www.ncbi.nlm.nih.gov/pubmed/6028915
https://www.researchgate.net/publication/17157192_Loomis_W_F_Skin-pigment_regulation_of_Vitamin-D_biosynthesis_in_man_Science_157_501-506.

Síntesis cutánea



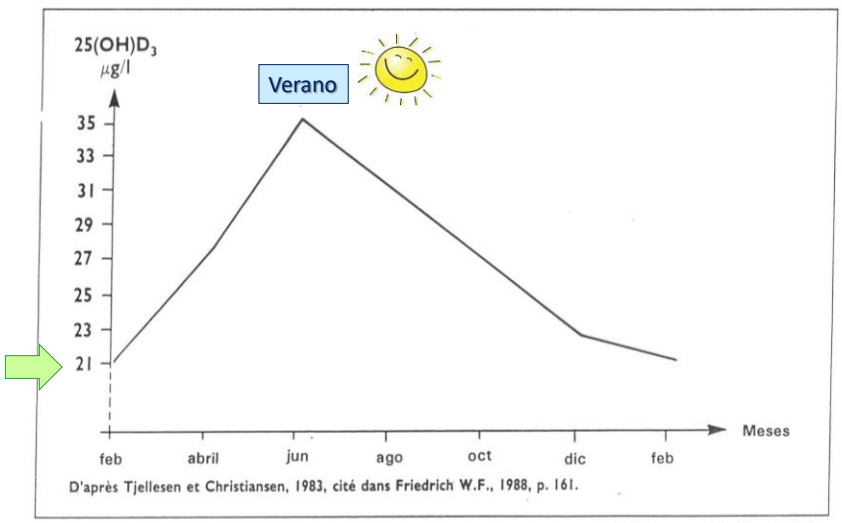
Holick et al, 1981

Inactivo

Control de la síntesis endógena
El exceso de irradiación solar incrementa poco la eficacia de la activación.
Sin embargo, se incrementa la foto-producción de formas biológicamente inactivas (ej. lumisterol, taquisterol, y 5,6-trans-vitamina D3).

Factores que influyen en la síntesis cutánea de vitamina D

- **Ambientales:**
  - Estación del año (pico verano)
  - Latitud (>paralelo 35º – no UVB en invierno, nov-feb)
  - Momento del día (60% se produce entre 10:00 y 14:00 h)
  - Nubes, sombra, contaminación, polvo, cristales, cortinas, ..
- **Individuales:**
  - Edad:
    - ↓ almacenes (↓ 25%) (↓ síntesis: ↓ 75%)
    - ↓ actividad física: menor exposición al sol
    - *(↓ hidroxilación renal)*
    - *(↓ ingesta)*
  - Pigmentación de la piel (melanina, raza negra, bronceado)
  - Grosor de la capa córnea
  - Cremas protectoras (F8 reduce la síntesis un 97%)
  - Estilo de vida:
    - No exposición al sol (trabajo, inmovilización)
  - Indumentaria (piel cubierta)



le Grusse y Watier, 1993

1990s ~~Deficiente <12.5 nmol/L~~ ~~Marginal 12.5-30~~ ~~Adecuado 30-60~~ ~~Óptimo >60 nmol/L~~

2015 Nuevo límite: deficiencia de vitamina D (<12 ng/mL o <30 nmol/L)
https://onlinelibrary.wiley.com/doi/full/10.1111/nbu.12108

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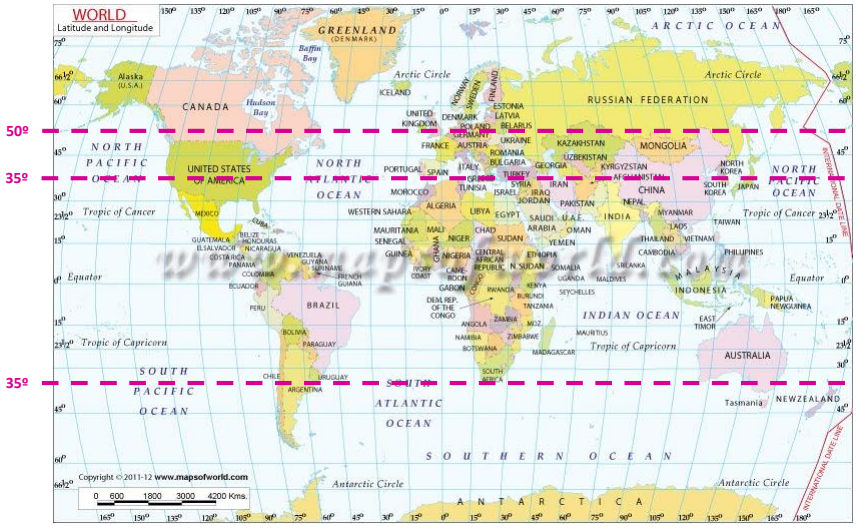
50º latitud norte: Frankfurt, Praga, Kiev, París



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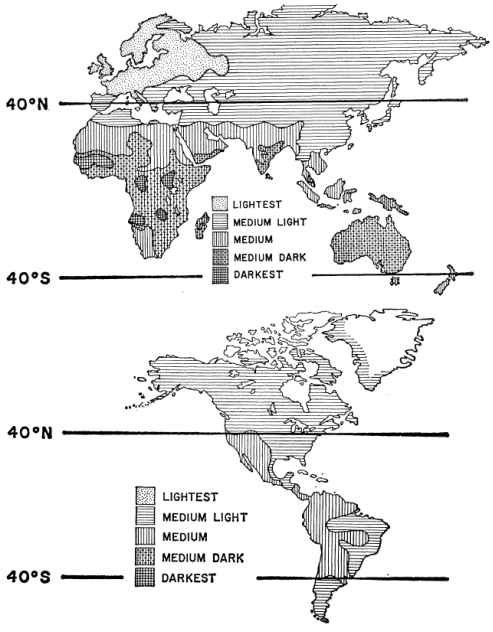

Fig. 2. Distribution of human skin color before 1492. [Adapted from Brace and Montague, *Man's Evolution* (Macmillan, New York, 1965), p. 272]

Loomis, W. F. Skin-pigment regulation of Vitamin-D biosynthesis in man. Science 1967;157, 501-506.
https://www.ncbi.nlm.nih.gov/pubmed/6028915
https://www.researchgate.net/publication/17157192_Loomis_W_F_Skin-pigment_regulation_of_Vitamin-D_biosynthesis_in_man_Science_157_501-506.

