Ubier Gómez

Médico y Toxicólogo Clínico de la Universidad de Antioquia de Medellín.

Profesor de Farmacología y Toxicología pre y posgrado de la Universidad de Antioquia.

Vicepresidente de la Asociación Colombiana de Toxicología Clínica

Toxicólogo Clínica CES de Medellín.

Farmacoeconomía, Universidad Jorge Tadeo Lozano.

Gestión en Salud, Universidad de la Sabana.

Farmacología Clínica y Farmacoepidemiología, Universidad de Antioquia.

Galardonado con la distinciones: “Excelencia Docente” y “Egresado Honorífico” de la Universidad de Antioquia.

96 publicaciones en libros y revistas nacionales e internacionales en el campo de la farmacología y toxicología.

El speaker ha recibido remuneración de las siguientes casas farmacéuticas por asesorías, capacitaciones y conferencias, en el campo de la farmacología y la toxicología:

Abbie

Abbott

Aztra Zeneca

Bayer

Biopass

Euroetika

Glaxo Smith Kline

Grunenthal

Heel

Janssen Cilag

MSD

Mundipharma

Novartis

Ophtha

Pfizer

Recordati

Roche

Sandoz

Sanofi-Aventis

Schering-Plough

Histotal: Usos y controversias en el uso de la Vitamina D

Ubier Eduardo Gómez Calzada M.D.

Toxicólogo Clínico

Profesor Departamento de Farmacología y Toxicología

Facultad de Medicina

Universidad de Antioquia

LIME
LABORATORIO INTEGRADO DE MEDICINA ESPECIALIZADA

UNIVERSIDAD DE ANTIOQUIA
1803
Facultad de Medicina

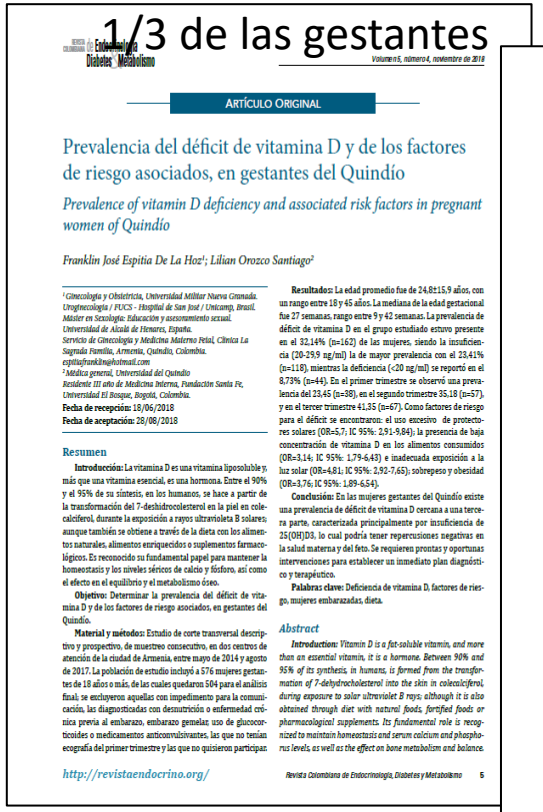
Referencia Histórica

- Adolf Windaus:
  - Aisló las tres formas de la vitamina D:
    - D1 y D2 derivadas de esteroles vegetales irradiados.
    - D3 derivada de piel irradiada.
  - Premio Nobel de Química en 1928.
- En 1971 se reclasificó la vitamina D como la hormona que controla el metabolismo del calcio.

https://www.researchgate.net/publication/263426096

Epidemiología del Déficit de Vitamina D en Colombia

1/3 de las gestantes

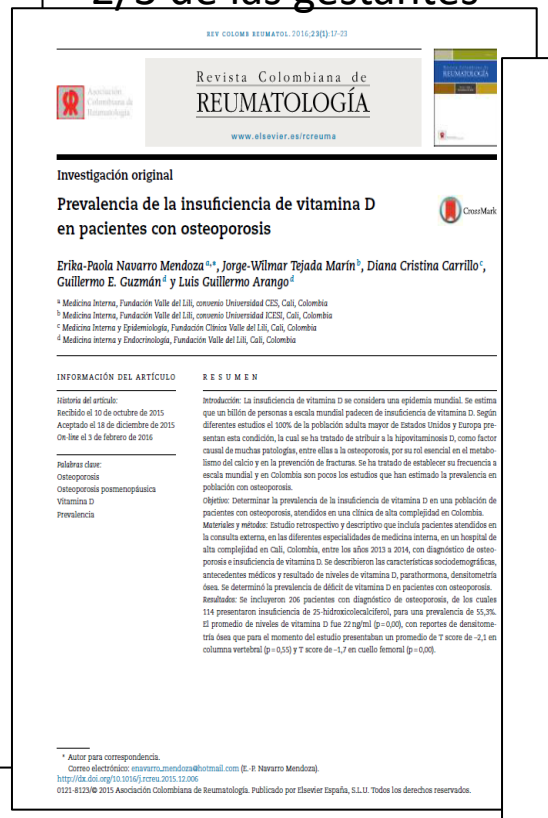


Prevalencia del déficit de vitamina D y de los factores de riesgo asociados, en gestantes del Quindío

Prevalence of vitamin D deficiency and associated risk factors in pregnant women of Quindío

Quindío, n=576

2/3 de las gestantes



Revista Colombiana de REUMATOLOGÍA

Prevalencia de la insuficiencia de vitamina D en pacientes con osteoporosis

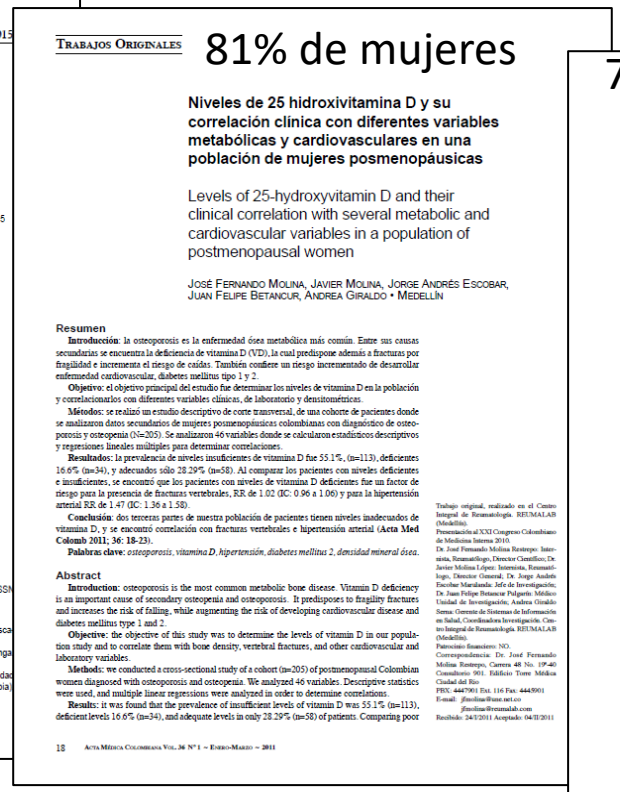
Valle de Lilly, n=846

55,3% de mujeres

MASA OSEA REDUCIDA E HIPOVITAMINOSIS D EN MUJERES POSMENOPAUSICAS: ESTUDIO EXPLORATORIO EN VILLAVICENCIO, COLOMBIA. 2012-2013

Villa Vicencio, n=106

81% de mujeres

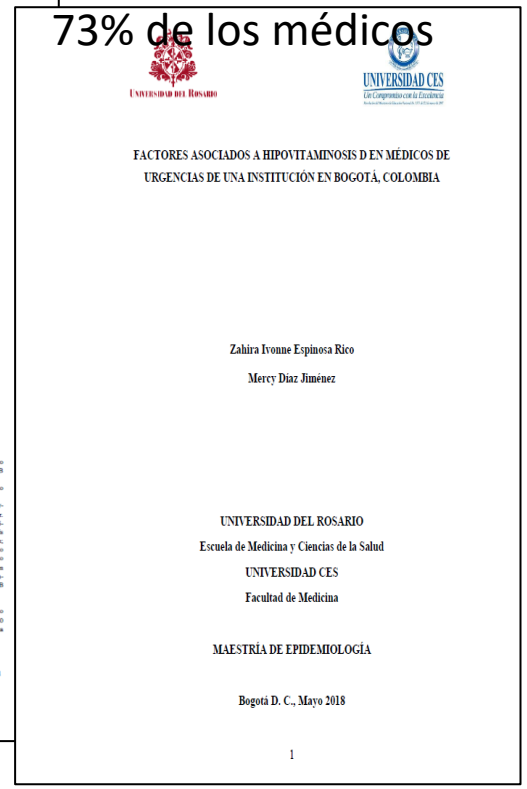


Niveles de 25 hidroxivitamina D y su correlación clínica con diferentes variables metabólicas y cardiovasculares en una población de mujeres posmenopáusicas

Levels of 25-hydroxyvitamin D and their clinical correlation with several metabolic and cardiovascular variables in a population of postmenopausal women

Medellín, n=205

73% de los médicos



FACTORES ASOCIADOS A HIPOVITAMINOSIS D EN MÉDICOS DE URGENCIAS DE UNA INSTITUCIÓN EN BOGOTÁ, COLOMBIA

Zahira Ivonne Espinosa Rico

Mercy Diaz Jiménez

UNIVERSIDAD DEL ROSARIO

Escuela de Medicina y Ciencias de la Salud

UNIVERSIDAD CES

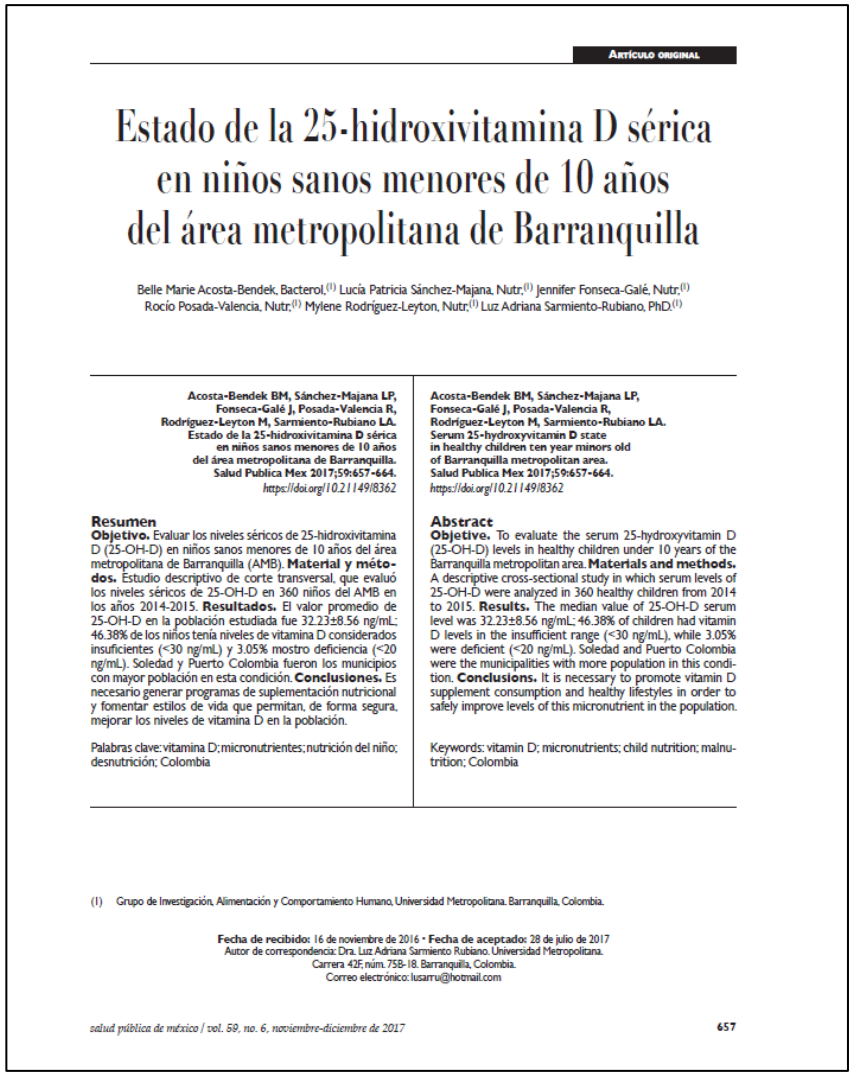
Facultad de Medicina

MAESTRÍA DE EPIDEMIOLOGÍA

Bogotá D. C., Mayo 2018

Bogotá, n=44

Epidemiología del Déficit de Vitamina D en Barranquilla



ARTÍCULO ORIGINAL

Estado de la 25-hidroxivitamina D sérica en niños sanos menores de 10 años del área metropolitana de Barranquilla

Belle Marie Acosta-Bendek, Bacterol,[I] Lucía Patricia Sánchez-Majana, Nutr,[I] Jennifer Fonseca-Galé, Nutr,[I] Rocío Posada-Valencia, Nutr,[I] Mylene Rodríguez-Leyton, Nutr,[I] Luz Adriana Sarmiento-Rubiano, PhD.[I]

Acosta-Bendek BM, Sánchez-Majana LP, Fonseca-Galé J, Posada-Valencia R, Rodríguez-Leyton M, Sarmiento-Rubiano LA. Estado de la 25-hidroxivitamina D sérica en niños sanos menores de 10 años del área metropolitana de Barranquilla. Salud Publica Mex 2017;59:657-664.
https://doi.org/10.21149/8362

Resumen
Objetivo. Evaluar los niveles séricos de 25-hidroxivitamina D (25-OH-D) en niños sanos menores de 10 años del área metropolitana de Barranquilla (AMB). **Material y métodos.** Estudio descriptivo de corte transversal, que evaluó los niveles séricos de 25-OH-D en 360 niños del AMB en los años 2014-2015. **Resultados.** El valor promedio de 25-OH-D en la población estudiada fue 32.23±8.56 ng/mL; 46.38% de los niños tenía niveles de vitamina D considerados insuficientes (<30 ng/mL) y 3.05% mostro deficiencia (<20 ng/mL). Soledad y Puerto Colombia fueron los municipios con mayor población en esta condición. **Conclusiones.** Es necesario generar programas de suplementación nutricional y fomentar estilos de vida que permitan, de forma segura, mejorar los niveles de vitamina D en la población.

Palabras clave: vitamina D; micronutrientes; nutrición del niño; desnutrición; Colombia

Acosta-Bendek BM, Sánchez-Majana LP, Fonseca-Galé J, Posada-Valencia R, Rodríguez-Leyton M, Sarmiento-Rubiano LA. Serum 25-hydroxyvitamin D state in healthy children ten year minors old of Barranquilla metropolitan area. Salud Publica Mex 2017;59:657-664.
https://doi.org/10.21149/8362

Abstract
Objetive. To evaluate the serum 25-hydroxyvitamin D (25-OH-D) levels in healthy children under 10 years of the Barranquilla metropolitan area. **Materials and methods.** A descriptive cross-sectional study in which serum levels of 25-OH-D were analyzed in 360 healthy children from 2014 to 2015. **Results.** The median value of 25-OH-D serum level was 32.23±8.56 ng/mL; 46.38% of children had vitamin D levels in the insufficient range (<30 ng/mL), while 3.05% were deficient (<20 ng/mL). Soledad and Puerto Colombia were the municipalities with more population in this condition. **Conclusions.** It is necessary to promote vitamin D supplement consumption and healthy lifestyles in order to safely improve levels of this micronutrient in the population.

Keywords: vitamin D; micronutrients; child nutrition; malnutrition; Colombia

(I) Grupo de Investigación, Alimentación y Comportamiento Humano, Universidad Metropolitana. Barranquilla, Colombia.

Fecha de recibido: 16 de noviembre de 2016 • **Fecha de aceptado:** 28 de julio de 2017
Autor de correspondencia: Dra. Luz Adriana Sarmiento Rubiano. Universidad Metropolitana.
Carrera 42E núm. 75B-18. Barranquilla, Colombia.
Correo electrónico: lusarru@hotmail.com

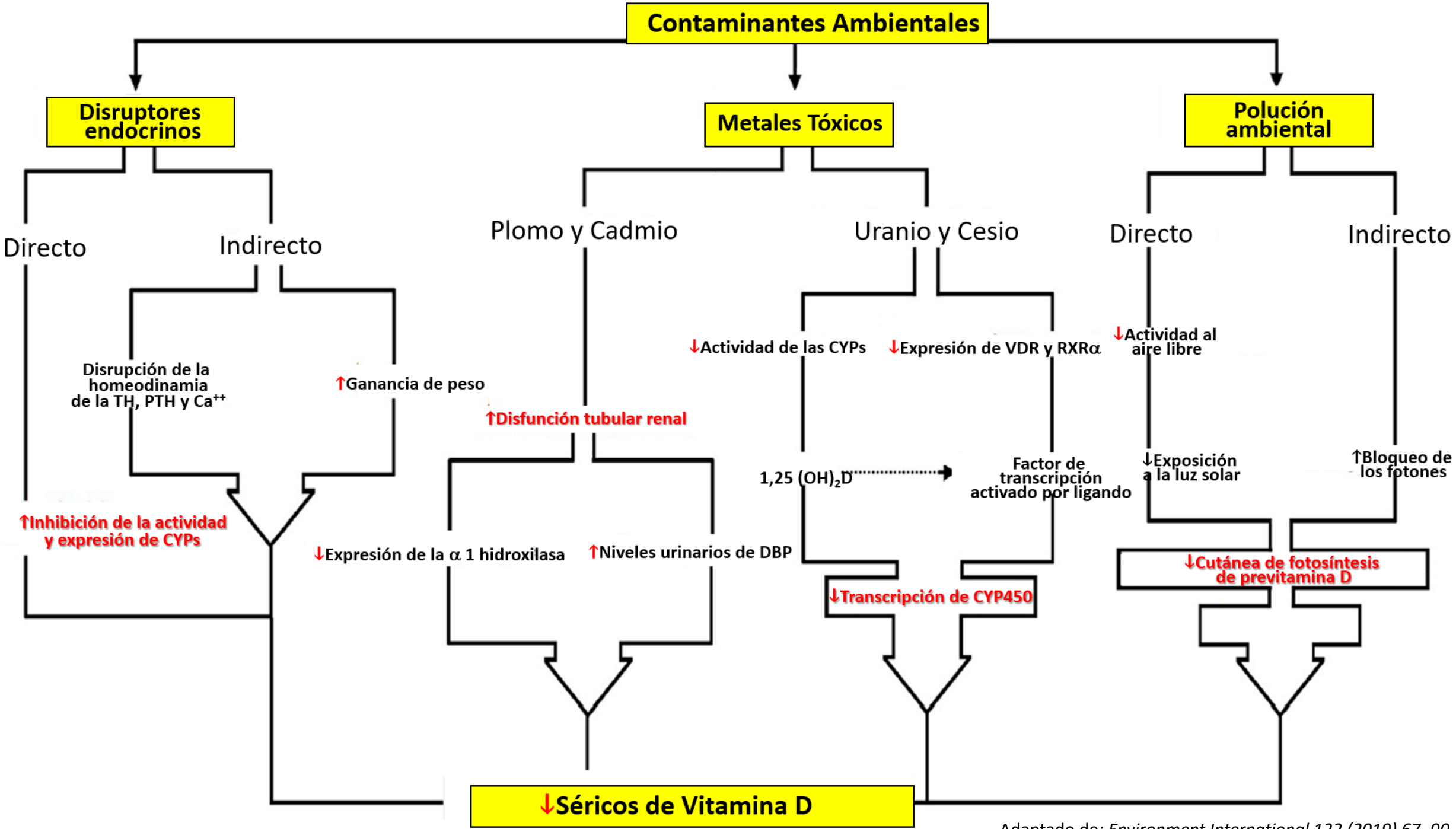
ESTADO DE LOS NIVELES SÉRICOS DE 25-HIDROXIVITAMINA D EN NIÑOS MENORES DE 10 AÑOS, DE LOS MUNICIPIOS DEL ÁREA METROPOLITANA DE BARRANQUILLA (AMB). COLOMBIA, OCTUBRE DE 2014 Y ABRIL DE 2015*,‡

	Condición de los niveles séricos de 25-hidroxivitamina D			
	% Deficientes <20 ng/mL	*% Insuficientes 20-30 ng/mL*	*% Deficientes + insuficientes*	*% Suficientes >30 ng/mL*
Municipios del AMB				
Barranquilla Distrito	4.05[a] (4)	28.37[a] (52)	32.43[a] (56)	67.56[a] (53)
Galapa	3.79[a] (3)	35.44[ab] (21)	39.24[ab] (24)	60.75[ab] (53)
Malambo	3.66[a] (1)	47.70[bc] (32)	51.37[bc] (33)	48.62[bc] (22)
Puerto Colombia	0.00[a] (3)	53.48[c] (28)	53.48[c] (31)	46.51[c] (48)
Soledad	1.81[a] (0)	58.18[c] (23)	60.00[c] (23)	40.00[c] (20)
Total	3.05 (11)	43.33 (156)	46.38 (167)	53.61 (193)
Grupos etarios				
De 0 a 5 años	4.47[a] (6)	35.82[a] (48)	40.30[a] (54)	59.70[a] (80)
De 6 a 10 años	2.21[a] (5)	47.78[a] (108)	50.00[a] (113)	50.00[a] (113)

* Valores corresponden al porcentaje de niños con condición de deficiencia, insuficiencia o suficiencia de 25-OH-D sérica en cada municipio del AMB, entre paréntesis población (n)
‡ Los porcentajes por columna que no comparten la letra del superíndice (a,b,c) son diferentes estadísticamente ($p^5 \leq 0.000$ para los municipios y $p^2 \geq 0.05$ para los grupos etarios, test de ji cuadrada)

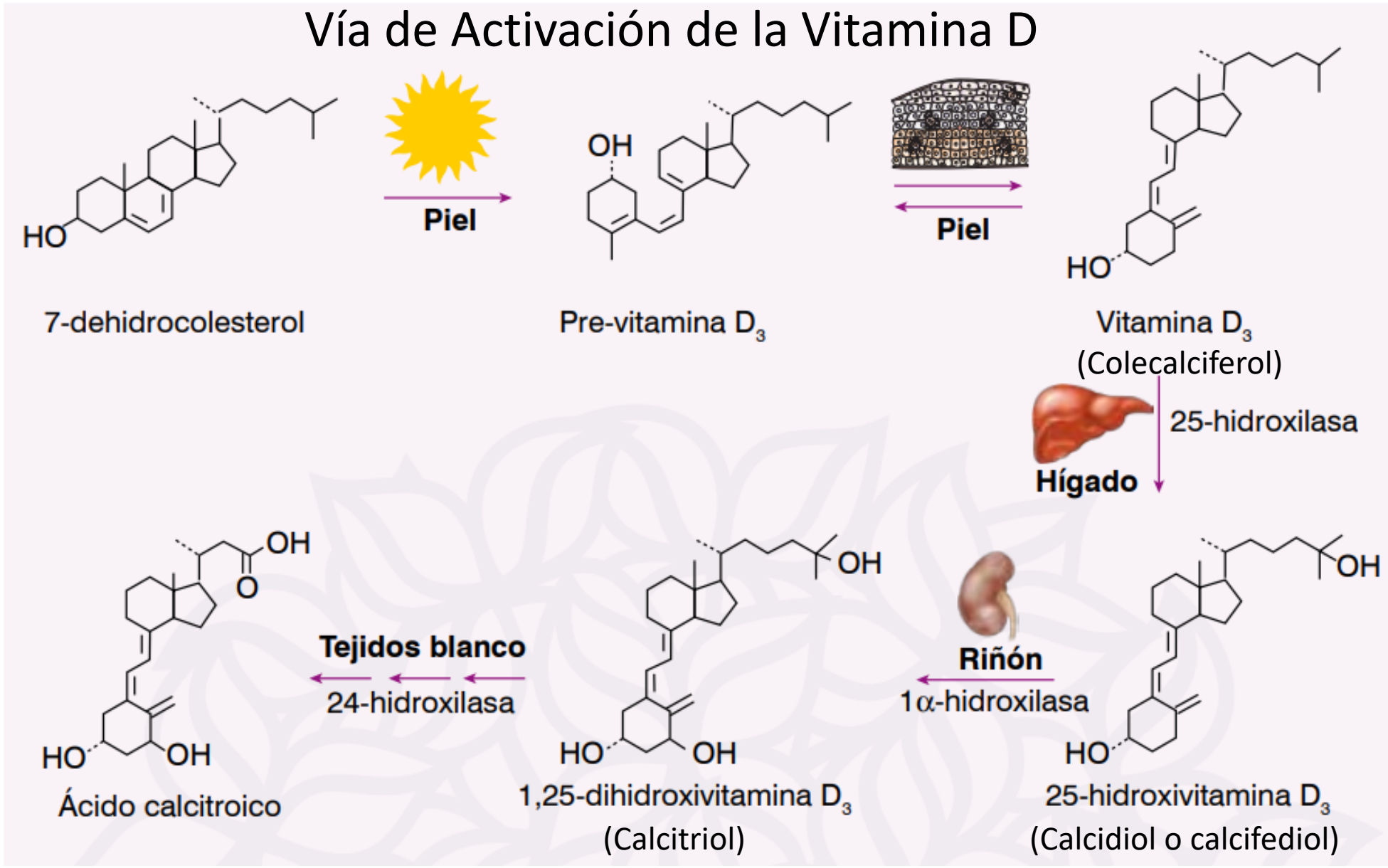
Grupos etarios	% Deficientes + insuficientes
De 0 a 5 años	40.30[a] (54)
De 6 a 10 años	50.00[a] (113)

Bendek, Belle Marie Acosta, Patricia Sánchez, Lucía Patricia *et al*. Estado de la 25-hidroxivitamina D sérica en niños sanos menores de 10 años del área metropolitana de Barranquilla *Salud Pública de México . Vol. 59, No. 6, noviembre-diciembre de 2017*



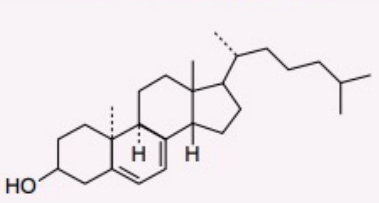
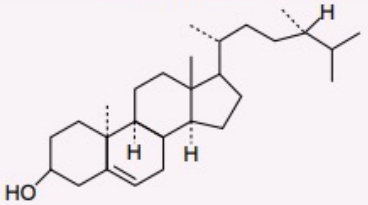
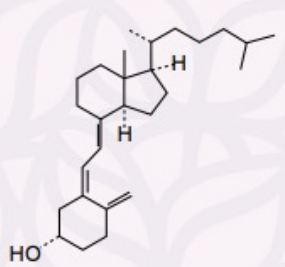
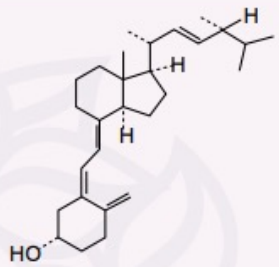
Adaptado de: *Environment International 122 (2019) 67–90*

Vía de Activación de la Vitamina D

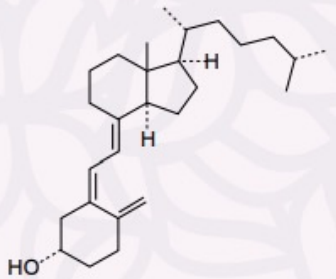


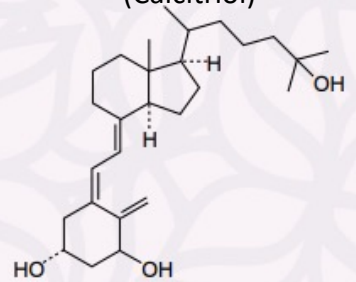
Zuluaga Espinosa, Nora Alejandra, Alfaro Velásquez, Juan Manuel *et al*. Vitamina D Nuevos Paradigmas. La Clínica y el Laboratorio. Medicina y Laboratorio 2011, Volumen 17, Números 5-6

Diferencias entre Vitamina D2 y D3

	Vitamina D_3 *versus*	Vitamina D_2
Precursor	7-dehidrocolesterol	Ergosterol
		
Producción en humanos	Piel por UVB	No!!
		
Actividad en humanos	Completa	Solo 1/3 de la D_3

Vitamina D_3 (Colecalciferol) *versus* **1,25-dihidroxivitamina D_3** (Calcitriol)



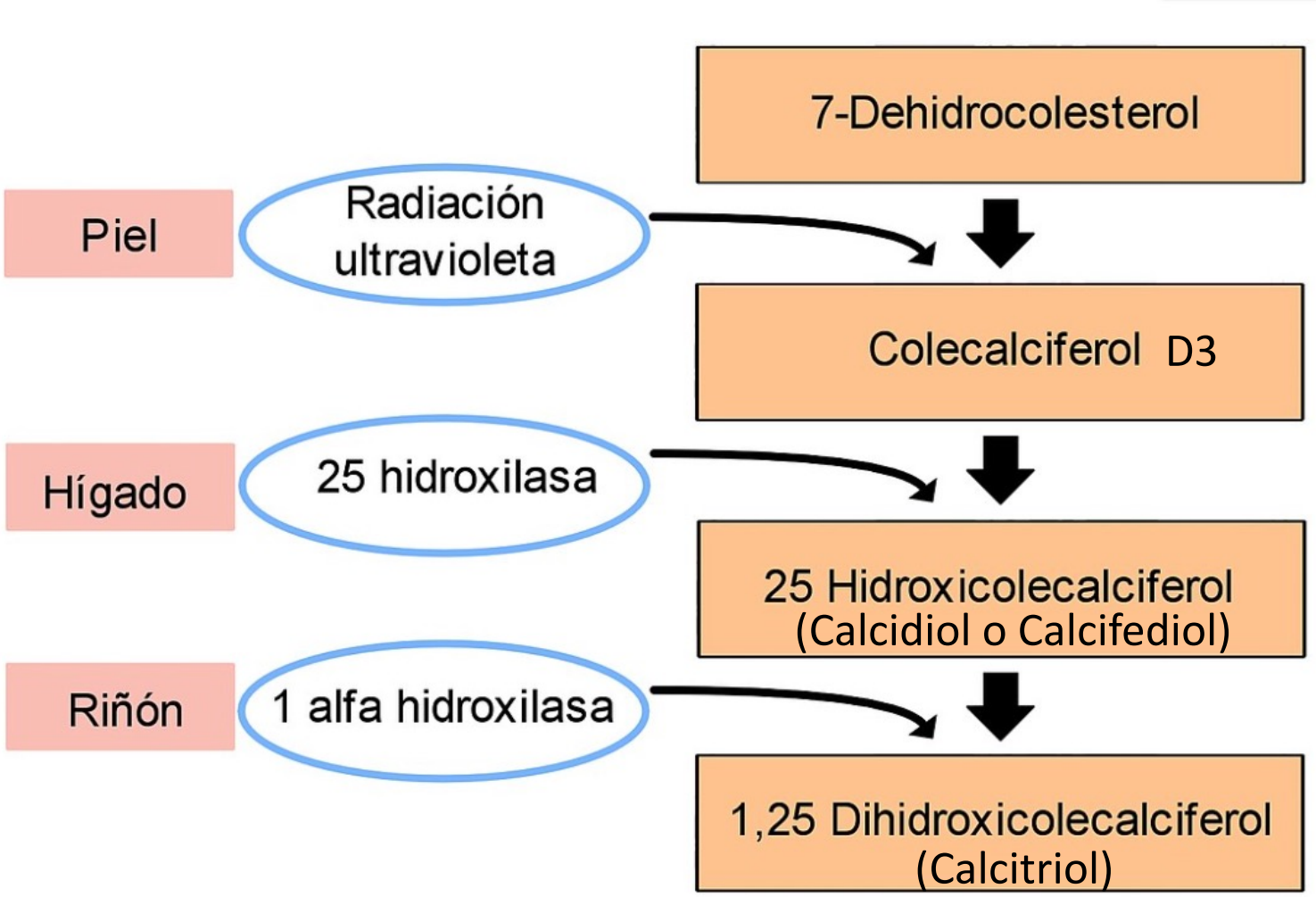


- Biológicamente inactiva
- No se une al receptor VDR

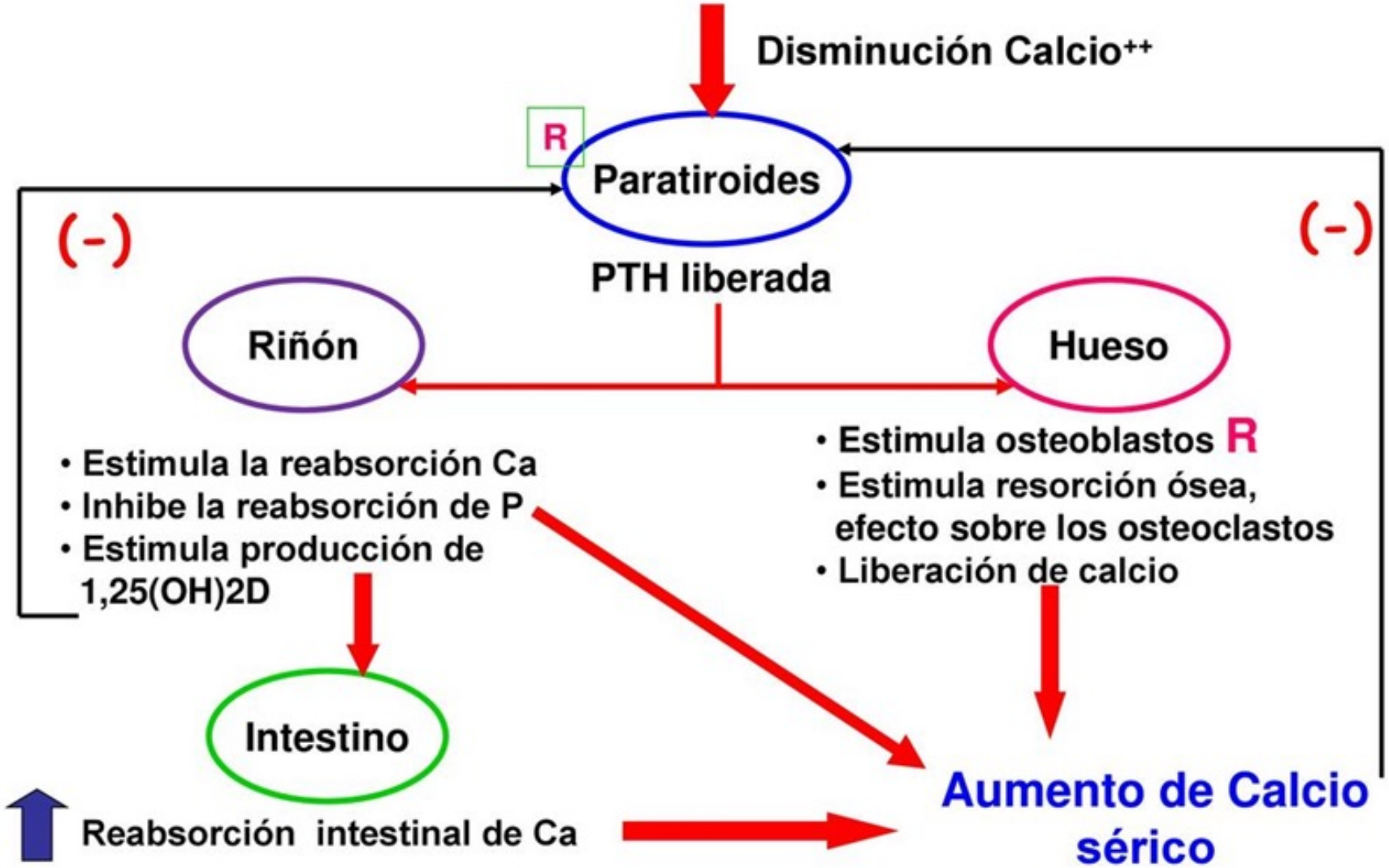
- Hormona esteroide
- Actúa a través del receptor VDR

Zuluaga Espinosa, Nora Alejandra, Alfaro Velásquez, Juan Manuel *et al*. Vitamina D Nuevos Paradigmas. La Clínica y el Laboratorio. Medicina y Laboratorio 2011, Volumen 17, Números 5-6