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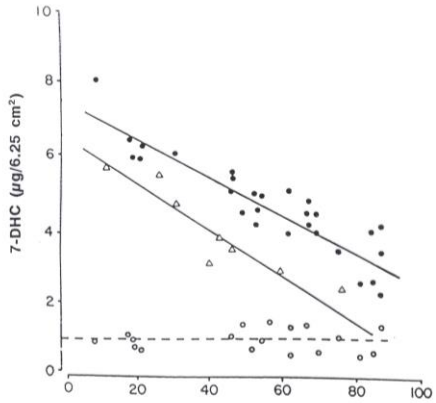
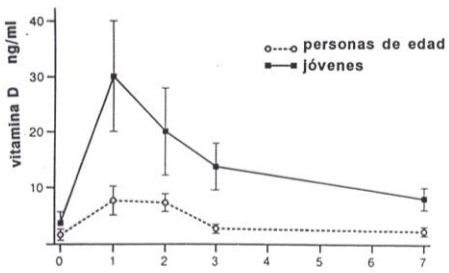
Edad



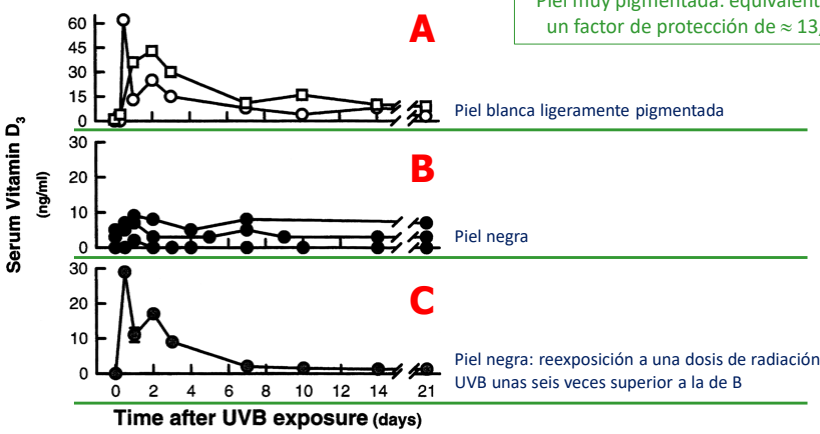
MacLaughlin et al, 1985



Holick et al, 1989

Pigmentación, melanina

Piel muy pigmentada: equivalente a un factor de protección de ≈ 13,4



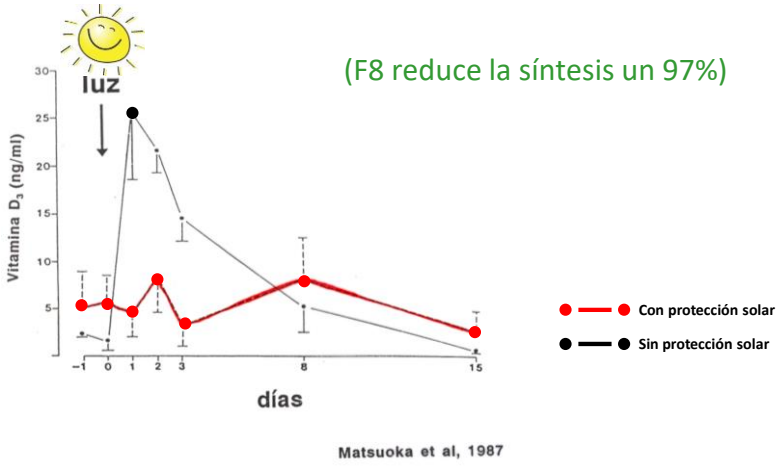
Piel blanca ligeramente pigmentada

Piel negra

Piel negra: reexposición a una dosis de radiación UVB unas seis veces superior a la de B

En **A**, cambios en las concentraciones séricas de vitamina D por el efecto de la radiación UVB en dos sujetos de piel blanca ligeramente pigmentada. En **B**, tres sujetos de piel negra después de una exposición del cuerpo total a una radiación UVB. En **C**, cambios sucesivos de la vitamina D circulante después de una reexposición de un sujeto negro a una dosis de radiación UVB unas seis veces superior que en B (Holick, 2004).

Efecto de las cremas protectoras



(F8 reduce la síntesis un 97%)

Matsuoka et al, 1987

Otros factores individuales

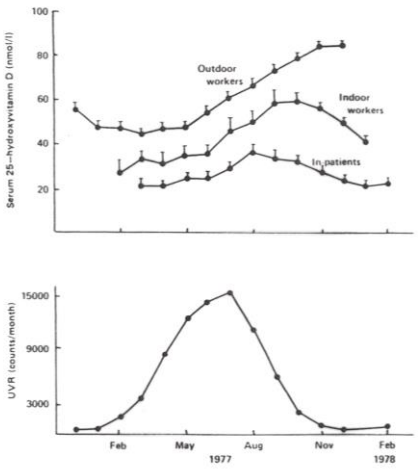
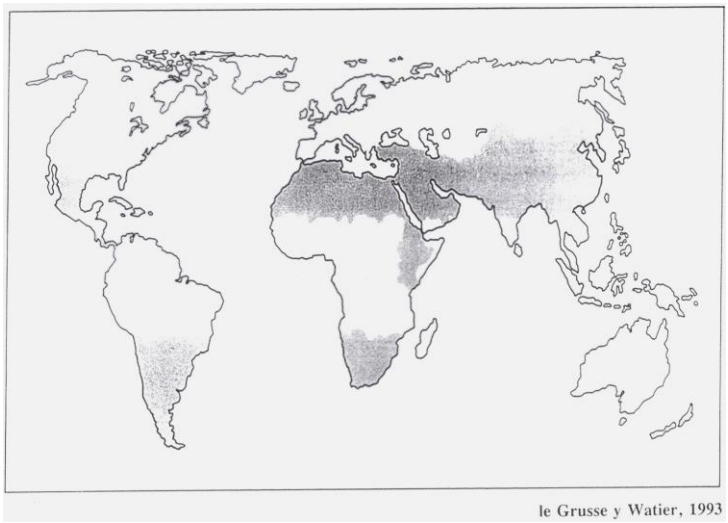


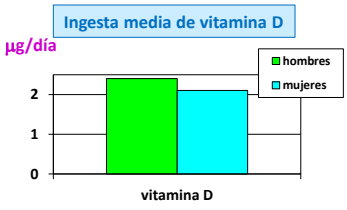
FIG. 1. Seasonal variation in serum 25-OHD levels in three groups of subjects: Parks Department staff (outdoor workers, mean age 41 yr), laboratory staff (indoor workers, mean age 32 yr), and elderly hospital inpatients (mean age 80 yr). Results are presented as means with *vertical bars* representing the SEM. The simultaneous measurements of the environmental UVR in the range 290 to 330 nm are also shown.

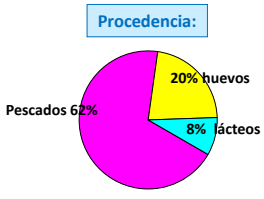
Raquitismo en el mundo

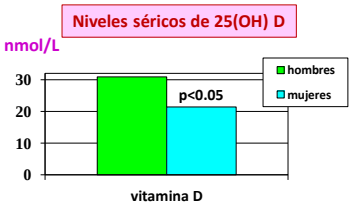


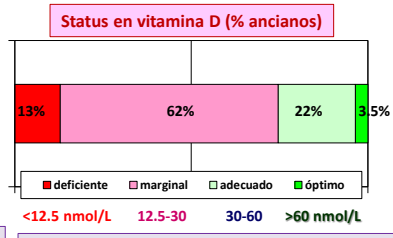
Vitamina D en personas de edad

SENECA: Survey in Europe on Nutrition and the Elderly, a Concerted Action
Estudio de cohortes longitudinal (>70 años)
The influence of dietary intake and sunlight exposure on the vitamin D status in an elderly Spanish group, SENECA, 1992
https://www.ucm.es/data/cont/docs/458-2018-10-04-Moreiras-col-1992-Internat-J-Vit-Nutr-Res-62-303-307-vit-D.pdf









2015 Nuevo límite deficiencia vitamina D (<30 nmol/L o <12 ng/mL)

Vitamina D en personas de edad

SENECA: Survey in Europe on Nutrition and the Elderly, a Concerted Action
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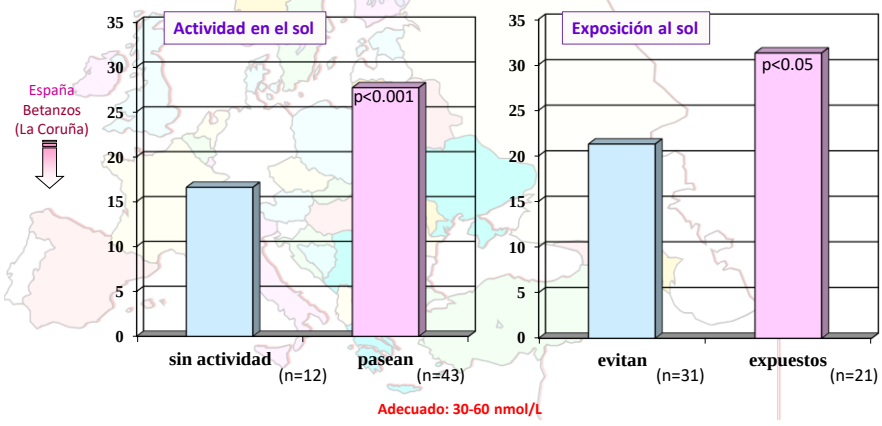
https://www.ucm.es/data/cont/docs/458-2018-10-04-Moreiras-col-1992-Internat-J-Vit-Nutr-Res-62-303-307-vit-D.pdf

Niveles séricos de vitamina D [25(OH)D; nmol/L]



Adecuado: 30-60 nmol/L

Vitamina D en personas de edad

SENECA: Survey in Europe on Nutrition and the Elderly, a Concerted Action
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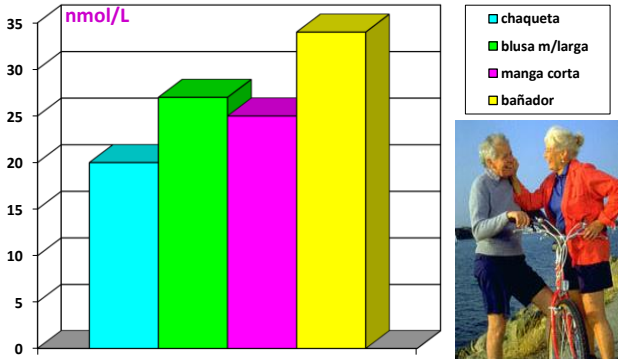
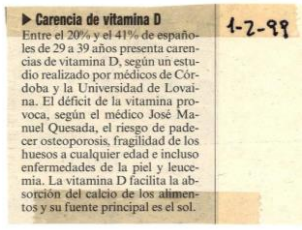
The influence of dietary intake and sunlight exposure on the vitamin D status in an elderly Spanish group, SENECA, 1992
https://www.ucm.es/data/cont/docs/458-2018-10-04-Moreiras-col-1992-Internat-J-Vit-Nutr-Res-62-303-307-vit-D.pdf

Niveles séricos de vitamina D [25(OH)D; nmol/L] según vestimenta





(Quesada y col., 1999)