Vía de Activación de la Vitamina D



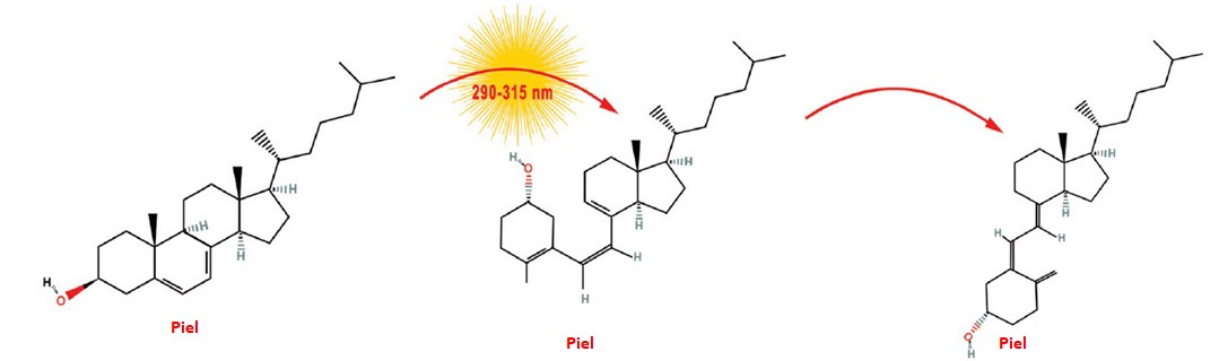
Sistema Endocrino de la Vitamina D



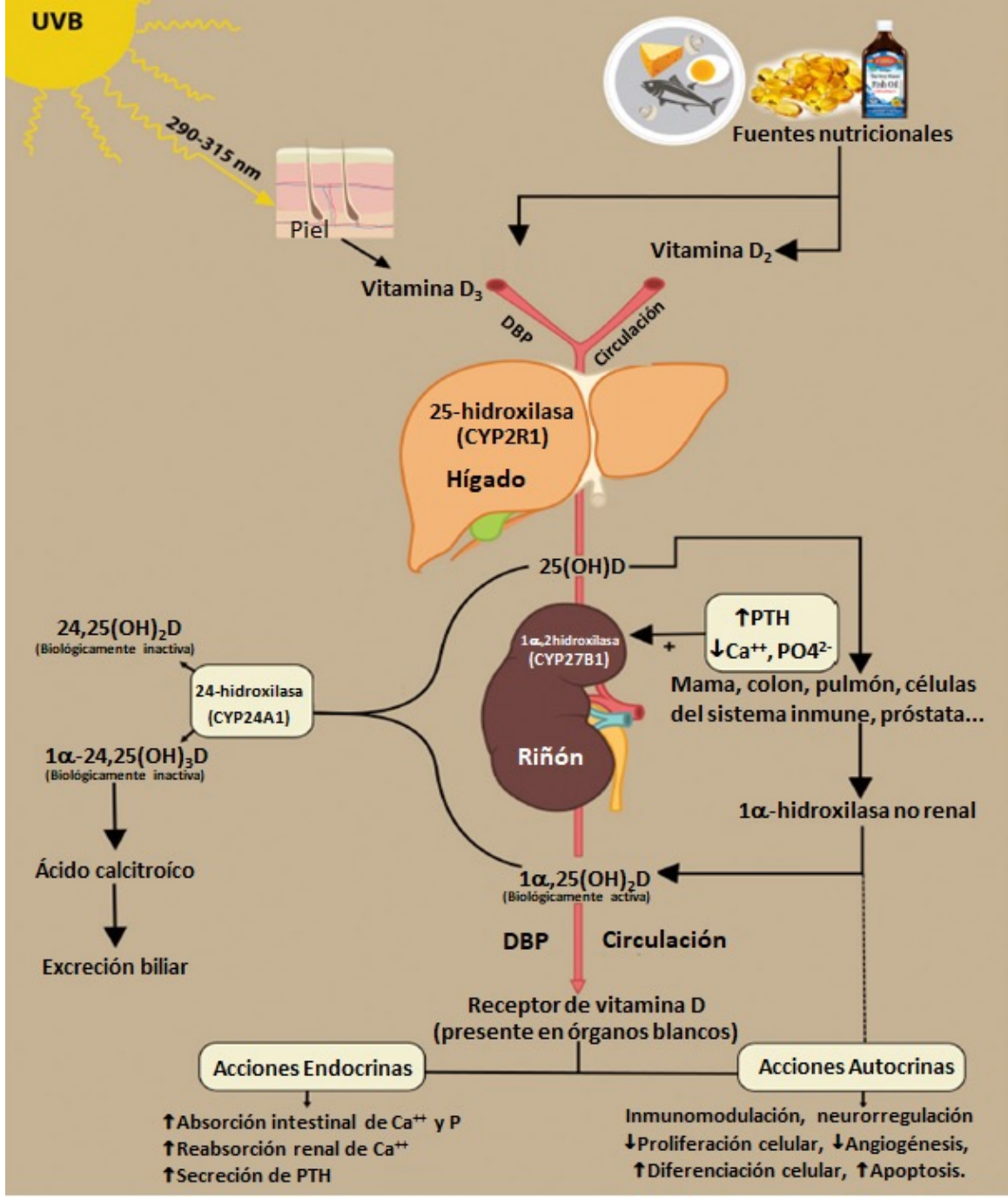
Causas de la disminución de la vitamina D

Polución
Químicos ambientales
Disruptores endocrinos.
Metales pesados.
Afectación hepática
Afectación tiroidea y paratiroidea.
Tabaquismo.
Dieta inadecuada.

Alteración en la producción cutánea de colecalciferol.
Disminución en la absorción de vitamina D
Modulación de genes involucrados en la homeodinamia de Vit. D
Disminución de producción local de calcitriol en tejidos blanco.

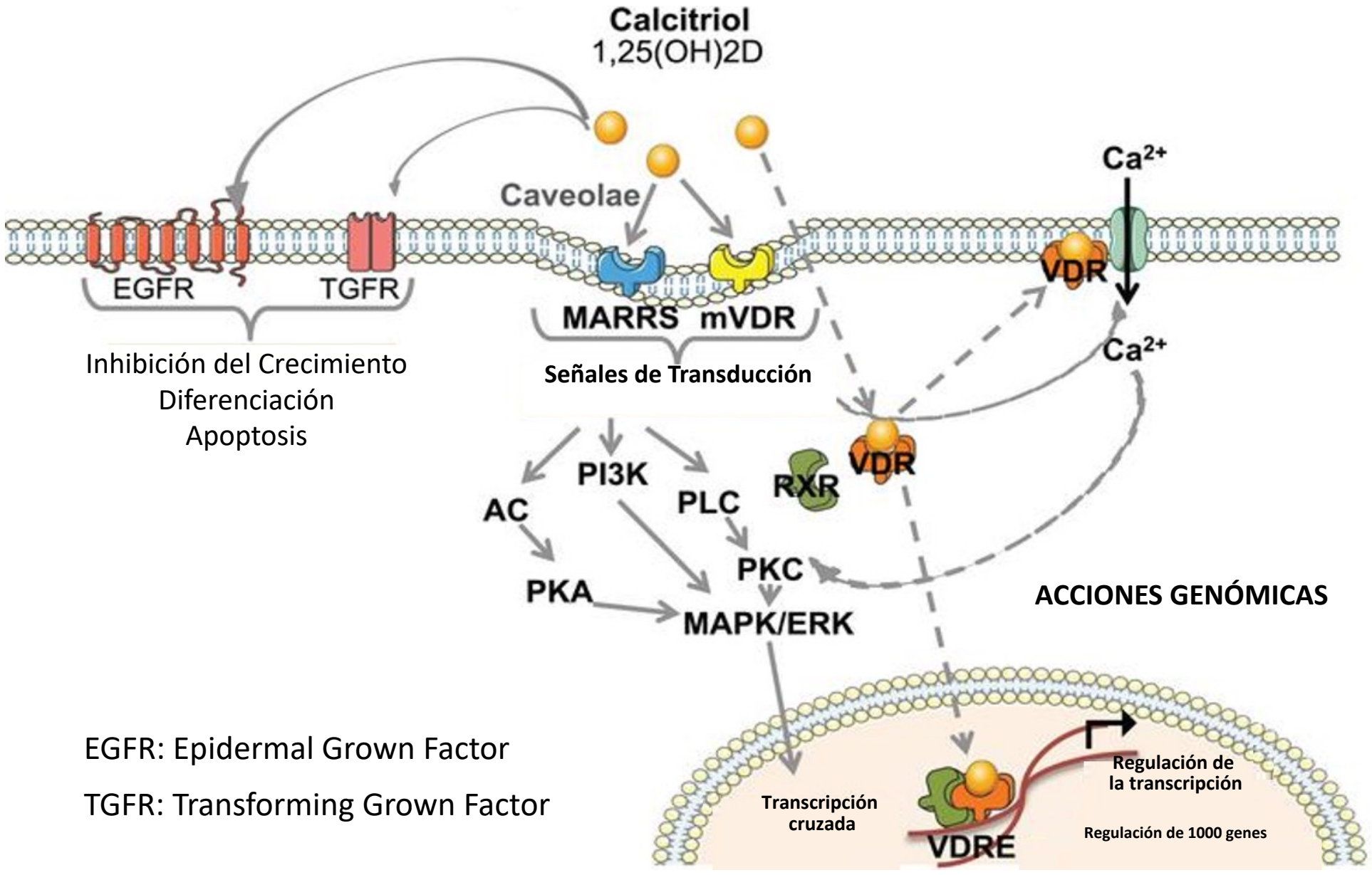


7-dehidrocolesterol (Provitamina D_3) Procolecalciferol (Previtamina D_3) Colecalciferol (Vitamina D_3)



Adaptado de: *Environment International 122 (2019) 67–90*

Acciones Genómicas de la Vitamina D



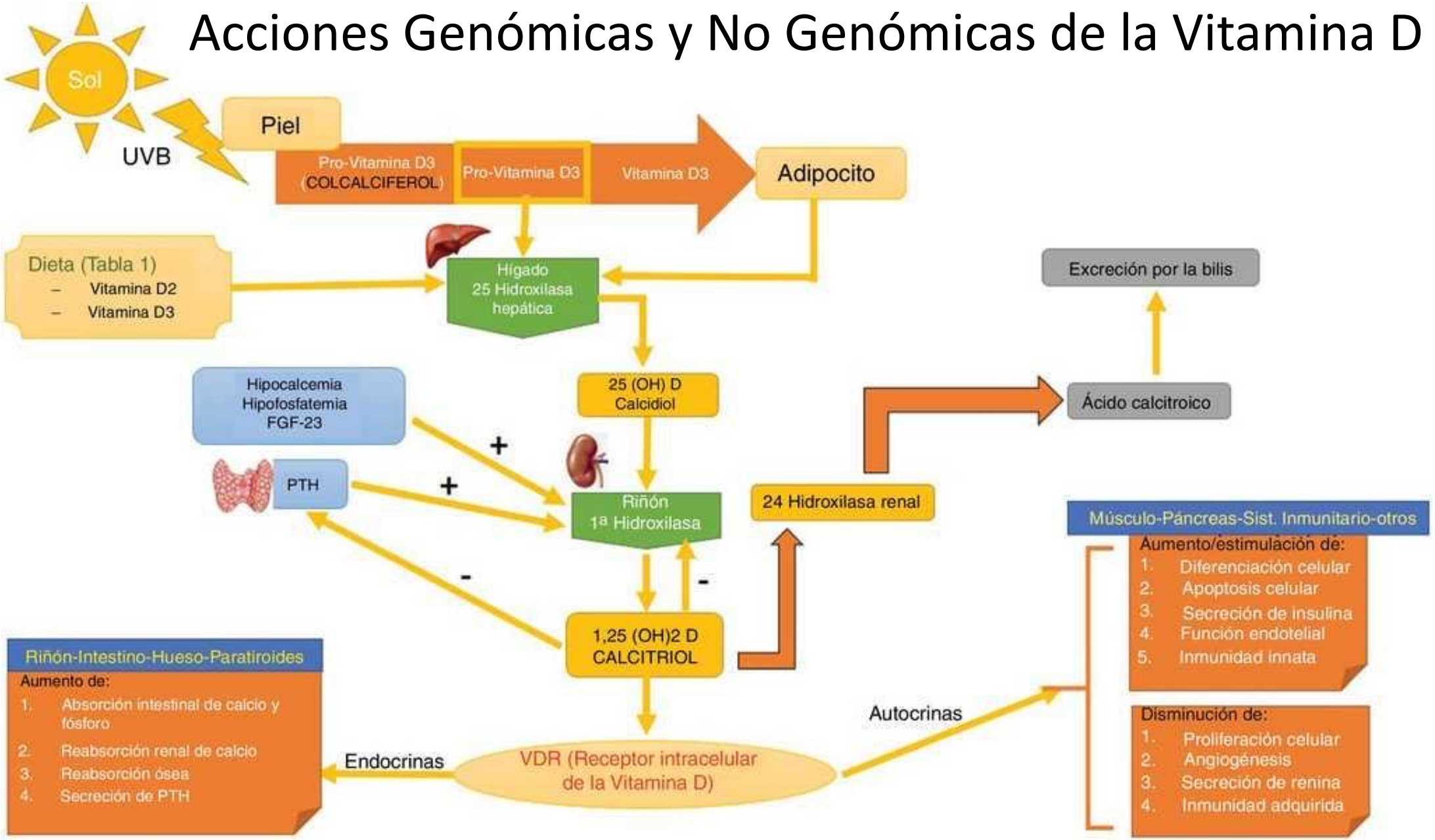
Inhibición del Crecimiento
Diferenciación
Apoptosis

EGFR: Epidermal Grown Factor

TGFR: Transforming Grown Factor

Front Endocrinol (Lausanne). 2018; 9: 250.

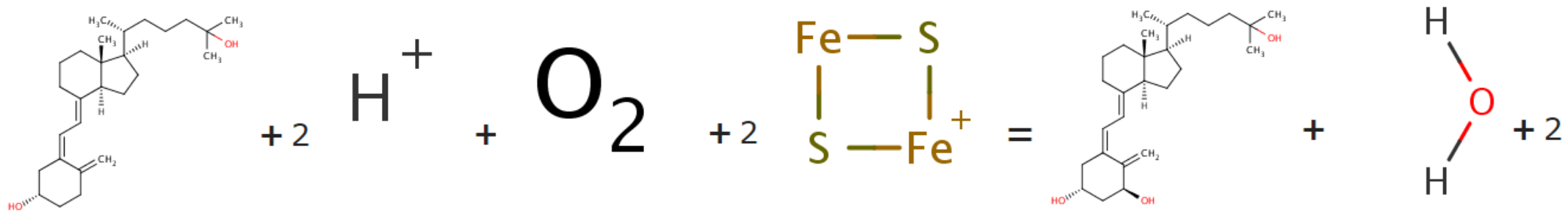
Acciones Genómicas y No Genómicas de la Vitamina D



Actas Dermosifiliogr. 2019;110:262–72

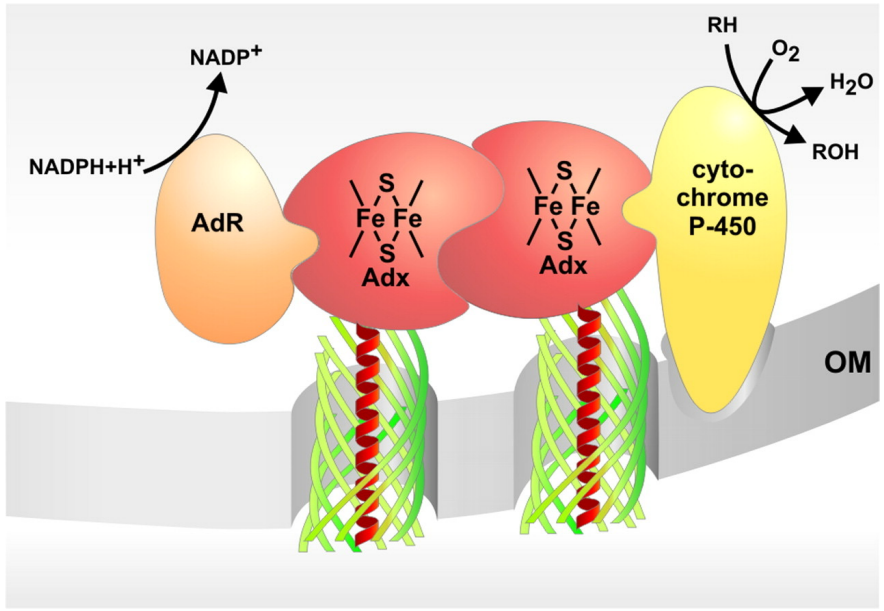
La 25-hidroxivitamina D_3 es una 1-alfa-hidroxilasa Mitocondrial

La hepatodoxina-$NADP^+$ reductasa es la primera enzima en los sistemas mitocondriales P450



Calcidiol +
(25-hidroxicolecalciferol)
(25-hdroxivitamina D)

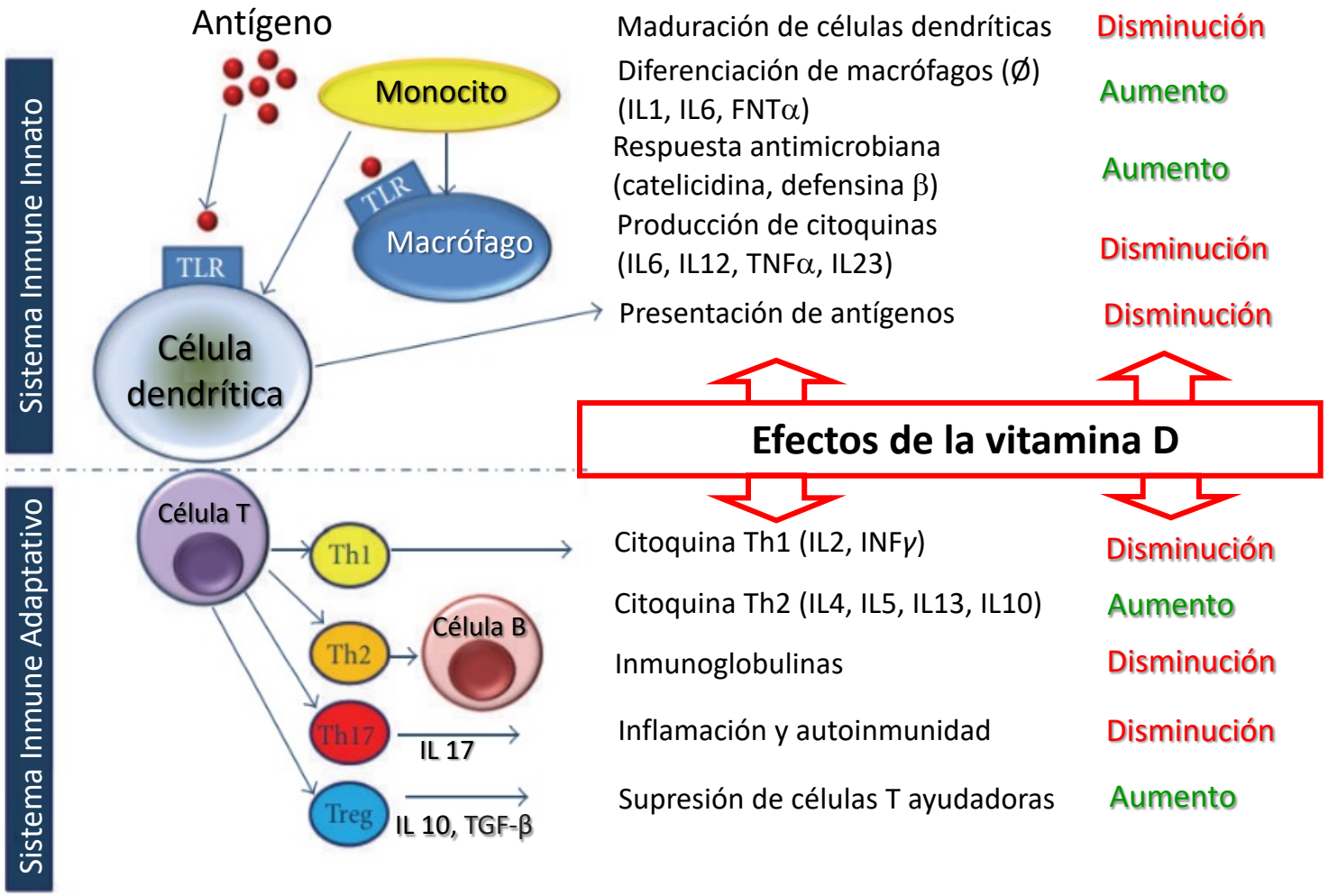
2H⁺

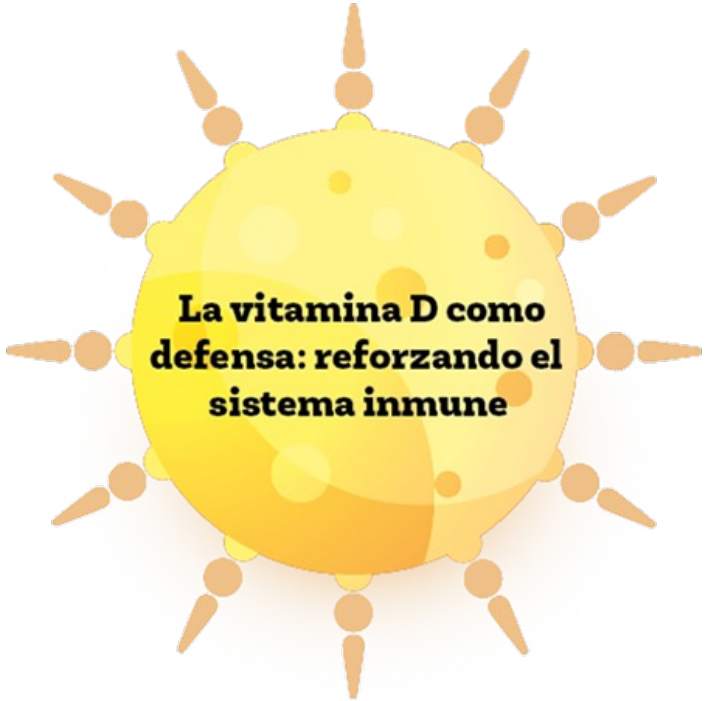


= **Calcitriol** + **hepatoredoxina oxidada**

The Journal Of Biological Chemistry. Vol. 255, No. 7, Issue of April 10. pp. 3057-3061. 1980