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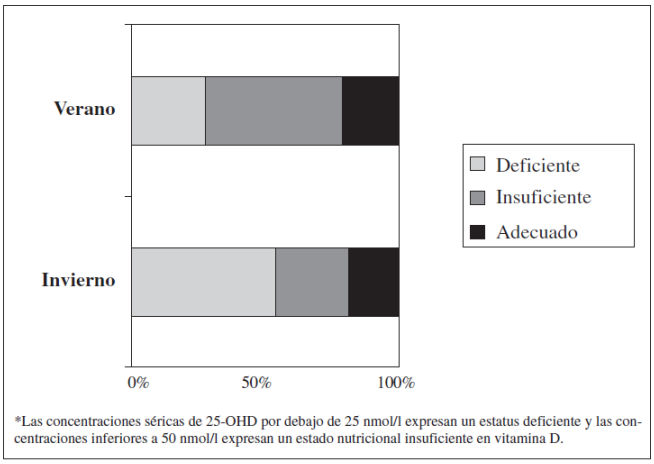
OPTIFORD. Ancianos españoles

(Rodríguez-Sangrador y col, 2008)
https://www.ncbi.nlm.nih.gov/pubmed/21892582
http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S0212-16112010000500012



*Las concentraciones séricas de 25-OHD por debajo de 25 nmol/l expresan un estatus deficiente y las concentraciones inferiores a 50 nmol/l expresan un estado nutricional insuficiente en vitamina D.

Fig. 2.—Distribución de la población según su estatus nutricional de vitamina D [n (%)].*

Table 1

Risk factors for low 25OHD concentrations

Risk factors that limit skin exposure to UVB rays
Latitudes above 40° north
Winter season
Exposure in early morning and evening (before 10 AM, after 4 PM)
Cloud cover and atmospheric pollution
Limited time spent outdoors
Customary dress that conceals large portions of the body
Sunscreen use
Dark skin pigmentation
Older age
Risk factors that limit dietary exposure to vitamin D
Low dietary intake of oily fish and egg yolks
Vegetarian diets
Low/no dietary intake of vitamin D fortified foods
Exclusive breastfeeding in infants
No intake of vitamin D supplements
Other risk factors that alter vitamin D supply or metabolism
Vitamin D status of infant depends on vitamin D status of mother during pregnancy
Low dietary calcium intake
Obesity
Genetic factors that affect vitamin D physiology and requirements
Poor renal function
Liver disease and cholestasis
Chronic disease
Malabsorption (coeliac, inflammatory bowel disease, cystic fibrosis, etc.)

Public Health Rev. 2017; 38: 19.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5809824/

Ingestas recomendadas

España:

[adultos: 2,5 µg/día (1980s) → 5 µg/día (1995)]
10 – 15 µg/día
60+ años: 20 µg/día

Holick, 2004
Personas que evitan el sol → 25 µg/día

EUROPA. EFSA has set dietary reference values (DRVs) for the intake of vitamin D. EFSA provides this advice to risk managers in European countries who use it for making recommendations to consumers.
The Panel on Dietetic Products, Nutrition and Allergies (NDA) defined an **adequate intake (AI) of 15 µg per day for healthy individuals over one year of age. This includes pregnant and lactating women. The DRVs for infants aged 7-11 months have been set at 10 µg per day.**
Dietary reference values for vitamin D | Vitamin D: EFSA sets dietary reference values - EFSA Journal 2016;14(10):4547
https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4547 - https://www.efsa.europa.eu/en/press/news/161028

The influence of dietary intake and sunlight exposure on the vitamin D status in an elderly Spanish group, SENECA, 1992
https://www.ucm.es/data/cont/docs/458-2018-10-04-Moreiras-col-1992-Internat-J-Vit-Nutr-Res-62-303-307-vit-D.pdf

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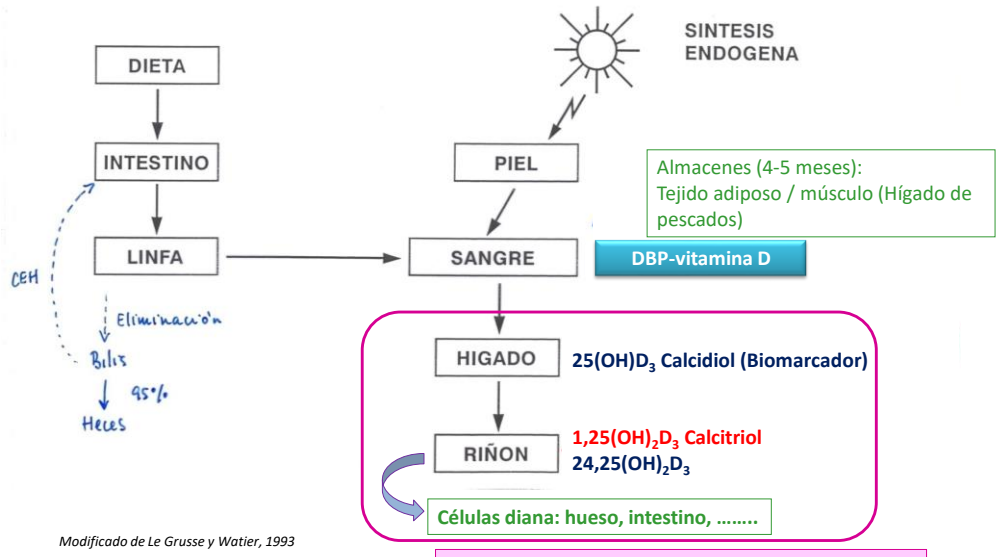
Metabolismo de la vitamina D



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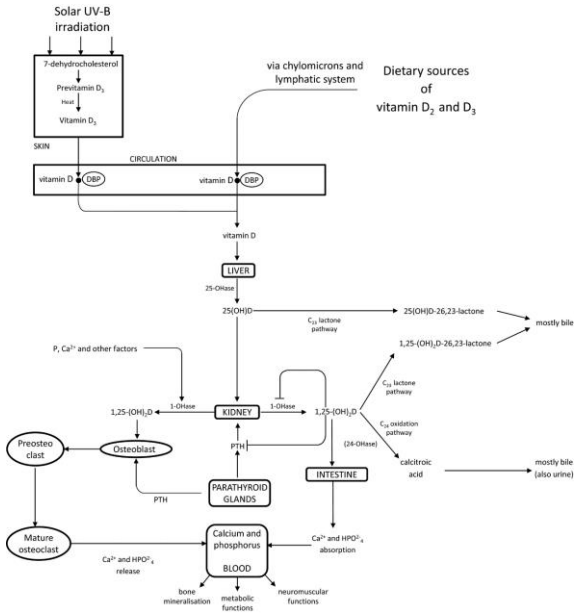
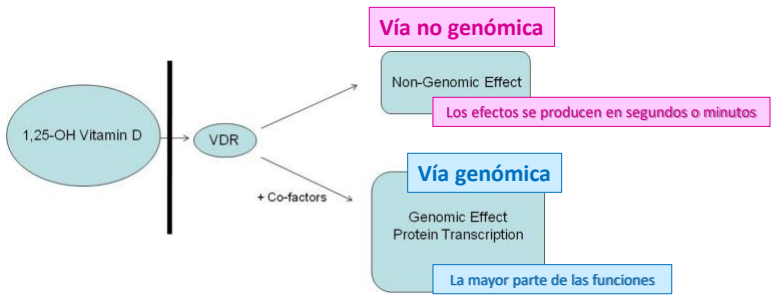