Efectos esenciales de la vitamina D en el sistema inmune

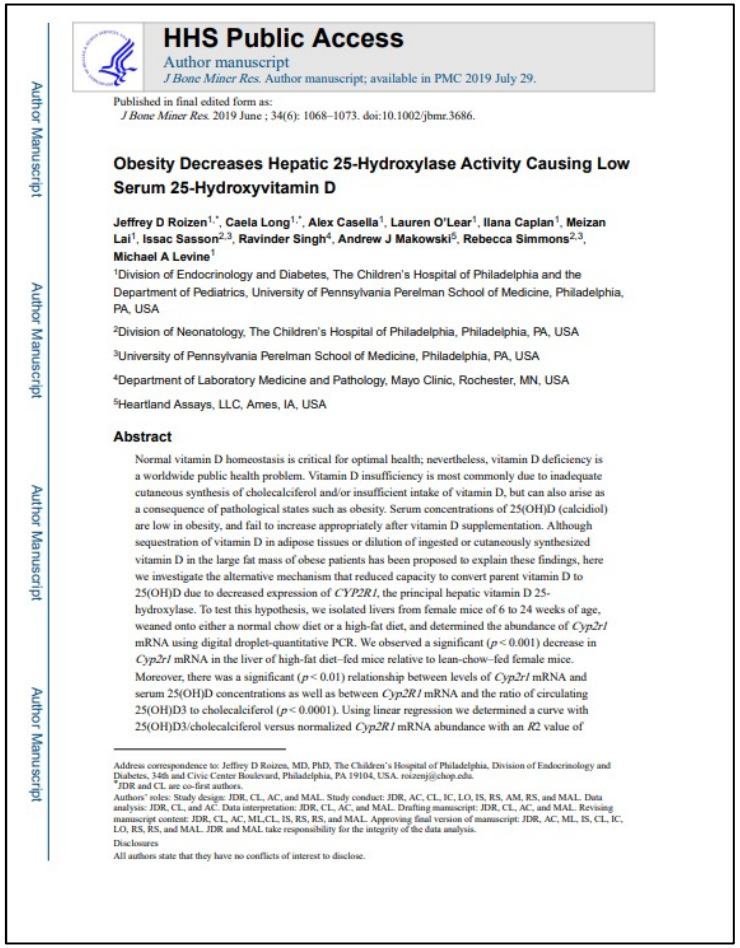




TLR: Receptor toll like TGF-β: Transforming growth factor beta

Modificado de: Journal of Aging Research Volume 2012, Article ID 806198, 8 pages

Vitamina D y Obesidad



Published in final edited form as:
J Bone Miner Res. 2019 June ; 34(6): 1068–1073. doi:10.1002/jbmr.3686.

Obesity Decreases Hepatic 25-Hydroxylase Activity Causing Low Serum 25-Hydroxyvitamin D

Jeffrey D Roizen[1,*], Caela Long[1,*], Alex Casella[1], Lauren O'Lear[1], Ilana Caplan[1], Meizan Lal[1], Issac Sasson[2,3], Ravinder Singh[4], Andrew J Makowski[5], Rebecca Simmons[2,3], Michael A Levine[1]

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[4]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

[5]Heartland Assays, LLC, Ames, IA, USA

Abstract

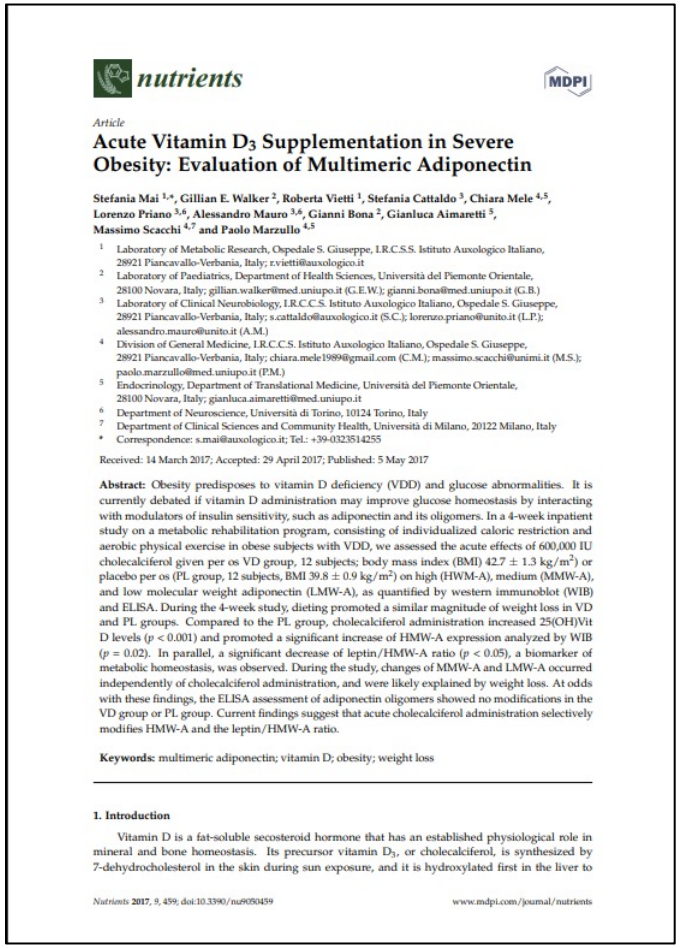
Normal vitamin D homeostasis is critical for optimal health; nevertheless, vitamin D deficiency is a worldwide public health problem. Vitamin D insufficiency is most commonly due to inadequate cutaneous synthesis of cholecalciferol and/or insufficient intake of vitamin D, but can also arise as a consequence of pathological states such as obesity. Serum concentrations of 25(OH)D (calcidiol) are low in obesity, and fail to increase appropriately after vitamin D supplementation. Although sequestration of vitamin D in adipose tissues or dilution of ingested or cutaneously synthesized vitamin D in the large fat mass of obese patients has been proposed to explain these findings, here we investigate the alternative mechanism that reduced capacity to convert parent vitamin D to 25(OH)D due to decreased expression of *CYP2R1*, the principal hepatic vitamin D 25-hydroxylase. To test this hypothesis, we isolated livers from female mice of 6 to 24 weeks of age, weaned onto either a normal chow diet or a high-fat diet, and determined the abundance of *Cyp2r1* mRNA using digital droplet-quantitative PCR. We observed a significant ($p < 0.001$) decrease in *Cyp2r1* mRNA in the liver of high-fat diet–fed mice relative to lean-chow–fed female mice. Moreover, there was a significant ($p < 0.01$) relationship between levels of *Cyp2r1* mRNA and serum 25(OH)D concentrations as well as between *Cyp2R1* mRNA and the ratio of circulating 25(OH)D3 to cholecalciferol ($p < 0.0001$). Using linear regression we determined a curve with 25(OH)D3/cholecalciferol versus normalized *Cyp2R1* mRNA abundance with an $R2$ value of

Address correspondence to: Jeffrey D Roizen, MD, PhD, The Children's Hospital of Philadelphia, Division of Endocrinology and Diabetes, 34th and Civic Center Boulevard, Philadelphia, PA 19104, USA. roizenj@chop.edu.
*JDR and CL are co-first authors.

Authors' roles: Study design: JDR, CL, AC, and MAL. Study conduct: JDR, AC, CL, IC, LO, IS, RS, AM, RS, and MAL. Data analysis: JDR, CL, and AC. Data interpretation: JDR, CL, AC, and MAL. Drafting manuscript: JDR, CL, AC, and MAL. Revising manuscript content: JDR, CL, AC, ML,CL, IS, RS, RS, and MAL. Approving final version of manuscript: JDR, AC, ML, IS, CL, IC, LO, RS, RS, and MAL. JDR and MAL take responsibility for the integrity of the data analysis.

Disclosures

All authors state that they have no conflicts of interest to disclose.



nutrients MDPI

Article

Acute Vitamin D_3 Supplementation in Severe Obesity: Evaluation of Multimeric Adiponectin

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Abstract: Obesity predisposes to vitamin D deficiency (VDD) and glucose abnormalities. It is currently debated if vitamin D administration may improve glucose homeostasis by interacting with modulators of insulin sensitivity, such as adiponectin and its oligomers. In a 4-week inpatient study on a metabolic rehabilitation program, consisting of individualized caloric restriction and aerobic physical exercise in obese subjects with VDD, we assessed the acute effects of 600,000 IU cholecalciferol given per os VD group, 12 subjects; body mass index (BMI) 42.7 ± 1.3 kg/m^2) or placebo per os (PL group, 12 subjects, BMI 39.8 ± 0.9 kg/m^2) on high (HWM-A), medium (MMW-A), and low molecular weight adiponectin (LMW-A), as quantified by western immunoblot (WIB) and ELISA. During the 4-week study, dieting promoted a similar magnitude of weight loss in VD and PL groups. Compared to the PL group, cholecalciferol administration increased 25(OH)Vit D levels ($p < 0.001$) and promoted a significant increase of HMW-A expression analyzed by WIB ($p = 0.02$). In parallel, a significant decrease of leptin/HMW-A ratio ($p < 0.05$), a biomarker of metabolic homeostasis, was observed. During the study, changes of MMW-A and LMW-A occurred independently of cholecalciferol administration, and were likely explained by weight loss. At odds with these findings, the ELISA assessment of adiponectin oligomers showed no modifications in the VD group or PL group. Current findings suggest that acute cholecalciferol administration selectively modifies HMW-A and the leptin/HMW-A ratio.

Keywords: multimeric adiponectin; vitamin D; obesity; weight loss

1. Introduction

Vitamin D is a fat-soluble secosteroid hormone that has an established physiological role in mineral and bone homeostasis. Its precursor vitamin D_3, or cholecalciferol, is synthesized by 7-dehydrocholesterol in the skin during sun exposure, and it is hydroxylated first in the liver to

- Inflamación: La obesidad es un estado proinflamatorio y dado que la vitamina D modula el sistema inmune reduciendo la inflamación, su déficit tiene efecto sinérgico con la inflamación obesogénica.
- Leptina: es la responsable de generar la señal de saciedad en el cerebro, bajas concentraciones de vitamina D se asocian a disminución de la producción de leptina y tendencia a almacenar grasa.

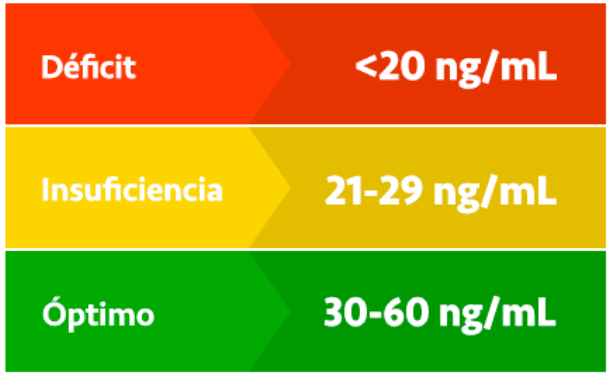
1. J Bone Miner Res. 2019 June ; 34(6): 1068–1073. **2**. Int J Obes Suppl. 2019 Apr; 9(1): 20–31.

Indicaciones de Medición de Vitamina D

- Osteomalacia
- Osteoporosis
- Hepatopatía
- Fibrosis quística
- Cirugía bariátrica
- Enfermedad de Crohn
- Enfermedad renal crónica
- Síndrome de malabsorción
- Enteritis por radioterapia
- Enfermedad inflamatoria intestinal
- Medicamentos:

  Anticonvulsivantes, colestiramina, glucocorticoides, orlistat, antimicóticos y antirretrovirales.

- Beriliosis
- Linfomas.
- Sarcoidosis
- Tuberculosis
- Histoplasmosis
- Coccidiomicosis
- Hiperparatiroidismo
- Niños o adultos obesos
- Enfermedades granulomatosas
- Mujeres embarazadas y lactando
- Adultos mayores con historia de caídas
- Niños y adultos afroamericanos e hispanos
- Adultos mayores con fracturas no traumáticas



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Suplencia de Vitamina D e Hipertensión

Journal of the American Society of Hypertension 9(3) (2015) 176–183

Research Article

The effect of vitamin D supplementation on arterial stiffness in an elderly community–based population

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Abstract

Vitamin D deficiency may lead to impaired vascular function and abnormalities in central arterial stiffness. We compared the effects of two different doses of vitamin D3 on arterial stiffness in an elderly population with deficient serum 25–hydroxy–vitamin D levels. A total of 119 known vitamin D deficient (<50 nmol/L) subjects were randomized to receive either 50,000 international units (IU) or 100,000 IU single intramuscular vitamin D3. In the group that received 100,000 IU vitamin D, median pulse wave velocity decreased from 12.2 m/s (range, 5.1–40.3 m/s) to 11.59 m/s (range, 4.3–14.9 m/s) after 8 weeks ($P = .22$). A mean decrease of 3.803 ± 1.7 ($P = .032$) in augmentation index (a measure of systemic stiffness) was noted. Only 3/51 (5.8%) who received 100,000 IU vitamin D reached levels of sufficiency (>75 nmol/L). A significant decrease in augmentation index was seen in the group that received 100,000 IU vitamin D. Serum levels of 25–hydroxy–vitamin D were still deficient at 8 weeks in the majority of patients, which may be attributable to impaired bioavailability. J Am Soc Hypertens 2015;9(3):176–183.

Keywords: Older patients; arterial stiffness; cholecalciferol; pulse wave velocity.

Introduction

Along with its well established role in osteoporosis, animal studies have linked vitamin D insufficiency with cardiovascular dysfunction, including cardiac hypertrophy and elevated blood pressure.[1] Previous studies have supported a role for vitamin D in maintaining cardiovascular health through both a direct action on cardiomyocytes and indirect actions on circulating hormones and calcium.[2] The vitamin D receptor (VDR) is found throughout the body in several tissue types including colonic, hepatic, lymphocytes, and cardiac cells.[3,4] Low serum 25–hydroxy–vitamin D (25OHD) levels have been found to be associated with a higher level of peripheral arterial disease, supporting the theory that vitamin D may have potent anti–atherosclerotic properties.[5,6] A number of molecules such as osteoprotegrin (OPG) and matrix metallopeptidase 9 (MMP–9) may be elevated in association with calcification of vessels, ischemic heart disease, and stroke,[7,8] resulting in increased interest in their potential as possible biomarkers of vascular disease.

Previous studies have demonstrated that vitamin D deficiency (defined as serum 25OHD levels below 50 nmol/L[9]) may lead to impairment of vascular function, eventually leading to abnormalities in central arterial stiffness.[5,10]

Pulse wave velocity (PWV) is recognized as a simple, non–invasive, validated, robust, and reproducible surrogate measure of arterial stiffness.[11] The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave (Figure 1). The stiffer the arteries are, the faster the wave returns, adding to the forward wave and augmenting the

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There are no conflicts of interest to declare.

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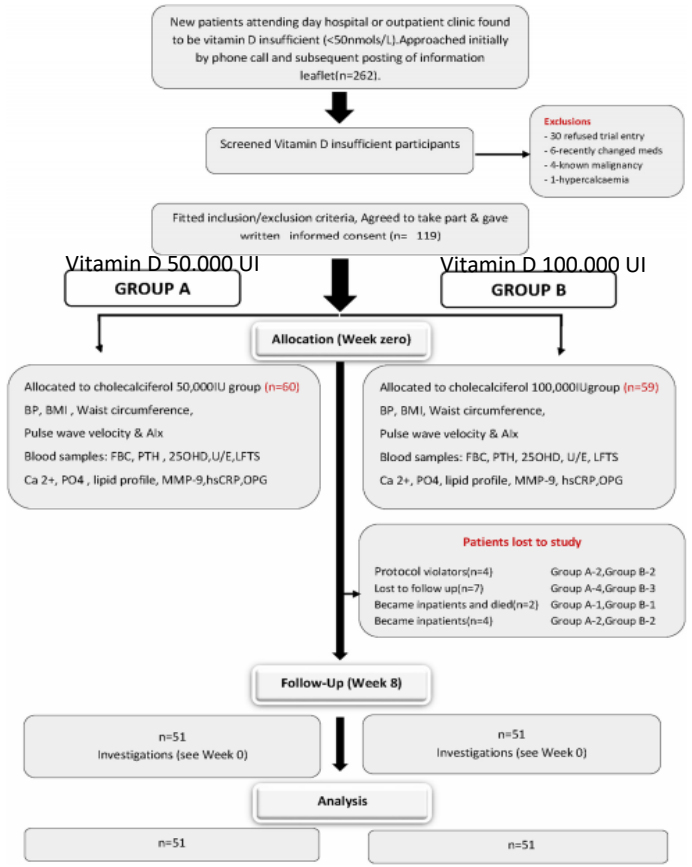

Figure 2. CONSORT diagram of vitamin D/arterial stiffness clinical trial study design.