Dietary reference values for vitamin D - EFSA Journal 2016;14(10):4547
https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4547 - https://www.efsa.europa.eu/en/press/news/161028

Mecanismo de acción



Potential action of Vitamin D on cells VDR: Vitamin D Receptor

Asian J Sports Med. 2011 December; 2(4): 211–219.

Mecanismo de acción

Vía no genómica

A través del receptor de membrana, VDRm por mecanismos que se denominan transcaltaquia, 1,25(OH)$_2$D estimula el paso de calcio a través de los canales de Ca^{2+} de la membrana.

El transporte de calcio en la célula ocurre contra gradiente por lo que precisa energía y es llevado a cabo por proteínas ligadoras de calcio llamadas calbindinas.

Este mecanismo de acción por vía no genómica se ha observado en intestino, hígado, músculo, células paratiroides, riñón, ... Los efectos se producen en segundos o minutos.

Vía genómica

A través del receptor nuclear, VDRn. Este es el mecanismo más importante.

Receptores en prácticamente en todos los tejidos: cerebro, páncreas, hueso, músculo esquelético, riñón, intestino, piel, paratiroides, hipófisis, mama, linfocitos y monocitos.

La mayor parte de las funciones del calcitriol -homeostasis del calcio, diferenciación y proliferación celular- se producen por la interacción con este receptor y se desarrollan en minutos, horas e incluso días.

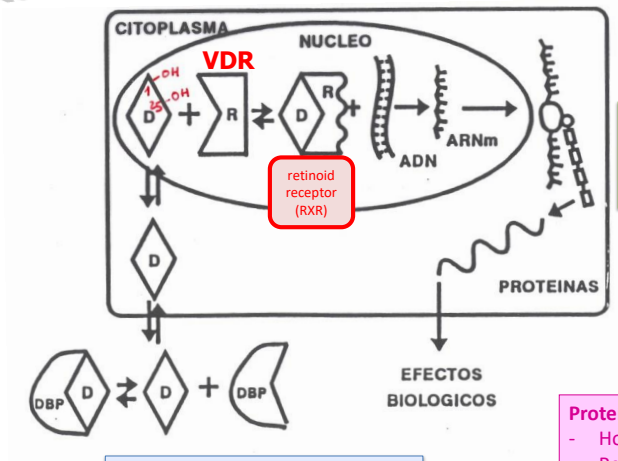
1,25(OH)2D, al igual que las hormonas esteroideas, se une a receptores nucleares (VDR) y se heterodimeriza principalmente con receptores retinoides (RXR).

Modificado de Rodríguez-Sangrador, Tesis Doctoral, UCM, 2006 - http://eprints.ucm.es/7430/1/T29549.pdf

Nutrigenómica

Primer ejemplo de nutrientes que modulan la expresión génica

Célula diana



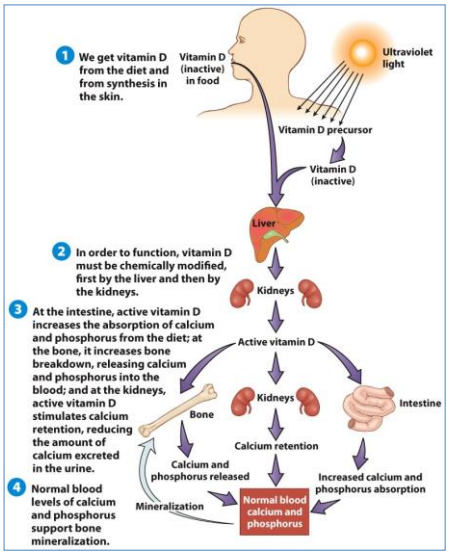
D=1,25(OH)$_2$D
R=receptor

> 30 tejidos con VDR (intestino, riñón, hueso, corazón, músculo, piel, ...)
> 50 genes regulados por vit. D
Regula la síntesis de:

CaBP = CALBINDINA
Fibronectina
Osteocalcina
c-fos
c-fms
Interleuquina-2
-Interferón
GM-CSF

Proteínas relacionadas con:
- Homeostasis calcio/fósforo
- Respuesta inmune
- Diferenciación/proliferación celular
- .....

Vitamin D receptor (VDR)
Polimorfismos (nutrigenética)



Visualizing Nutrition: Everyday Choices
Mary B. Grosvenor, Lori A. Smolin

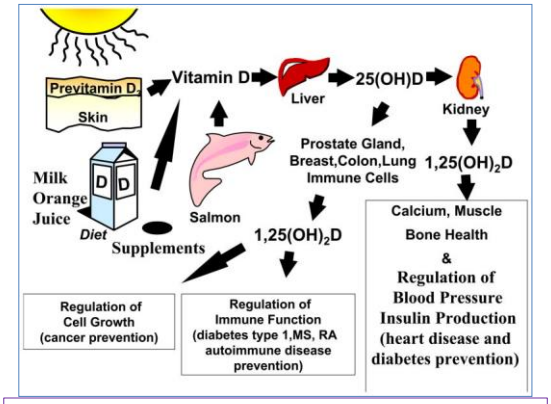


Figure 1. Once vitamin D is made in the skin or ingested from the diet, it travels to the liver where it is converted to 25-hydroxyvitamin D [25(OH)D]. This major circulating form of vitamin D is then converted in the kidneys to its active form 1,25-dihydroxyvitamin D [1,25(OH)$_2$D]. The renal production of 1, 25(OH)$_2$D is for regulating calcium and phosphorus metabolism. 25(OH)D is also converted in many tissues including prostate, colon, breast, lung, immune cells including monocytes and macrophages to 1, 25(OH)$_2$D. The local production of 1, 25(OH)$_2$D is to regulate cell growth, control immune function as well as affect up to 200 different genes responsible for health. Holick, Mol Aspects Med. 2008 December; 29(6): 361–368.

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Funciones de 1,25(OH)$_2$-D

- **Homeostasis de Ca y P** —evita→ Raquitismo, Osteomalacia, Osteoporosis
  - . Aumenta la absorción **intestinal** de Ca y P
  - . Moviliza los almacenes de Ca y P del **hueso**
  - . Aumenta la reabsorción de Ca y P a nivel **renal**

PTH
CT

pool sanguíneo

mineralización del hueso

Ppal efecto biológico de calcitriol:
Mantenimiento de niveles séricos de Ca

Raquitismo:
Precipita osteopenia, osteoporosis y fracturas en etapa adulta

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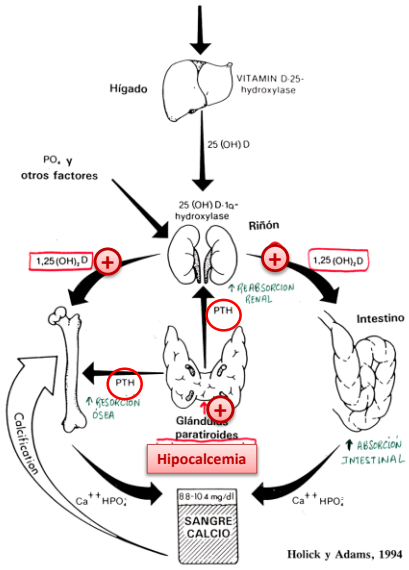
Vitamina D y economía del Ca



Hipocalcemia	↑ PTH ↓ [fosfato] → ↑ 1,25 $(OH)_2D_3$	↑ Calcemia
Hipercalcemia	↑ CT	↓ Calcemia

Trabaja en combinación con otros nutrientes y hormonas:

- Vit. A, vit. C, vit. K
- PTH y CT
- Colágeno
- Ca, P, Mg, fluoruro

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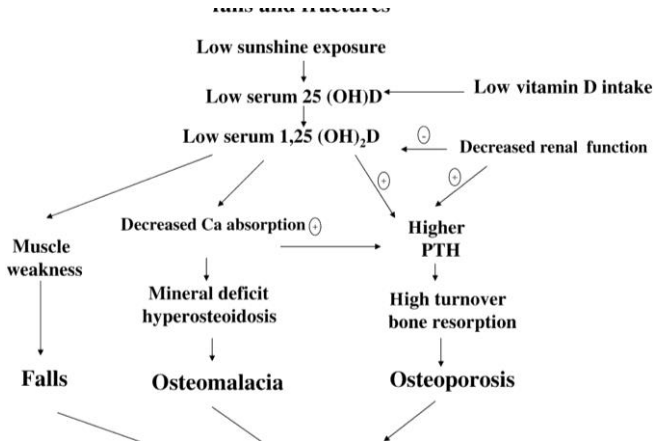

FIGURE 1. The pathophysiologic pathways from vitamin D deficiency to osteoporosis, osteomalacia, falls, and fracture.
Lips and van Schoor (2011). - https://www.bprcem.com/article/S1521-690X(11)00041-8/fulltext

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(Brandi, 2010)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3213838/

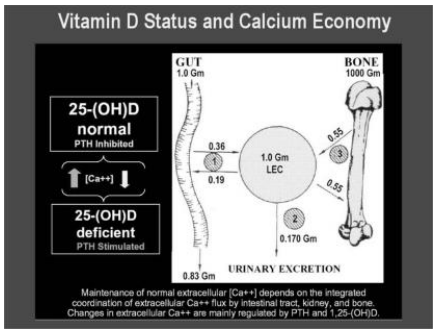
Biomarkers

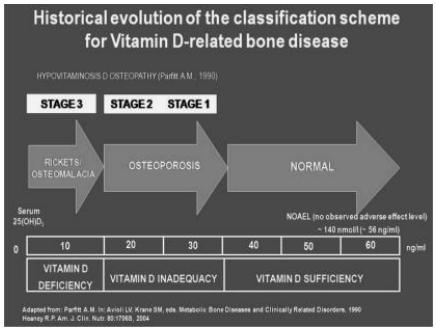
- Plasma/serum concentration of 25(OH)D
- Free serum 25(OH)D concentration
- Plasma/serum 1,25(OH)2D concentration
- **Serum parathyroid hormone (PTH) concentration**

The Panel considers that serum PTH concentration is not a biomarker of vitamin D intake, as serum PTH is also influenced by, e.g. serum calcium and phosphate concentrations and other factors. The Panel also considers that serum PTH concentration in healthy subjects is not a useful biomarker for vitamin D status as assessed by serum 25(OH)D concentration.

The Panel considers that serum 25(OH)D concentration can be used as a biomarker of vitamin D intake in a population with low exposure to UV-B irradiation (from sunlight, Section 2.3.1), and of vitamin D status at population level. The Panel notes that, due to the high variability in 25(OH)D measurements obtained with different analytical methods (Section 2.4.1), comparison of results from different studies as well as to reference range values has to be done with caution.

EFSA Journal 2016;14(10):4547
https://efsa.onlinelibrary.wiley.org/doi/10.2903/j.efsa.2016.4547





Funciones (2)

- Glándula mamaria: Regulación del Ca de la leche
- Transporte de Ca a través de la placenta
- Regulación del Ca en músculo

- Diferenciación y crecimiento celular (piel)
- Inhibición de la proliferación celular (cél. tumorales)
- Regulación de la función inmune
- Secreción de insulina (páncreas)
- Síntesis y secreción de hormonas de tiroides y paratiroides
- Regulación de la presión arterial
- Inhibición de la producción de interleucinas e inmunoglobulinas por linfocitos activados
- Diferenciación de células precursoras de monocitos
- .....