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Vitamina D y fatiga

Medicine

OPEN

Clinical Trial/Experimental Study

Effect of vitamin D3 on self-perceived fatigue

A double-blind randomized placebo-controlled trial

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Abstract

Background: Vitamin D deficiency is frequent and has been associated with fatigue in uncontrolled trials.

Methods: This is the first double-blind placebo-controlled clinical trial to investigate the efficacy of per os vitamin D3 (cholecalciferol) in treating fatigue among otherwise healthy persons with low serum 25-hydroxyvitamin D (25(OH)D) levels. We enrolled 120 individuals (mean age 29±6 years, 53% women) presenting with fatigue and vitamin D deficiency (serum 25(OH)D< 20 μg/L). Participants were randomized to a single oral dose of 100,000 units of vitamin D or placebo. The primary endpoint was intra-individual change in the fatigue assessment scale (FAS) at 4 weeks after treatment.

Result: The mean age of the participants was 29±6 years, 53% were women. Mean FAS decreased significantly more in the vitamin D group (−3.3±5.3; 95% confidence interval [CI] for change −14.1 to 4.1) compared with placebo (−0.8±5.3; 95% CI for change −9.0 to 8.7); (P=0.01). Amelioration of fatigue was reported more frequently in vitamin D than in placebo group (42 [72%] vs. 31 [50%]; P=0.01; odds ratio [OR] 2.63, 95% CI for OR 1.23–5.62). Among all participants, improvement in fatigue score correlated with the rise in 25(OH)D level (R=−0.22, P=0.02).

Conclusion: Vitamin D treatment significantly improved fatigue in otherwise healthy persons with vitamin D deficiency. This study was registered at the www.ClinicalTrials.gov Protocol ID NCT02022475.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D, BDI = beck depression inventory, BMI = body mass index, BQF = basic questionnaire for fatigue, CFS = chronic fatigue syndrome, FAS = fatigue assessment scale, FCA = fatigue course assessment, IQR = interquartile range, ISI = insomnia severity index, IU = international unit, M.I.N.I = mini international neuropsychiatric interview, MD = medical doctor, OR = odds ratio, PTH = parathyroid hormone, RCT = randomized clinical trial, TSH = thyroid stimulating hormone.

Keywords: fatigue, randomized clinical trial, vitamin D

1. Introduction

Fatigue is a frequent complaint in primary care in developed and developing countries.[1] It can lead to impaired quality of life and loss of productive work time.[2] Physicians are likely to prescribe vitamins—especially vitamin D, iron, and nutritional supplements to treat the symptom presumptively. In consequence, such preparations account for a large number of drugs dispensed. However, there is little scientific evidence to support this procedure and practitioners may experience uncertainty due to lack of available scientific data.

Vitamin D deficiency is frequent[3] and has been associated with fatigue and other unspecific symptoms including headache,[4] musculoskeletal pain and weakness,[5] depression,[6] and impaired cognitive performance.[4] One randomized controlled trial tested the effect of high-dose vitamin D3 on symptoms in chronic fatigue syndrome (CFS), where no improvement of fatigue was found.[7] In another randomized controlled trial, muscle pains improved in a population of primary care patients with vitamin D deficiency.[8] Several uncontrolled studies suggested that fatigue may improve after correction of low vitamin D levels in individuals with stable chronic diseases,[9] breast cancer,[10] and myasthenia gravis.[11] However, the results of these studies need to be confirmed by a double-blind randomized clinical trial (RCT) because strong placebo effect can influence investigation of any therapeutic approach to reduce fatigue.[12]

In this study, we aimed to test if a single vitamin D dose improves fatigue after 30 days among vitamin D deficient individuals who report fatigue but are otherwise healthy.

2. Methods

2.1. Study design

This investigator-initiated double-blinded RCT was conducted in accordance with the Declaration of Helsinki and the Guidelines on Good Clinical Practice. The protocol and its amendment were

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The authors report no conflicts of interest.

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PLOS ONE

Cholecalciferol (Vitamin D_3) Improves Myelination and Recovery after Nerve Injury

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Abstract

Previously, we demonstrated i) that ergocalciferol (vitamin D_2) increases axon diameter and potentiates nerve regeneration in a rat model of transected peripheral nerve and ii) that cholecalciferol (vitamin D3) improves breathing and hyper-reflexia in a rat model of paraplegia. However, before bringing this molecule to the clinic, it was of prime importance i) to assess which form – ergocalciferol versus cholecalciferol – and which dose were the most efficient and ii) to identify the molecular pathways activated by this pleiotropic molecule. The rat left peroneal nerve was cut out on a length of 10 mm and autografted in an inverted position. Animals were treated with either cholecalciferol or ergocalciferol, at the dose of 100 or 500 IU/kg/day, or excipient (Vehicle), and compared to unlesioned rats (Control). Functional recovery of hindlimb was measured weekly, during 12 weeks, using the peroneal functional index. Ventilatory, motor and sensitive responses of the regenerated axons were recorded and histological analysis was performed. In parallel, to identify the genes regulated by vitamin D in dorsal root ganglia and/or Schwann cells, we performed an *in vitro* transcriptome study. We observed that cholecalciferol is more efficient than ergocalciferol and, when delivered at a high dose (500 IU/kg/day), cholecalciferol induces a significant locomotor and electrophysiological recovery. We also demonstrated that cholecalciferol increases i) the number of preserved or newly formed axons in the proximal end, ii) the mean axon diameter in the distal end, and iii) neurite myelination in both distal and proximal ends. Finally, we found a modified expression of several genes involved in axogenesis and myelination, after 24 hours of vitamin supplementation. Our study is the first to demonstrate that vitamin D acts on myelination via the activation of several myelin-associated genes. It paves the way for future randomised controlled clinical trials for peripheral nerve or spinal cord repair.

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Introduction

In a previous study, using a rat model of nerve trauma, we demonstrated that vitamin D_3 is a potent compound that promoted axon sparing/regeneration and improved physiological maturation [1]. We also observed that vitamin D_3 supplementation induced an increase in axon diameter, suggesting that myelination was probably enhanced [1]. However, we had no direct evidence that vitamin D is a true myelinating agent.

Vitamin D is a group of seco-steroid hormones, including the fungi-derived form of vitamin D, named vitamin D_2 or ergocalciferol, and the animal-derived form of vitamin D, named vitamin D_3 or cholecalciferol. After two separate hydroxylations, performed by two P450 enzymes (25-hydroxylase and 1-alpha-hydroxylase, respectively), both calciferols give rise to the active form (1,25(OH)2D), referred to as calcitriol [2]. Initially, it was thought that liver and kidneys were the only organs responsible for the production of calcitriol. However, it is now clearly established that many tissues, including the brain [3], express vitamin D 1-alpha-hydroxylase. Moreover, vitamin D receptors (VDRs) are widely distributed throughout the brain, in rats [4,5,6,7,8] as well as in humans [3].

Like other neurosteroids, the genomic action of calcitriol is mediated by a nuclear receptor, the VDR, a member of the steroid/thyroid hormone super-family of transcription regulation factors. After hetero-dimerisation with nuclear receptors of the retinoic X receptor (RXR) family, the VDR and its ligand bind to vitamin D responsive elements (VDRE), located in the promoter regions of hundreds of target genes [9]. For example, a VDRE has been found upstream from genes coding for Brain Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF) and

nutrients

MDPI

Review

Anti-Inflammatory Diets and Fatigue

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Abstract: Accumulating data indicates a link between a pro-inflammatory status and occurrence of chronic disease-related fatigue. The questions are whether the observed inflammatory profile can be (a) improved by anti-inflammatory diets, and (b) if this improvement can in turn be translated into a significant fatigue reduction. The aim of this narrative review was to investigate the effect of anti-inflammatory nutrients, foods, and diets on inflammatory markers and fatigue in various patient populations. Next to observational and epidemiological studies, a total of 21 human trials have been evaluated in this work. Current available research is indicative, rather than evident, regarding the effectiveness of individuals' use of single nutrients with anti-inflammatory and fatigue-reducing effects. In contrast, clinical studies demonstrate that a balanced diet with whole grains high in fibers, polyphenol-rich vegetables, and omega-3 fatty acid-rich foods might be able to improve disease-related fatigue symptoms. Nonetheless, further research is needed to clarify conflicting results in the literature and substantiate the promising results from human trials on fatigue.

Keywords: chronic fatigue; myalgic encephalomyelitis; inflammation; cytokines; anti-inflammatory nutrition; omega-3 fatty acids; polyphenols; probiotics; fatigue reduction diet; cancer

1. Introduction

Fatigue is described as an unusual overwhelming tiredness which is not comparable to physiologic exhaustion after physical or mental effort and which cannot be recovered by restful sleep [1]. It can show temporary or chronic (>6 months) dimensions [1]. The etiology is not yet fully understood but is probably of heterogeneous origin [2,3]. Fatigue can occur within psychiatric, i.e., depressive, disorders [4], as well as in patients with non-neurological diseases such as fibromyalgia/chronic widespread pain, or in diseases accompanied by chronic (low-grade) inflammation, e.g., cancer, inflammatory bowel disease (IBD), and various other auto-immune diseases [1,5]. Among these patient populations, disease-related fatigue can be experienced by up to 90% of the individuals, with patients with cancer reporting the highest prevalence during and after treatment [1,6].

Although disease-related fatigue usually occurs in the diseased population, the percentage of almost healthy community-dwelling adults experiencing considerable pathological fatigue is estimated to be nearly 40% [1], and is more often present in women than men [7,8]. This unexplained, idiopathic, and generalized or chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), typically emerges spontaneously with flu-like symptoms [3]. It is characterized by a cluster of unspecific clinical symptoms such as cognitive dysfunction ("brain fog"), headaches, enlarged and painful lymph nodes, irritable bowels, unrefreshing sleep, sore throat, muscle/joint pain or morning stiffness, and severe unphysiologic postexertional malaise [3,9], which simultaneously serve as diagnostic criteria

Clinical review

Lesson of the week

Musculoskeletal pain in female asylum seekers and hypovitaminosis D_3

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Female asylum seekers with persistent non-specific musculoskeletal pain should be screened for hypovitaminosis D_3

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Deficiency of vitamin D_3 which can lead to osteomalacia, is common in elderly patients in Western countries. However, it is still widely underdiagnosed in young immigrant women, even though the condition has been extensively reported in the immigrant Indo-Asian population in the United Kingdom since the 1960s.[1-3] A recent study reports an average 59 months before diagnosis was established,[4] and another study found a prevalence of 78% of hypovitaminosis D_3 (compared with 58% in controls) in an Indo-Asian population attending a UK rheumatology clinic.[5] When recognised, hypovitaminosis D_3 is easily treatable. A study on osteomalacic myopathy in veiled Arabic women in Denmark found that muscle strength returned to normal (except in maximal voluntary contraction) after six months' treatment.[7]

We expected to see this disease in female asylum seekers, especially in those from societies with different customs regarding exposure to sunlight and diet. We report 11 cases of symptomatic hypovitaminosis D_3 in female asylum seekers (table 1). We focus on the pathology encountered by the primary care doctors caring for these 11 patients, the length of time between the appearance of symptoms, and the establishment of the diagnosis of hypovitaminosis D_3 as well as the women's response to treatment by the improvement of a wide range of clinical symptoms—bone pain, muscular weakness, and fatigue.

Case reports

The primary care doctors of an academic primary care centre serving a population of 100 000 provided the cases. The patients presented with minimal exposure to sunlight and a history of bone pain, proximal muscular weakness, change in gait, or fatigue. Treatment for most patients was two intramuscular injections of 18 750 nmol (300 000 IU) of cholecalciferol at monthly intervals and an ongoing course of oral calcium (1000 mg) and cholecalciferol (20 μg). All patients gave their informed consent.

We measured 25-hydroxycholecalciferol (the best laboratory indicator of vitamin D status) with a radioimmunoassay and an iodine-125 labelled tracer and calcium concentrations with spectrophotometry.[6] The reference ranges are 21-131 nmol/l and 2.15-2.55 mmol/l. The reference range for 25-hydroxycholecalciferol is from a healthy predominately white group of 20 men and 24 women from the midwest United States, aged between 23 and 67 years who volunteered during the month of October.

The first diagnoses, before the diagnoses of hypovitaminosis D_3 were made, were possible somatisation disorder in three patients, chronic back pain in four patients, and multiple unexplained somatic symptoms in three patients. Doctors considered and mentioned hypovitaminosis D_3 in only one case after being formerly told of the possible high prevalence of the disease and suspecting it on presentation.

The mean duration of symptoms before diagnosis was 38 months and 3 days (3.18 (standard deviation 4.15) years). Most complaints (with the exception of those of patient 11) were typical of hypovitaminosis D_3 from the outset. With treatment, most patients' symptoms disappeared within one to three months. One patient needed seven months of treatment.

At diagnosis, the mean serum 25-hydroxycholecalciferol concentration was 10.9 (3.8) nmol/l (table 2). These concentrations were during November to May, when the intensity of the sun is low at latitude 46.3°. For 10 patients, the mean concentration of blood calcium on diagnosis was 2.19 (0.09) mmol/l, and four patients had hypocalcaemia (<2.15 mmol/l).

Table 1 Demographic and clinical data for 11 female asylum seekers with hypovitaminosis D_3

Patient	Age	Origin	Time in Switzerland (years)	Veil	Complaints
1	52	Bosnia	11	Yes	Pain in ribs and neck then lower back and thighs
2	37	Afghanistan	3	Yes	Weakness and pain in thighs; occasional lower back pain
3	37	Somalia	10	Yes	Lower back pain, occasional mid-back and rib pain
4	30	Albania	6	No	Lower back and pelvic pain
5	42	Somalia	4	Yes	Back, knee, and shoulder pain
6	43	Bosnia	4	Yes	Back pain then diffuse bone pain
7	45	Somalia	10	Yes	Diffuse back and lower limb pain; fatigue
8	63	Somalia	3.5	Yes	Back pain with diffuse lower limb pain
9	20	Ethiopia	6.5	No	Lower back and lower limb pain; scapular pain
10	51	Bosnia	1	Yes	Lower limb pain
11	62	Bosnia	6	Yes	Lower right limb pain

Discussion

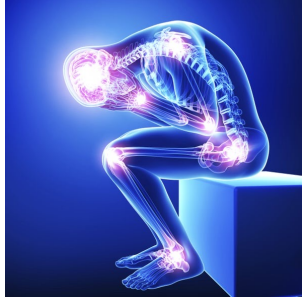
Asylum seekers are at risk because of the possible high prevalence of hypovitaminosis D_3 and difficulty in recognising the condition. The first diagnosis considered, in an often psychologically difficult context, is one suggestive either of somatoform disorder, as described in ICD-10 (international classification of diseases, 10th revision)[7] or somatisation. Patients with psychological disorders may report multiple unexplained somatic symptoms,[8] but pain due to hypovitaminosis D_3 is well defined. Generally, this pain is symmetrical and starts in the lower back then spreads to the pelvis, upper legs, and ribs. It is felt mainly in the bones; not in the joints. Patients may also have proximal muscle weakness.

Symptoms may last for some time before diagnosis, causing important psychosocial repercussions in an already vulnerable population. This confirms the poor knowledge of hypovitaminosis D_3 in doctors.[1]

With treatment, complete resolution is rapid—usually within three months. Doctors simultaneously treated patient 11 for a suspected venous insufficiency

1.Medicine (Baltimore). 2016 Dec; 95(52): e5353. **2**.PLoS One. 2013; 8(5): e65034. **3**. Nutrients. 2019 Oct; 11(10): 2315. **4**. BMJ VOLUME 329 17 JULY 2004 bmj.com

Vitamina D y dolor



Rev Soc Esp Dolor
2016; 23(4): 211-214

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Vitamina D y dolor crónico

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Alcántara Montero A. Vitamina D y dolor crónico. Rev Soc Esp Dolor 2016;23(4):211-214.

ABSTRACT

Vitamin D, a fat-soluble vitamin found in few natural food sources, is synthesized in human skin after sun exposure. Insufficient and deficiency of vitamin D is very common in the world, which is thought to contribute to a wide range of health issues. Vitamin D has long been utilized in combination with calcium to improve bone health and reduce the risk of fractures. Vitamin D supplementation has been linked to the prevention of high blood pressure, cancer, and other diseases. Recent research also points to a possible association between vitamin D deficiency and chronic pain.

Key words: Vitamin D, chronic pain.

RESUMEN

La vitamina D, una vitamina liposoluble que se encuentra en algunas fuentes de alimentos naturales, se sintetiza en la piel humana después de la exposición al sol. La insuficiencia y la deficiencia de vitamina D son muy frecuentes en el mundo, lo cual se cree que contribuye a una gran variedad de problemas de salud. La vitamina D durante mucho tiempo ha sido utilizada en combinación con el calcio para mejorar la salud ósea y reducir el riesgo de fracturas. Los suplementos de vitamina D se han relacionado con la prevención de la hipertensión arterial, cáncer y otras enfermedades. Investigaciones recientes también apuntan a una posible asociación entre la deficiencia de vitamina D y el dolor crónico.

Palabras clave: Vitamina D, dolor crónico.

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Aceptado: 15-08-15.

INTRODUCCIÓN

La vitamina D es una vitamina liposoluble. En los seres humanos existen 2 formas: ergocalciferol (vitamina D2) y colecalciferol (vitamina D3). Mientras que la vitamina D2 es sintetizada principalmente por las plantas, la luz solar puede promover la síntesis de vitamina D3 en la piel humana. Pocos alimentos contienen la forma natural de la vitamina D, por lo que la síntesis cutánea suele ser la principal fuente de la misma. Las yemas de huevo y el pescado son fuentes naturales de vitamina D, aunque ciertas variedades de cereales, leche y zumo de naranja están enriquecidos con vitamina D (1,2).

En los seres humanos, la vitamina D ayuda a mantener las concentraciones normales de calcio y fósforo sérico mediante la regulación de la absorción y la excreción. Por lo tanto, la vitamina D es clave en la homeostasis ósea. La vitamina D ha sido administrada durante mucho tiempo sola, o en combinación con calcio, para mejorar la salud ósea y reducir el riesgo de fracturas. Algunas fuentes sugieren que los suplementos de vitamina D pueden prevenir la hipertensión arterial, el cáncer y otras enfermedades (3,4). En la actualidad, niveles insuficientes o incluso franca deficiencia de vitamina D determinada como 25-hidroxi vitamina D constituye una "epidemia" en todo el mundo que afecta a más de la mitad de la población, descrita en niños, jóvenes, adultos, mujeres postmenopáusicas y ancianos; sobre todo si tienen fracturas osteoporóticas, donde la pre-

nutrients MDPI

Article

Hypovitaminosis D in Postherpetic Neuralgia—High Prevalence and Inverse Association with Pain: A Retrospective Study

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check for updates

Abstract: Hypovitaminosis D (25-hydroxyvitamin D (25(OH)D) <75 nmol/L) is associated with neuropathic pain and varicella-zoster virus (VZV) immunity. A two-part retrospective hospital-based study was conducted. Part I (a case-control study): To investigate the prevalence and risk of hypovitaminosis D in postherpetic neuralgia (PHN) patients compared to those in gender/index-month/age-auto matched controls who underwent health examinations. Patients aged ≥50 years were automatically selected by ICD-9 codes for shingle/PHN. Charts were reviewed. Part II (a cross-sectional study): To determine associations between 25(OH)D, VZV IgG/M, pain and items in the DN4 questionnaire at the first pain clinic visit of patients. Independent predictors of PHN were presented as adjusted odds ratios(AOR) and 95% confidence intervals (CI). Prevalence (73.9%) of hypovitaminosis D in 88 patients was high. In conditional logistic regressions, independent predictors for PHN were hypovitaminosis D (AOR3.12, 95% CI1.73–5.61), malignancy (AOR3.21, 95% CI 1.38–7.48) and *Helicobacter pylori*-related peptic ulcer disease (AOR3.47, 95% CI 1.71–7.03). 25(OH)D was inversely correlated to spontaneous/brush-evoked pain. Spontaneous pain was positively correlated to VZV IgM. Based on the receiver operator characteristic curve, cutoffs for 25(OH)D to predict spontaneous and brush-evoked pain were 67.0 and 169.0 nmol/L, respectively. A prospective, longitudinal study is needed to elucidate the findings.

Keywords: hypovitaminosis D; 25-hydroxyvitamin D; postherpetic neuralgia; spontaneous pain; brush-evoked pain; varicella-zoster virus immunoglobulin; DN4questionnaire

1. Introduction

Vitamin D is essential for musculoskeletal health in humans. The major circulating form of vitamin D is serum 25-hydroxyvitamin D (25(OH)D)—the main storage form. Currently, serum total 25(OH)D is considered to be the best marker of vitamin D status among the possible markers [1]. However, the definition of hypovitaminosis D is a central controversy in vitamin D research [1]. In the present study, sufficiency of vitamin D is defined as 25(OH)D ≥ 75 nmol/L (30 ng/mL) as defined by the Endocrine Society Clinical Practice Guideline [2]. Low vitamin D (hypovitaminosis D) includes insufficiency

Lesson of the week

Musculoskeletal pain in female asylum seekers and hypovitaminosis D_3

Gabrielle de Torrenté de la Jara, Alain Pécoud, Bernard Favrat

Female asylum seekers with persistent non-specific musculoskeletal pain should be screened for hypovitaminosis D_3

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BMJ 2004;329:156-7

Deficiency of vitamin D, which can lead to osteomalacia, is common in elderly patients in Western countries. However, it is still widely underdiagnosed in young immigrant women, even though the condition has been extensively reported in the immigrant Indo-Asian population in the United Kingdom since the 1960s.[1–3] A recent study reports an average 59 months before diagnosis was established,[1] and another study found a prevalence of 78% of hypovitaminosis D_3 (compared with 58% in controls) in an Indo-Asian population attending a UK rheumatology clinic.[3] When recognised, hypovitaminosis D_3 is easily treatable. A study on osteomalacic myopathy in veiled Arabic women in Denmark found that muscle strength returned to normal (except in maximal voluntary contraction) after six months' treatment.[1]

We expected to see this disease in female asylum seekers, especially in those from societies with different customs regarding exposure to sunlight and diet. We report 11 cases of symptomatic hypovitaminosis D_3 in female asylum seekers (table 1). We focus on the pathology encountered by the primary care doctors caring for these 11 patients, the length of time between the appearance of symptoms, and the establishment of the diagnosis of hypovitaminosis D_3 as well as the women's response to treatment by the improvement of a wide range of clinical symptoms—bone pain, muscular weakness, and fatigue.

Case reports

The primary care doctors of an academic primary care centre serving a population of 100 000 provided the cases. The patients presented with minimal exposure to sunlight and a history of bone pain, proximal muscular weakness, change in gait, or fatigue. Treatment for most patients was two intramuscular injections of 18 750 nmol (300 000 IU) of cholecalciferol at monthly intervals and an ongoing course of oral calcium (1000 mg) and cholecalciferol (20 µg). All patients gave their informed consent.

We measured 25-hydroxycholecalciferol (the best laboratory indicator of vitamin D status) with a radioimmunoassay and an iodine-125 labelled tracer and calcium concentrations with spectrophotometry.[3] The reference ranges are 21-131 nmol/l and 2.15-2.55 mmol/l. The reference range for 25-hydroxycholecalciferol is from a healthy predominately white group of 20 men and 24 women from the midwest United States, aged between 23 and 67 years who volunteered during the month of October.

The first diagnoses, before the diagnoses of hypovitaminosis D_3 were made, were possible somatisation disorder in three patients, chronic back pain in four patients, and multiple unexplained somatic symptoms in three patients. Doctors considered and mentioned hypovitaminosis D_3 in only one case after being formerly told of the possible high prevalence of the disease and suspecting it on presentation.

The mean duration of symptoms before diagnosis was 38 months and 3 days (3.18 (standard deviation 4.15) years). Most complaints (with the exception of those of patient 11) were typical of hypovitaminosis D_3 from the outset. With treatment, most patients' symptoms disappeared within one to three months. One patient needed seven months of treatment.

At diagnosis, the mean serum 25-hydroxycholecalciferol concentration was 10.9 (3.8) nmol/l (table 2). These concentrations were during November to May, when the intensity of the sun is low at latitude 46.3°. For 10 patients, the mean concentration of blood calcium on diagnosis was 2.19 (0.09) mmol/l, and four patients had hypocalcaemia (<2.15 mmol/l).

Table 1 Demographic and clinical data for 11 female asylum seekers with hypovitaminosis D_3

Patient	Age	Origin	Time in Switzerland (years)	Veil	Complaints
1	52	Bosnia	11	Yes	Pain in ribs and neck then lower back and thighs
2	57	Afghanistan	3	Yes	Weakness and pain in thighs; occasional lower back pain
3	27	Somalia	10	Yes	Lower back pain, occasional mid-back and rib pain
4	30	Albania	6	No	Lower back and pelvic pain
5	42	Somalia	4	Yes	Back, knee, and shoulder pain
6	43	Bosnia	4	Yes	Back pain then diffuse bone pain
7	45	Somalia	10	Yes	Diffuse back and lower limb pain; fatigue
8	63	Somalia	2.5	Yes	Back pain with diffuse lower limb pain
9	20	Ethiopia	6.5	No	Lower back and lower limb pain; scapular pain
10	51	Bosnia	1	Yes	Lower limb pain
11	62	Bosnia	6	Yes	Lower right limb pain

Discussion

Asylum seekers are at risk because of the possible high prevalence of hypovitaminosis D_3 and difficulty in recognising the condition. The first diagnosis considered, in an often psychologically difficult context, is one suggestive either of somatoform disorder, as described in ICD-10 (international classification of diseases, 10th revision)[4] or somatisation. Patients with psychological disorders may report multiple unexplained somatic symptoms,[5,6] but pain due to hypovitaminosis D_3 is well defined. Generally, this pain is symmetrical and starts in the lower back then spreads to the pelvis, upper legs, and ribs. It is felt mainly in the bones; not in the joints. Patients may also have proximal muscle weakness.

Symptoms may last for some time before diagnosis, causing important psychosocial repercussions in an already vulnerable population. This confirms the poor knowledge of hypovitaminosis D_3 in doctors.[1]

With treatment, complete resolution is rapid—usually within three months. Doctors simultaneously treated patient 11 for a suspected venous insufficiency

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Association of Vitamin D and Incident Statin Induced Myalgia—A Retrospective Cohort Study

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Abstract

Background and Objectives: Evidence is conflicting with regards to the role of vitamin D in statin induced myalgia (SIM). Studies so far have assessed cross-sectional association and were limited by study sample selected predominantly from cardiology clinics. In this retrospective cohort study we assessed the association between vitamin D and SIM and attempted to establish a serum vitamin D cutoff to identify patients at risk for developing SIM.

Methods: Medical charts of 5526 consecutive patients from a primary care practice in Scranton, Pennsylvania from 2005–2012 were reviewed. Vitamin D level (25-hydroxy cholecalciferol) at statin initiation was considered "Exposure level". Vitamin D levels were categorized into quartiles (≤ 10, 11–20, 21–30, >30 ng/ml). SIM was identified by patient report.

Results: 1160 out of 5526 patients were treated with statins. The mean age was 55.9 years. 276 (24%) developed SIM. Unadjusted 7-yr cumulative incidences of SIM for quartiles 1–4 of vitamin D were 32.3, 21.5, 18.3 and 14.6% respectively. The lowest quartile of vitamin D was independently associated with 1.21 times the hazard of the fourth quartile for developing SIM (95% CI: 1.09, 1.33; P-trend = 0.001). Vitamin D cut-off ≤15 ng/ml, showed a positive predictive value, negative predictive value, likelihood ratio (LR) + and LR- of 81, 90, 5.1 and 0.1, respectively for predicting SIM.

Conclusions: Low vitamin D level at statin initiation is associated with SIM, levels ≤15 ng/ml have a high predictive accuracy for SIM. Randomized controlled trials are needed to validate our results.

Citation: Palamaner Subash Shantha G, Ramos J, Thomas-Hemak L, Pancholy SB (2014) Association of Vitamin D and Incident Statin Induced Myalgia—A Retrospective Cohort Study. PLoS ONE 9(2): e88877. doi:10.1371/journal.pone.0088877

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Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Statins are effective therapy for primary prevention of cardiovascular events in high risk populations [1,2]. In patients with cardiovascular disease, statins reduce mortality, morbidity, recurrent cardiovascular events, atrial fibrillation and stroke [1,2,3,4,5]. Observational studies have reported pleiotropic benefits of statins including reduction in sepsis, pneumonia related mortality [6] and cancer risk [7], though randomized controlled trials have failed to validate these findings.

In spite of proven benefit and the established increased risk of cardiovascular events in patients with coronary artery disease who discontinue statin therapy [8,9], adherence to statin therapy remains poor and is estimated to be <50% in various patient populations [10,11,12,13]. Among the factors considered, statin induced myalgia (SIM) is reported to the predominant factor associated with poor statin compliance [14,15]. In a recent study involving multiple primary care practices in Boston, 27% of Statin users reported SIM [16].

Vitamin D has been associated with the development of SIM [17,18,19,20]. However, evidence is conflicting with regards to the cross-sectional association of vitamin D and SIM [17,18,19,20] and studies assessing prospective association between vitamin D and SIM are lacking.

In this retrospective cohort study, involving a large population of unselected patients from a primary care practice in rural Pennsylvania, we have explored the prospective association of vitamin D and SIM and attempted to identify a serum vitamin D cut-off with significant predictive accuracy to identify patients at risk for SIM.

Materials and Methods

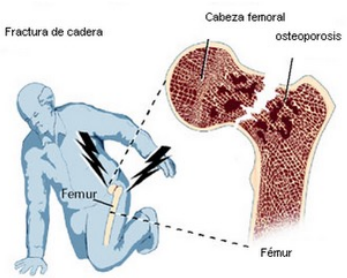
Study setting and design

This retrospective cohort study was conducted in a primary care outpatient clinic located in Scranton, Pennsylvania. Institutional review board approval was obtained from the Wright Center for Graduate Medical Education institutional review board for conducting the study. Informed consent was not obtained from the participants, as the data was analyzed anonymously per institutional review board guidelines. Institutional review board waived the need for written informed consent from the participants.

Case records of 6946 consecutive adult patients who attended the primary care clinic during the period March 2005 to November 2012 were reviewed. All patients with a minimum of 2 recorded follow-up visits and complete data for the study

1. Rev Soc Esp Dolor. 2016; 23(4): 211-214 **2**. Nutrients 2019, 11, 2787; **3**. BMJ VOLUME 329 17 JULY 2004 bmj.com **4**. PLOS ONE www.plosone.org 1 February 2014. Volume 9, Issue 2, e88877

¿Dosis altas de vitamina D y riesgo de caídas en adultos mayores?



Research

Original Investigation | LESS IS MORE

Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline
A Randomized Clinical Trial

Heike A. Bischoff-Ferrari, MD, DrPH; Bess Dawson-Hughes, MD; E. John Orav, PhD; Hannes B. Staehelin, MD; Otto W. Meyer, MD; Robert Theiler, MD; Walter Dick, MD; Walter C. Willett, MD, DrPH; Andreas Egli, MD

IMPORTANCE Vitamin D deficiency has been associated with poor physical performance.

OBJECTIVE To determine the effectiveness of high-dose vitamin D in lowering the risk of functional decline.

DESIGN, SETTING, AND PARTICIPANTS One-year, double-blind, randomized clinical trial conducted in Zurich, Switzerland. The screening phase was December 1, 2009, to May 31, 2010, and the last study visit was in May 2011. The dates of our analysis were June 15, 2012, to October 10, 2015. Participants were 200 community-dwelling men and women 70 years and older with a prior fall.

INTERVENTIONS Three study groups with monthly treatments, including a low-dose control group receiving 24 000 IU of vitamin D_3 (24 000 IU group), a group receiving 60 000 IU of vitamin D_3 (60 000 IU group), and a group receiving 24 000 IU of vitamin D_3 plus 300 µg of calcifediol (24 000 IU plus calcifediol group).

Editorial

Supplemental content at jamainternalmedicine.com

Published online January 4, 2016.

Switzerland (heike.bischoff@usz.ch).

Conclusions

Compared with a monthly standard-of-care dose of 24 000 IU of vitamin D_3, two monthly higher doses of vitamin D (60 000 IU and 24 000 IU plus calcifediol) conferred no benefit on the prevention of functional decline and increased falls in seniors 70 years and older with a prior fall event. Therefore, high monthly doses of vitamin D or a combination with calcifediol may not be warranted in seniors with a prior fall because of a potentially deleterious effect on falls. Future research is needed to confirm our findings for daily dosing regimens.

Cochrane Library

Cochrane Database of Systematic Reviews

Exercise for preventing falls in older people living in the community (Review)

Sherrington C, Fairhall NJ, Wallbank GK, Tiedemann A, Michaleff ZA, Howard K, Clemson L, Hopewell S, Lamb SE

AUTHORS' CONCLUSIONS

Implications for practice

Well-designed exercise programmes reduce the rate of falls and the number of people experiencing falls amongst older people living in the community (high-certainty evidence).

Como prevenir las caídas:

Haga una cita con su médico.

Practique la actividad física.

Use zapatos cómodos.

Evite los peligros en el hogar.

Ilumine su espacio vital.

Use dispositivos de asistencia.

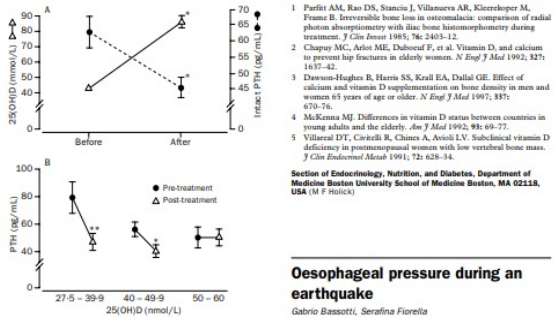
Exercise for preventing falls in older people living in the community (Review). 2019 The Cochrane Collaboration.

https://www.mayoclinic.org/healthy-lifestyle/healthy-aging/in-depth/fall-prevention/art-20047358

Recordando la Utilidad, Seguridad y Comodidad de las Dosis Altas de Vitamina D

Redefining vitamin D insufficiency

A Malabanan, I E Veronikis, M F Holick



Relations between 25(OH)D and PTH before and after therapy with 50 000 IU of vitamin D, and calcium supplementation once a week for 8 weeks
A=serum 25(OH)D and PTH; B=serum PTH changes in patients stratified by pretreatment serum 25(OH)D between 27·5–60 nmol/L. *p<0·001, **p<0·02.

[5] to 45 [3] pg/mL) (figure A). Calcium did not change (2·33 [0·03] to 2·35 [0·03] mmol/L, p=0·31). 40% overall had secondary hyperparathyroidism (PTH >65 pg/mL). Serum PTH values were evaluated with respect to stratified pre-treatment 25(OH)D levels (figure B). After vitamin D and calcium therapy, PTH decreased by 35% (80 [12] to 48 [6] pg/mL, p<0·02) for 25(OH)D levels of 27·5–39·9 nmol/L (n=11, 55% had secondary hyperparathyroidism) and by 26% (57 [5] to 41 [5] pg/mL, p<0·001) for 25(OH)D values of 40–49·9 nmol/L (n=17; 35% had secondary hyperparathyroidism). For 25(OH)D of 50 to 60 nmol/L (n=7), PTH decreases were not significant although 25(OH)D levels increased by 66%. Notably, in patients without secondary hyperparathyroidism (n=16) (pre-treatment 25(OH)D levels of 27·5–47·5 nmol/L), PTH still decreased by 22% (47 [3] to 37 [5] pg/mL, p<0·01).

Adults over the age of 49 years may require a serum 25(OH)D of at least 50 nmol/L to achieve the optimum PTH levels. When 25(OH)D levels were below 50 nmol/L, PTH tended to increase, potentially resulting in increased bone calcium mobilisation and accompanying bone loss. After reviewing 169 patients seen in our bone health clinic (86% women, 14% men; average age is 62 [16] years), 41% were found at risk for vitamin D deficiency with 25(OH)D concentrations less than 50 nmol/L. Therefore, secondary hyperparathyroidism as well as inappropriately high normal PTH levels exist in patients (ages 49–83 years) with 25(OH)D levels previously believed to be sufficient.

1 Parfitt AM, Rao DS, Stanciu J, Villanueva AR, Kleerekoper M, Frame B. Irreversible bone loss in osteomalacia: comparison of radial photon absorptiometry with iliac bone histomorphometry during treatment. *J Clin Invest* 1985; 76: 2403–12.
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4 McKenna MJ. Differences in vitamin D status between countries in young adults and the elderly. *Am J Med* 1992; 93: 69–77.
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Section of Endocrinology, Nutrition, and Diabetes, Department of Medicine Boston University School of Medicine Boston, MA 02118, USA (M F Holick)

Oesophageal pressure during an earthquake

Gabrio Bassotti, Serafina Fiorella

Stress can alter gastrointestinal motility;[1] in particular, oesophageal motility may be altered by stress, although most studies have investigated only the body of the oesophagus and the upper oesophageal sphincter.[2] Almost all studies have been done in a controlled setting. We had the opportunity to observe the behaviour of the lower oesophageal sphincter during a natural stress.

On Oct 3, 1997, while doing a manometric examination in a 62-year-old woman complaining of non-obstructive dysphagia, in Perugia in Umbria, Italy, there was an earthquake. The epicentre was in the Colfiorito area, about 35 miles from the city, and the magnitude of the earthquake was 5·2° on the Richter scale and 7°–8° on the Mercalli scale. We were half way through the manometry when the seismic event struck. Sphincter pressure immediately dropped from about 20 mm Hg to about 5 mm Hg. The examination was stopped, and when repeated 3 days later average sphincter pressure was within the normal range (21 mm Hg) and the oesophagus showed no abnormalities.