Atherosclerosis. 2009 Jul;205(1):255-60. doi: 10.1016/j.atherosclerosis.2008.10.033. Epub 2008 Nov 11.

25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey

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[b] Section of Endocrinology, Department of Biomedical and Surgical Sciences, University o

25-Hydroxyvitamin D deficiency has been identified as a potential novel cardiovascular disease risk factor

ABSTRACT

Objective: Serum 25-hydroxyvitamin D [25(OH)D] levels are inversely as vascular disease (CVD) risk factors. However, the association between 25 has not been extensively examined in the general population.

Methods: We performed a cross-sectional analysis of data from the Thir Examination Survey (1988–1994) and examined the association between s lence of CVD in a representative population-based sample of 16,603 me older. Prevalence of CVD was defined as a composite measure inclusive of s infarction or stroke.

Results: In the whole population, there were 1308 (8%) subjects with self- CVD had a greater frequency of 25(OH)D deficiency [defined as serum 2 those without (29.3% vs. 21.4%; $p < 0.0001$). After adjustment for age, g measurement, physical activity, body mass index, smoking status, hyper density lipoprotein cholesterol, hypertriglyceridemia, low high-density kidney disease and vitamin D use, participants with 25(OH)D deficiency h CVD (odds ratio 1.20 [95% confidence interval (CI) 1.01–1.36; $p = 0.03$]).

Conclusions: These results indicate a strong and independent relationship of 25(OH)D deficiency with prevalent CVD in a large sample representative of the US adult population.

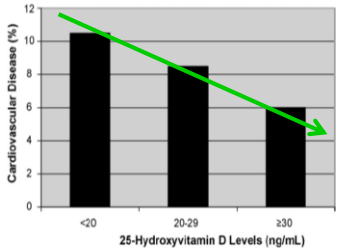


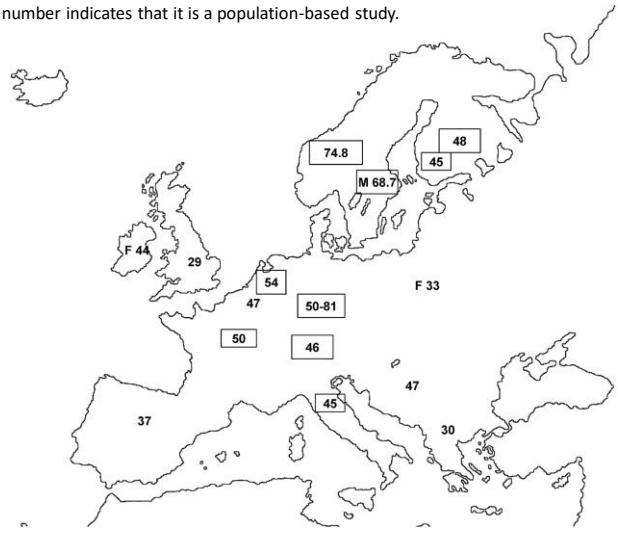
Fig. 1. Age-adjusted prevalence of clinical cardiovascular disease by levels of 25-hydroxyvitamin D.

https://www.ncbi.nlm.nih.gov/pubmed/19091317

Grupos de población en riesgo

- *Personas mayores*
- *de países poco soleados*
- *con alta melanización*
- *que permanecen en interiores*
- *que usan protectores solares*
- *de raza negra que viven en zonas templadas*
- *obesas ("secuestración" en tej. adiposo)*
- *con alteraciones gastrointestinales (malabsorción), hepáticas, renales*
- *Fármacos (glucocorticoides, anticonvulsivantes, ..)*

Fig. 1. **Mean serum 25(OH)D levels in Europe**. The data come from different studies.[14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28] A rectangle around the number indicates that it is a population-based study.



Worldwide vitamin D status. Natasja M. van Schoor, Paul Lips. Best Practice & Research Clinical Endocrinology & Metabolism. Volume 25, Issue 4, Pages 671-680 (August 2011) DOI: 10.1016/j.beem.2011.06.007 - https://www.bprcem.com/article/S1521-690X(11)00071-6/fulltext

Ingestas recomendadas (IR)

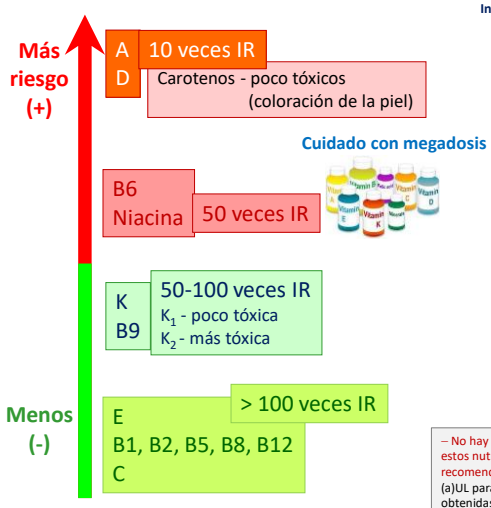
Tabla 2. Ingestas diarias recomendadas de energía y nutrientes para la población española
En: Moreiras O, Carbajal A, Cabrera L, Cuadrado C. Tablas de composición de alimentos. Ediciones Pirámide (Grupo Anaya, SA). 18ª edición. 2016. REVISADAS 2015