It appears that, unlike in the oesophageal body or at the upper oesophageal sphincter, where the responses to stress are usually excitatory, the effects of stress on the lower sphincter is to inhibit tone. This inhibition might be due to a sudden increase in adrenergic activity,[3] which has been suggested as one cause of the increased incidence of sudden cardiac deaths triggered by an earthquake.[4]

As previously noted,[1] these observations exemplify the tradition in medical science of extracting information from a catastrophe.

1 Bass C. Life events and gastrointestinal symptoms. *Gut* 1986; 27: 123–26.
2 Holtmann G, Enck P. Stress and gastrointestinal motility in humans: a review of the literature. *J Gastrointest Motility* 1991; 3: 245–54.
3 Diamant NE. Physiology of the esophagus. In: Sleisenger MH, Fordtran JS, eds. Gastrointestinal disease, 5th edition. Philadelphia: WB Saunders Company, 1993: 319–30.

Therapy with 50 000 IU of oral vitamin D_2 weekly for 8 weeks along with supplemental calcium safely and effectively corrects secondary hyperparathyroidism, potentially leading to decreased fracture risk in the elderly.

THE LANCET • Vol 351 • March 14, 1998

SPECIAL FEATURE

Clinical Practice Guideline

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

Boston University School of Medicine (M.F.H.), Boston, Massachusetts 02118; University of Wisconsin (N.C.B.), Madison, Wisconsin 53706; University Hospital Zurich (H.A.B.-F.), CH-8091 Zurich, Switzerland; Children's Hospital Boston (C.M.G.), Boston, Massachusetts 02115; University of Calgary Faculty of Medicine (D.A.H.), Calgary, Alberta, Canada T2N 1N4; Creighton University (R.P.H.), Omaha, Nebraska 68178; Mayo Clinic (M.H.M.), Rochester, Minnesota 55905; and Purdue University (C.M.W.), West Lafayette, Indiana 47907

Objective: The objective was to provide guidelines to clinicians for the evaluation, treatment, and prevention of vitamin D deficiency with an emphasis on the care of patients who are at risk for deficiency.

Participants: The Task Force was composed of a Chair, six additional experts, and a methodologist. The Task Force received no corporate funding or remuneration.

Consensus Process: Consensus was guided by systematic reviews of evidence and discussions during several conference calls and e-mail communications. The draft prepared by the Task Force was reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Core Committee, and cosponsoring associations, and it was posted on The Endocrine Society web site for member review. At each stage of review, the Task Force received written comments and incorporated needed changes.

Conclusions: Considering that vitamin D deficiency is very common in all age groups and that few foods contain vitamin D, the Task Force recommended supplementation at suggested daily intake and tolerable upper limit levels, depending on age and clinical circumstances. The Task Force also suggested the measurement of serum 25-hydroxyvitamin D level by a reliable assay as the initial diagnostic test in patients at risk for deficiency. Treatment with either vitamin D_2 or vitamin D_3 was recommended for deficient patients. At the present time, there is not sufficient evidence to recommend screening individuals who are not at risk for deficiency or to prescribe vitamin D to attain the noncalcemic benefit for cardiovascular protection. (*J Clin Endocrinol Metab* 96: 1911–1930, 2011)

Summary of Recommendations

1.0 Diagnostic procedure

assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. Vitamin D deficiency is de-

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|⊕⊕⊕⊕).

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

What do Cochrane systematic reviews say about interventions for vitamin D supplementation? | COCHRANE HIGHLIGHTS

Table 1. Main characteristics relating to clinical situation, intervention, findings and quality of evidence among the systematic reviews included

Clinical situation	Vitamin D	Findings	Quality of evidence (GRADE approach*)
Asthma[6]	500 IU/day to 4000 IU/day	Reduction of risk of exacerbations requiring systemic corticosteroids and risk of having at least one exacerbation requiring an emergency department visit or hospitalization or both. No difference in predicted percentage of forced expiratory volume in one second, asthma control test scores or risk of serious adverse events.	Moderate to high
Atopic eczema[7]	1000 IU/day to 1600 IU/day	No reliable evidence for benefits or harm.	-
Sickle cell disease[8]	240,000 to 600,000 IU in six weeks	Higher serum vitamin D levels at eight, 16 and 24 weeks.	-

Prevention of adverse outcomes in pregnancy[12]	200 IU/day to 2000 IU/day 35,000 IU/week 200,000 IU to 600,000 IU in single dose
Chronic painful conditions in adults[13]	1,200 IU/day to 100,000 IU/day 50,000 IU/week 150,000 IU in single dose
Prevention of cancer in adults[14]	300 IU/day to 3333 IU/day
Cystic fibrosis[15]	800 IU/day to 1600 IU/day 250,000 IU in single dose
Prevention of mortality among adults[16]	400 IU/day to 100,000 IU/day 18,000 IU/day to 100,000 IU/day 300,000 IU in single dose
Recovery from hip fracture among elderly people[17]	800 IU/day to 2,000 IU/day 50,000 IU in single dose to 100,000 IU in single dose

Sao Paulo Med J. 2017; 135(5):497-507 497

Recordando la Utilidad, Seguridad y Comodidad de las Dosis Altas de Vitamina D

Para tratar la deficiencia de vitamina D en EEUU, se han administrado 50.000 UI vitamina D_2, una vez por semana durante 8 semanas, alcanzando 75 nmol/L.[1]

Para obtener la suficiencia de vitamina D, se han recomendado 50.000 UI de vitamina D_2, cada 2 semanas, para mantenerla en 75 nmol/L.[2]

1. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet 1998;351:805– 6
2. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.

Tratamiento y de Prevención del Déficit de Vitamina D

NIÑOS < 1 año

- Deficiencia: 1 ampolla cada semana x 6 semanas
- Mantenimiento: 1 ampolla Cada dos meses

NIÑOS 1 a 18 años

- Deficiencia: 1 ampolla cada semana x 6 semanas
- Mantenimiento: 1 ampolla mes

ADULTOS

- Deficiencia: 2 ampollas semanal x 8 semanas
- Mantenimiento: 2 ampollas mes

Recommendation

3.2 For infants and toddlers aged 0–1 yr who are vitamin D deficient, we suggest treatment with 2000 IU/d of vitamin D_2 or vitamin D_3, or with 50,000 IU of vitamin D_2 or vitamin D_3 once weekly for 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml followed by maintenance therapy of 400-1000 IU/d (2|⊕⊕⊕⊕).

Recommendation

3.3 For children aged 1–18 yr who are vitamin D deficient, we suggest treatment with 2000 IU/d of vitamin D_2 or vitamin D_3 for at least 6 wk or with 50,000 IU of vitamin D_2 once a week for at least 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml followed by maintenance therapy of 600-1000 IU/d (2|⊕⊕⊕⊕).

Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline J Clin Endocrinol Metab, July 2011, 96(7):1911–1930

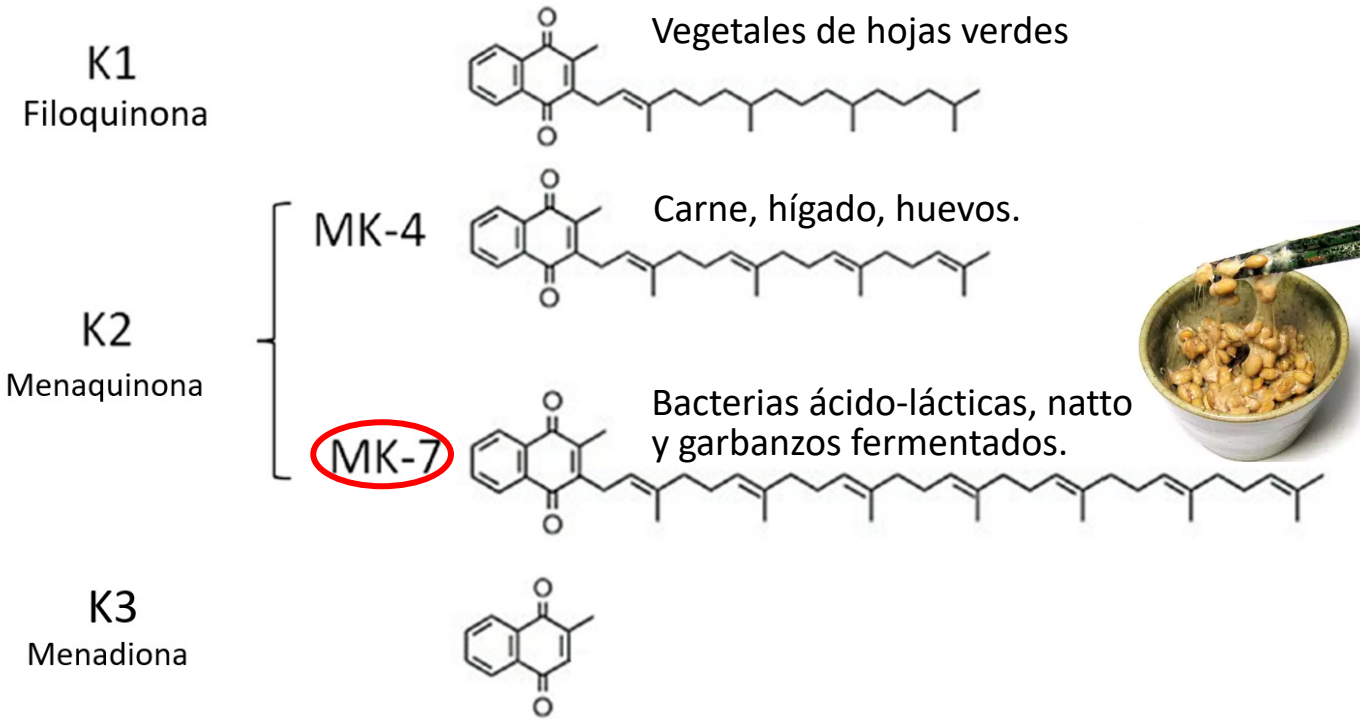
Evidencia Cochrane del Empleo de Vitamina D

Clinical situation	Vitamin D	Findings	Quality of evidence (GRADE approach*)
Asthma[6]	500 IU/day to 4000 IU/day	Reduction of risk of exacerbations requiring systemic corticosteroids and risk of having at least one exacerbation requiring an emergency department visit or hospitalization or both. No difference in predicted percentage of forced expiratory volume in one second, asthma control test scores or risk of serious adverse events.	Moderate to high
Prevention of fractures in postmenopausal women and older men[11]	Many schemes and formulations of vitamin D. For detailed explanations, see full version.	No statistical difference in prevention of hip fracture or any new fracture (vitamin D alone, without calcium).	High
Prevention of adverse outcomes in pregnancy[12]	200 IU/day to 2000 IU/day 35,000 IU/week 200,000 IU to 600,000 IU in single dose	Reductions in preterm birth and in low birthweight. No difference in preeclampsia, gestational diabetes or adverse events.	Moderate
Prevention of cancer in adults[14]	300 IU/day to 3333 IU/day	No reduction in cancer occurrence rate. Slightly reduction in all-cause mortality. Slight reduction in cancer mortality favoring vitamin D (only for cholecalciferol form).	Low to moderate
Prevention of infections in children under five years of age[27]	400 IU/day to 2500 IU/day	No differences in all-cause mortality, cause-specific mortality, risk of pneumonia or risk of diarrhea.	Low to moderate
Children and adults with HIV infection[28]	4,000 IU/day to 7,000 IU/day 100,000 IU in single dose	No difference in mortality among HIV patients with active tuberculosis or in CD4 cell count.	Very low to moderate
Active tuberculosis[29]	200/day to 600 IU/day	No differences in mortality, tuberculosis cure at 6 months or sputum-smear or sputum-culture positivity at 8 weeks.	-

Sao Paulo Med J. 2017; 135(5):497-507 497

¿Es necesario combinar la Vitamina K con la Vitamina D?

Estructuras de la Vitamina K



La proteína Matrix Gla (MGP) potente inhibidor local de calcificaciones vasculares, se fosforila y carboxila mediante un proceso dependiente de vitamina K2 del tipo MK-7.

Molecules **2019**, 24, 829; doi:10.3390/molecules24050829
Delanaye et al. BMC Nephrology 2014, 15:145

Biodisponiblidad Comparativa de la Menaquinona 4 y Menaquinona 7

Sato et al. Nutrition Journal 2012, 11:93
http://www.nutritionj.com/content/11/1/93

SHORT REPORT

Comparison of menaquinone-4 and menaquinone-7 bioavailability in health

Toshiro Sato[1*], Leon J Schurgers[2] and Kazuhiro Uenishi[3]

Abstract

Background: Vitamin K_2 contributes to bone and cardiovascular health. Therefore, two vitam menaquinone-4 (MK-4) and menaquinone-7 (MK-7), have been used as nutrients by the food nutritional supplements to support bone and cardiovascular health. However, little is known bioavailability of nutritional MK-4. To investigate MK-4 and MK-7 bioavailability, nutritional do to healthy Japanese women.

Findings: Single dose administration of MK-4 (420 μg; 945 nmol) or MK-7 (420 μg; 647 nmol) morning together with standardized breakfast. MK-7 was well absorbed and reached maxima after intake and was detected up to 48 h after intake. MK-4 was not detectable in the serum time point. Consecutive administration of MK-4 (60 μg; 135 nmol) or MK-7 (60 μg; 92 nmol) demonstrated that MK-4 supplementation did not increase serum MK-4 levels. However, con of MK-7 increased serum MK-7 levels significantly in all subjects.

Conclusions: We conclude that MK-4 present in food does not contribute to the vitamin K s serum vitamin K levels. MK-7, however significantly increases serum MK-7 levels and therefore importance for extrahepatic tissues.

Keywords: Vitamin K_2, Menaquinone-4, Menaquinone-7, Bioavailability, Absorption

Introduction

Vitamin K acts as a cofactor for the endoplasmic enzyme γ- glutamylcarboxylase during the post-translational conversion of glutamic acid residues of specific proteins to γ-carboxyglutamic acid (Gla) to form Gla-containing proteins. A number of blood coagulation factors including coagulation factors II (prothrombin), VII, IX, and X are well-known examples of Gla-containing proteins, which are synthesized in the liver. Osteocalcin, a bone-specific protein synthesized by osteoblasts, and matrix Gla protein synthesized in blood vessel and bone are Gla-containing proteins synthesized at extra-hepatic sites [1].

There are two naturally occurring forms of vitamin K: vitamin K_1 (phylloquinone) derived from green plants and vitamin K_2 (menaquinones, MK-n), which is a series of vitamers with multi-isoprene units at position 3 of the common 2-methyl-1,4-naphthoquinone ring structure.

In food, vitamin K_1 is bound t brane of leafy green vegetables. products such as eggs, meat, an from the conversion of menadi vitamin K only consisting of th quinone ring structure), which Long chain menaquinones (ie. M are found in fermented foods su sauerkraut [2]. The Japanese fern tains MK-7 at an exceptionally hi

The effects of long chain MK-n blood coagulation is greater and min K_1 and MK-4 [3-5]. The effe was attributed to its very long ha a better carboxylation-grade of Vitamin K_1 [5].

Recent studies revealed that vi both bone and cardiovascular h and MK-7 have been used as n has been shown that all vitamir converted to MK-4 *in vivo* [9-1

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Full list of author information is available at the end of the article

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RESEARCH ARTICLE

Safety and toxicological evaluation of a synthetic vitamin K2, menaquinone-7

Kresimir Pucaj[1], Henrik Rasmussen[2], Mona Møller[3], and Tom Preston[1]

[1]*NucroTechnics, Scarborough, Ontario, Canada,* [2]*Norwegianl Institute of Public Health, Oslo, Norway, and* [3]*Kappa Bioscience AS, Oslo, Norway*

Abstract

Menaquinone-7 (MK-7) is part of a family of vitamin K that are essential co-factors for the enzyme γ-glutamyl carboxylase, which is involved in the activation of γ-carboxy glutamate (Gla) proteins in the body. Gla proteins are important for normal blood coagulation and normality of bones and arteries. The objective of this study was to examine the potential toxicity of synthetic MK-7 in BomTac:NMRI mice and in Sprague-Dawley rats. In an acute oral toxicity test, mice were administered a single oral dose of 2000 mg/kg body weight (limit dose) and no toxicity was observed during the 14-day observation period. In the subchronic oral toxicity test in rats, animals were administered MK-7 for 90 days by gavage at the following doses: 0 (vehicle control, corn oil), 2.5, 5, and 10 mg/kg body weight/day. All generated data, including clinical observations, ophthalmology, clinical pathology, gross necropsy, and histopathology, revealed no compound-related toxicity in rats. Any statistically significant findings in clinical pathology parameters and/or organ weights noted were considered to be within normal biological variability. Therefore, under the conditions of this experiment, the median lethal dose (LD_{50}) of MK-7 after a single oral administration in mice was determined to be greater than the limit dose level of 2000 mg/kg body weight. The no observed adverse effect level (NOAEL) of MK-7, when administered orally to rats for 90 days, was considered to be equal to 10 mg/kg body weight/day, the highest dose tested, based on lack of toxicity during the 90-day study period.

Keywords: Menaquinone-7, acute oral toxicity, 90-day oral subchronic toxicity study, histopathology

Introduction

Menaquinone-7 (MK-7) is part of a family of vitamin K, micronutrients necessary for the synthesis of blood coagulation factors and the activation of proteins involved in the building of bones and inhibition of vascular calcification (Cranenburg et al., 2007; Shearer and Newman, 2008).

The vitamin K consists of two main subfamilies: vitamin K1 (phylloquinone) and vitamin K2 or menaquinones. All the K vitamins have a similar structure; they share a "quinone" ring and an isoprenoid side chain. The difference lies in the side chain. Menaquinones are classified according to the length of their aliphatic side chain and are designated MK-*n*, where *n* represents the number of isoprenoid residues in that chain (Booth and Suttie, 1998; Shearer and Newman, 2008). Thus, MK-7 contains seven isoprenoid units. The vitamins K are highly lipophilic; MK-7 being more lipophilic than K1 and MK-4, resu in a much longer half-life (Schurgers and Vermeer, 2 Schurgers et al., 2007).