Categoría Edad (años)	Energía (1) (2)	Proteína (3)	Ca	Fe	I	Zn	Mg	K	P	Se	Tiamina (4)	Riboflavina (4)	Equivalentes de niacina (4) (5)	Vitamina B_6	Folato (6)	Vitamina B_{12}	Vitamina C	Vitamina A: éq. de retinol (7)	Vitamina D (8)	Vitamina E (9)	Vitamina K
	kcal	g	mg	mg	µg	mg	mg	mg	mg	µg	mg	mg	mg	mg	µg	µg	mg	µg	µg	mg	µg
Niños y niñas																					
0-6 meses	650	14	400	7	35	3	60	800	300	10	0,3	0,4	4	0,3	40	0,3	50	450	10	6	2
7-12 meses	950	20	525	7	45	5	85	700	250	15	0,4	0,6	6	0,5	60	0,3	50	450	10	6	2,5
1-3 años	1.250	23	600	7	55	10	125	800	400	20	0,5	0,8	8	0,7	100	0,9	55	300	15	6	30
4-5 años	1.700	30	700	9	70	10	200	1.100	500	20	0,7	1	11	1,1	200	1,5	55	300	15	7	55
6-9 años	2.000	36	800	9	90	10	250	2.000	700	30	0,8	1,2	13	1,4	200	1,5	55	400	15	8	55
Hombres																					
10-12	2.450	43	1.300	12	125	15	350	3.100	1.200	40	1	1,5	16	1,6	300	2	60	1.000	15	10	60
13-15	2.750	54	1.300	15	135	15	400	3.100	1.200	40	1,1	1,7	18	2,1	400	2	60	1.000	15	11	75
16-19	3.000	56	1.300	15	145	15	400	3.500	1.200	50	1,2	1,8	20	2,1	400	2	60	1.000	15	12	120
20-39	3.000	54	1.000	10	140	15	350	3.500	700	70	1,2	1,8	20	1,8	400	2	60	1.000	15	12	120
40-49	2.850	54	1.000	10	140	15	350	3.500	700	70	1,1	1,7	19	1,8	400	2	60	1.000	15	12	120
50-59	2.700	54	1.000	10	140	15	350	3.500	700	70	1,1	1,6	18	1,8	400	2	60	1.000	15	12	120
60 y más	2.400	54	1.200	10	140	15	350	3.500	700	70	1	1,4	16	1,8	400	2	60	1.000	20	12	120
Mujeres																					
10-12	2.300	41	1.300	18	115	15	300	3.100	1.200	45	0,9	1,4	15	1,6	300	2	60	800	15	10	60
13-15	2.500	45	1.300	18	115	15	330	3.100	1.200	45	1	1,5	17	2,1	400	2	60	800	15	11	75
16-19	2.300	43	1.300	18	115	15	330	3.500	1.200	50	0,9	1,4	15	1,7	400	2	60	800	15	12	90
20-39	2.300	41	1.000	18	110	15	330	3.500	700	55	0,9	1,4	15	1,6	400	2	60	800	15	12	90
40-49	2.185	41	1.000	18	110	15	330	3.500	700	55	0,9	1,3	14	1,6	400	2	60	800	15	12	90
50-59	2.075	41	1.200	10	110	15	300	3.500	700	55	0,8	1,2	14	1,6	400	2	60	800	15	12	90
60 y más	1.875	41	1.200	10	110	15	300	3.500	700	55	0,8	1,1	12	1,6	400	2	60	800	20	12	90
Gestación (2.ª mitad)	+250	+15	1.300	18	+25	20	+120	3.500	700	65	+0,1	+0,2	+2	1,9	600*	2,2	80	800	15	+3	90
Lactancia	+500	+25	1.300	18	+45	25	+120	3.500	700	75	+0,2	+0,3	+3	2	500	2,6	85	1.300	15	+5	90

* Primera y segunda mitad de la gestación

https://www.ucm.es/data/cont/docs/458-2018-01-26-IR-Tablas-Moreiras-col-2016-web.pdf

Vitaminas: márgenes de seguridad



Ingesta Máxima Tolerable [Tolerable Upper Intake Levels (UL)]

Nutriente	UL/día
Vitamina A	3000 µg
Carotenoides	–
Vitamina D	50 µg (2000 UI)
Vitamina E (a) (b)	1000 mg
Vitamina K	–
Vitamina B1	–
Vitamina B2	–
Vitamina B6	100 mg
Niacina (a)	35 mg
Folato de alimentos	–
Ác. fólico sintético (a)	1000 µg
Vitamina B12	–
Biotina	–
Colina	3,5 g
Ácido pantoténico	–
Vitamina C	2000 mg

– No hay información suficiente para establecer de momento UL para estos nutrientes. En estos casos, la ingesta de cantidades superiores a las recomendadas debe hacerse con mayor precaución.
(a)UL para vitamina E, niacina y folato se aplica a las formas sintéticas obtenidas a partir de suplementos, alimentos fortificados o a ambos.
(b)Como alfa-tocoferol: se aplica a cualquier suplemento de alfa-tocoferol.

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Toxicidad de vitamina D

- No toxicidad a partir del sol
- Riesgo con suplementos y alimentos fortificados

- Hipercalcemia
- Calcificación de tejidos blandos (riñón, corazón, vasos sanguíneos, pulmones, ..)
- Riesgo de muerte

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DE
RACHITIDE,
SIVE
MORBO PUERILI,
TRACTATUS;
Opera primo ac Potissimum
FRANCISCI GLISSONII Doctoris,
& publici Professoris Medicinæ in Alma Cantabrigia Academia, & Socii Collegii Medicorum Londinensium, conscriptus:
Adjicitur in operis Societatem
GEORGII BATE,
& ANASUERO REGEMORTERO,
Medicinæ quinque Doctoribus, & pariter Socia Collegii Medicorum *Londinensium*.
Editio tertia, priori adhuc auctior longe, & emendatior.
CORNELII DRIEHUYSEN,
&
FELICIS LOPEZ.

Niño negro con raquitismo. 1938, Wadesboro, Carolina del Norte, USA.
Fotografía de M. Wolcott, Farm Security Administration. The Library of Congress, USA

http://milksci.unizar.es/bioquimica/temas/vitamins/vitaminad.html

Curiosidades

Hobbit villains hobbled by "vitamin D deficiency (Los villanos de "El Hobbit" (Tolkien, 1937) cojeando por "la deficiencia de vitamina D")

http://www3.imperial.ac.uk/newsandeventspggrp/imperialcollege/newssummary/news_13-12-2013-16-45-46
The hobbit — an unexpected deficiency. Joseph A Hopkinson, Nicholas S Hopkinson. Med J Aust 2013; 199 (11): 805-806.
https://www.mja.com.au/journal/2013/199/11/hobbit-unexpected-deficiency