Vitamin K plays a critical role as a co-factor γ-glutamyl carboxylase-catalyzed reactions in posttranslational carboxylation of glutamic aci γ-carboxy glutamic acid, and both vitamin K1 K2 function in this way (Shearer and Newman, 20 These γ-carboxy glutamate (Gla) residues form c um-binding sites that are essential for the activi the proteins in which they are found (Rishavy et 2004). Gla-containing proteins are found in b and for this reason vitamin K may play an additi role in the homeostasis of bone metabolism and tribute to bone health (Binkley et al., 2002; Kna et al., 2007; Bügel, 2008; Shea and Booth, 2008 well as play a role in reducing fracture incide

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Article

High-Dose Menaquinone-7 Supplementation Reduces Cardiovascular Calcification in a Murine Model of Extraosseous Calcification

Daniel Scheiber [1,†], Verena Veulemans [1,†], Patrick Horn [1], Martijn L. Chatrou [2], Sebastian A. Potthoff [3], Malte Kelm [1,4], Leon J. Schurgers [2,†] and Ralf Westenfeld [1,†,*]

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Received: 15 May 2015 / Accepted: 6 August 2015 / Published: 18 August 2015

Abstract: Cardiovascular calcification is prevalent in the aging population and in patients with chronic kidney disease (CKD) and diabetes mellitus, giving rise to substantial morbidity and mortality. Vitamin K-dependent matrix Gla-protein (MGP) is an important inhibitor of calcification. The aim of this study was to evaluate the impact of high-dose menaquinone-7 (MK-7) supplementation (100 μg/g diet) on the development of extraosseous calcification in a murine model. Calcification was induced by 5/6 nephrectomy combined with high phosphate diet in rats. Sham operated animals served as controls. Animals received high or low MK-7 diets for 12 weeks. We assessed vital parameters, serum chemistry, creatinine clearance, and cardiac function. CKD provoked increased aortic (1.3 fold; $p < 0.05$) and myocardial (2.4 fold; $p < 0.05$) calcification in line with increased alkaline phosphatase

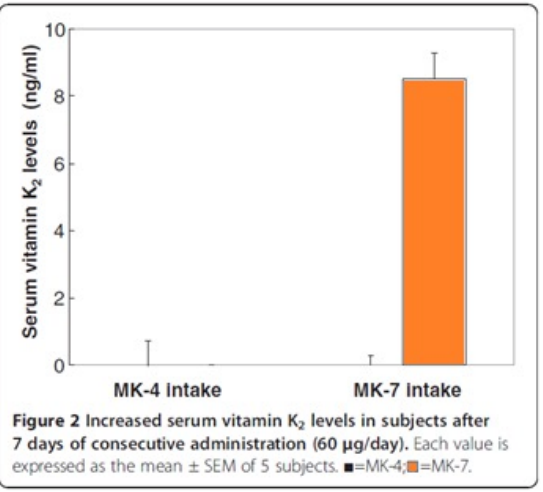


Figure 2 Increased serum vitamin K_2 levels in subjects after 7 days of consecutive administration (60 μg/day). Each value is expressed as the mean ± SEM of 5 subjects. ■=MK-4;■=MK-7.

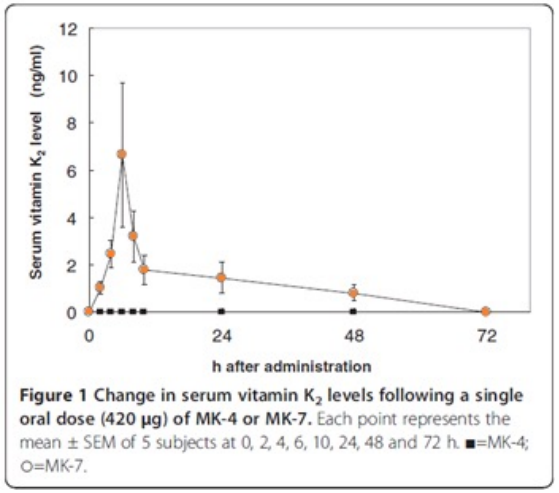


Figure 1 Change in serum vitamin K_2 levels following a single oral dose (420 μg) of MK-4 or MK-7. Each point represents the mean ± SEM of 5 subjects at 0, 2, 4, 6, 10, 24, 48 and 72 h. ■=MK-4; ○=MK-7.

Nutr J. 2012; 11: 93.

Toxicol Mech Methods. 2011 Sep; 21(7): 520–532.

Sato et al. Nutrition Journal 2012, 11:93

Fórmula líquida altamente concentrada de Vitamina D3 y Vitamina K2 (MK-4).

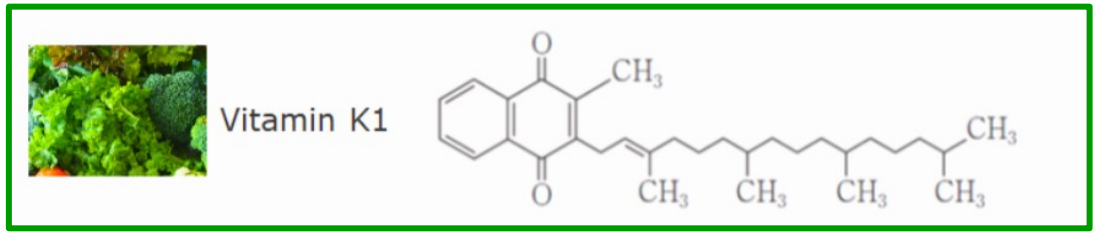
Es la **única fórmula natural** científicamente desarrollada con presentación líquida altamente concentrada, que contiene en cada gota 1000 UI de Vit D3, y combina 25 mcg de VIT K2 para evitar una disfunción de la osteocalcina brindando efectividad con seguridad. [1]

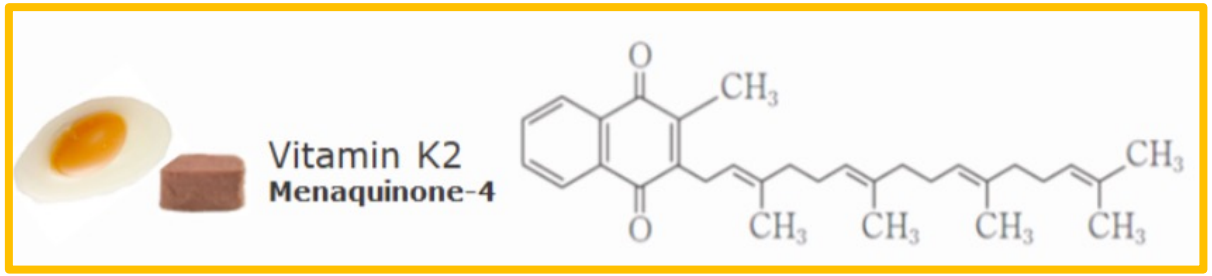
Es la única fórmula natural científicamente desarrollada en presentación líquida altamente concentrada, que contiene en cada gota 1000 UI de Vit D3 y combina 25 mcg de Vit K2 para habilitar una carboxilación de la osteocalcina proporcional a la dosis de Vit D3 utilizada, lo que permite utilizar megadosis, sin riego de disregulación de la calcemia. [2]

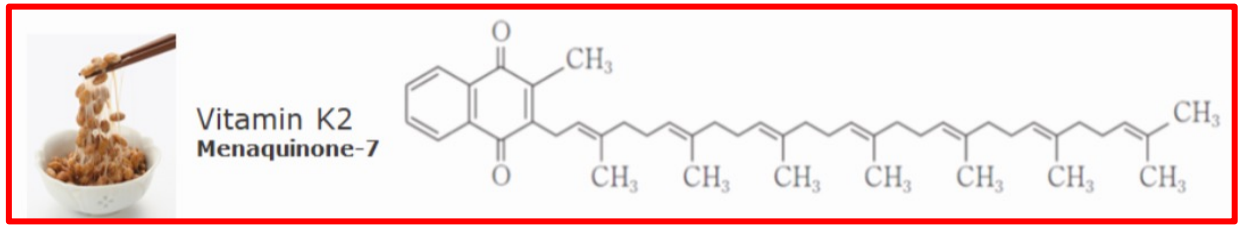
1. https://web.ruizpharma.com/producto/dk-mulsion/ 2. https://www.locatelcolombia.com/7708970476599-dk-mulsion-solucion-oral-x-30ml/p

Diferencias sustanciales entre MK-4 y MK-7

- Se requiere una dosis muy alta de MK-4 (600-1500 µg/día) para activar la osteocalcina, debido a que tiene una vida media muy corta en humanos y se absorbe mal: las dosis de 60 µg/día son ineficaces.
- En contraste la administración de MK-7 en dosis de 90-180 ug/día favorece la carboxilación y su posterior conversión a MK-4 en órganos extrahepáticos, la aumenta en órganos como el fémur, el cerebro y los testículos.







Toshiro Sato,Naoko Inaba e*t al*. MK-7 and Its Effects on Bone Quality and Strength. *Nutrients* 2020, *12*, 965; doi:10.3390/nu12040965

¿Es necesario combinar el magnesio con la Vitamina D?

La vitamina D favorece la absorción del magnesio

Role of Magnesium in Vitamin D Activation and Function

Anne Marie Uwitonze, BDT, MS; Mohammed S. Razzaque, MBBS, PhD

From the Department of Preventive & Community Dentistry, University of Rwanda College of Medicine & Health Sciences, School of Dentistry in Kigali (Ms Uwitonze and Dr Razzaque); the Department of Pathology at Lake Erie College of Osteopathic Medicine in Erie, Pennsylvania (Dr Razzaque); the Department of Applied Oral Sciences at Forsyth Institute at Harvard School of Dental Medicine Affiliate in Cambridge, Massachusetts (Dr Razzaque). Dr Razzaque is a visiting professor at the Harvard School of Dental Medicine in Boston, Massachusetts, and an honorary professor at the University of Rwanda College of Medicine & Health Sciences. The current article is part of the Vitamin D & Oral Health project at the School of Dentistry at the University of Rwanda College of Medicine & Health Sciences through Rwanda Human Resources for Health Program in collaboration with Harvard University.

Financial Disclosures: None reported.

Support: None reported.

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Email: mrazzaque@kcomedu; mrazzaque@hms.harvard.edu

Submitted August 29, 2017; final revision received December 7, 2017; accepted December 12, 2017.

Nutrients usually act in a coordinated manner in the body. Intestinal absorption and subsequent metabolism of a particular nutrient, to a certain extent, is dependent on the availability of other nutrients. Magnesium and vitamin D are 2 essential nutrients that are necessary for the physiologic functions of various organs. Magnesium assists in the activation of vitamin D, which helps regulate calcium and phosphate homeostasis to influence the growth and maintenance of bones. All of the enzymes that metabolize vitamin D seem to require magnesium, which acts as a cofactor in the enzymatic reactions in the liver and kidneys. Deficiency in either of these nutrients is reported to be associated with various disorders, such as skeletal deformities, cardiovascular diseases, and metabolic syndrome. It is therefore essential to ensure that the recommended amount of magnesium is consumed to obtain the optimal benefits of vitamin D.

J Am Osteopath Assoc. 2018;118(3):181-189
doi:10.7556/jaoa.2018.037

Keywords: magnesium, vitamin D

The adequate balance of magnesium and vitamin D is essential for maintaining the physiologic functions of various organs. Vitamin D helps regulate calcium and phosphate balance to maintain healthy bone functions.[1-6] Skeletal muscles, heart, teeth, bones, and many other organs require magnesium to sustain their physiologic functions. Furthermore, magnesium is needed to activate vitamin D. Abnormal levels in either of these nutrients can lead to serious organ dysfunctions.[7-12] Magnesium is the fourth most abundant mineral in the human body after calcium, potassium, and sodium. Magnesium activates more than 600 enzymes and influences extracellular calcium levels.[13] It is essential for the stability of cell function, RNA and DNA synthesis, and cell repair, as well as maintaining the antioxidant status of the cell. It is an important cofactor for the activation of a wide range of transporters and enzymes.[14,15] Also, magnesium-dependent kinases are responsible for the activation of up to 30% of the functional body proteins. Approximately 40% of total body magnesium content is intracellular, and almost 60% of magnesium is present in bone and teeth, with less than 1% in extracellular fluids.[15-20] Approximately 0.3% of total body magnesium is found in serum; therefore, serum magnesium concentration does not reflect the total amount of body magnesium content and is a poor predictor of intracellular magnesium content.[7,14,20-23] Even when the skeletal or intracellular magnesium content of soft tissue may be depleted, the circulating levels of magnesium could remain within the normal range because of its tight homeostatic control[24]; severely reduced tissue and

Table 3.2 Mechanisms of magnesium deficits with aging

- Inadequate Mg nutrient intake
- Reduced efficiency of Mg absorption (associated with reduced vitamin D levels)
- Increased Mg urinary excretion (associated with age-dependent reduction of kidney function and Mg tubular reabsorption)
- Secondary Mg deficiency (associated with diseases and comorbidities, and/or increased urinary Mg loss linked to polypharmacy)

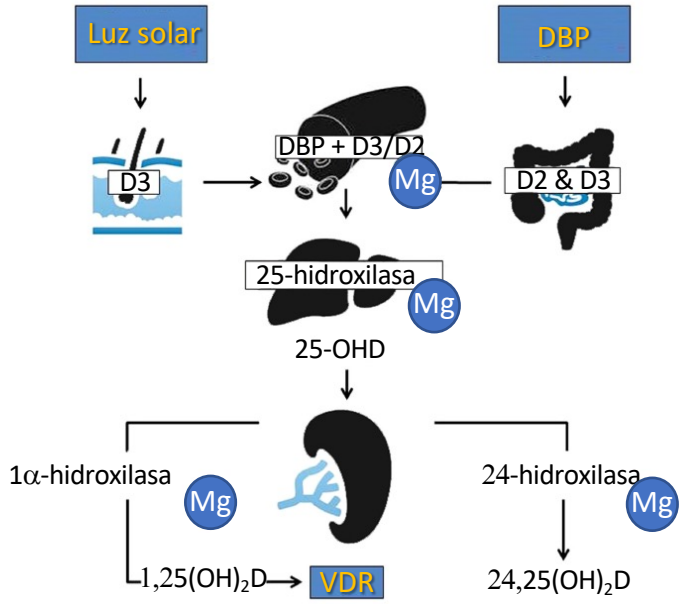
This is probably because the elderly tend to consume more processed foods with low content in whole grains and green vegetables. Although it has been shown that Mg requirements do not change with age,[28] dietary Mg deficiency in the elderly is more prevalent than generally suspected. Data from the National Health and Nutrition Examination Survey (NHANES) III found that Mg daily intake progressively decreases with age,[23] and that those affected by chronic conditions and/or on chronic drug treatment are less likely than younger adults to consume enough Mg to meet their needs. The NHANES III survey has confirmed that Mg intake in the older population is below the recommended minimal quantity (average of 225 and 166 mg/day vs. recommended 420 and 320 mg/day for men and women, respectively).[23] Among U.S. adults, 68% consume less than the recommended daily allowance (RDA) of Mg, 45% consume less than 75% of the RDA, and 19% consume less than 50% of the RDA.[29] In Europe, the "Suppléments en Vitamines et Minéraux Antioxidants" (SUVI.MAX) study showed that 77% of women and 72% of men have dietary Mg intakes

The efficiency of Mg absorption declines with age. Mg is absorbed by both passive and active processes mostly in the duodenum and in the ileum. A reduction of the absorption of Mg from the intestine in the elderly may be influenced by the reduction of vitamin D metabolism with age.[1–3]

ileum. A reduction of the absorption of Mg from the intestine in the elderly may be influenced by the reduction of vitamin D metabolism with age.[1–3]

Renal active reabsorption of Mg takes place in the loop of Henle, in the proximal convoluted tubule, and is influenced by both, the urinary concentration of sodium, and urinary pH. An increased renal Mg excretion may also contribute to the Mg deficit and is linked to a reduced tubular reabsorption associated with a reduced renal function, which is a common condition in the elderly. Drug use (i.e., long-term treatment with loop diuretics, digitalis) and/or pathological conditions associated with aging (i.e., type 2 diabetes mellitus, hyperadrenoglucocorticism, insulin resistance, alcoholism, acute myocardial infarction, stroke, among others) are also associated with secondary Mg deficiencies.[2,3,5,6]

El 1,25 $(OH)_2D$ estimula la absorción intestinal de magnesio en el duodeno y en el íleon.



The Journal of the American Osteopathic Association March 2018. Vol 118. No. 3. 118

Kupetsky. Erine A. Magnesium Applications in Clinical Medicine, Taylor & Francis Group. CRC Press. 2019

DBP: vitamin D binding protein. VDR: vitamin D receptors

Precaución con la administración conjunta de magnesio – vitamina D

Interactions between your drugs

Moderate **cholecalciferol ‹› magnesium oxide**

Applies to: Vitamin D3 (cholecalciferol) and magnesium oxide

EVITE GENERALMENTE: El uso de productos que contienen magnesio con un análogo de vitamina D puede aumentar el riesgo de hipermagnesemia, particularmente en pacientes con diálisis renal crónica, debido a efectos farmacológicos potencialmente aditivos. La hipermagnesemia crónica puede tener un papel en la patogénesis de la enfermedad ósea adinámica en pacientes en diálisis.

MANEJO: Los pacientes en diálisis renal crónica tratados con un análogo de vitamina D deben evitar los productos que contienen magnesio.

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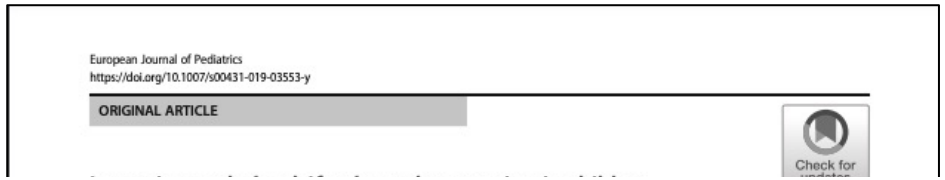
1. "Product Information. Zemplar (paricalcitol)." Abbott Pharmaceutical, Abbott Park, IL.
2. "Product Information. Hectorol (doxercalciferol)." Genzyme Corporation, Cambridge, MA.
3. "Product Information. One-Alpha (alfacalcidol)." Pharmel Inc, Montreal, IN.

https://www.drugs.com/drug-interactions/magnesium-oxide-with-vitamin-d3-1516-0-646-5790.html

www.drugs.com interactions checker

Dosis altas de vitamina D en pediatria


European Journal of Pediatrics
https://doi.org/10.1007/s00431-019-03553-y

ORIGINAL ARTICLE

Abstract

Vitamin D deficiency is frequent in pediatric nephrology. The 2017 European guidelines recommend keeping 25OH vitamin D (25-D) levels within the 75–120 nmol/L range, ideally with daily supplementation. Intermittent supplementation with D3 has also been proposed. We aimed to assess the influence of our local protocol of intermittent vitamin D supplementation on the evolution of 25-D levels between baseline and 2 months. VITATOL is a prospective single-center study performed in our tertiary unit in children and teenagers followed for chronic kidney disease (CKD), kidney transplantation, or stable chronic nephrotic syndrome with 25-D levels below 75 nmol/L. Intermittent oral cholecalciferol (100,000 IU) was administered depending on baseline vitamin D levels and body weight. The primary outcome was the change in 25-D levels between baseline and 2 months. Secondary outcomes were the evolution of the main mineral biomarkers. Thirty-seven patients were included. Two months after beginning supplementation, corresponding to a median(min-max) of 46 (14–79) days after the last dose of vitamin D, 25-D levels increased from 50 to 76 nmol/L ($p < 0.001$), 18 patients having 25-D levels within the target range and 2 above. All patients displayed 25-D levels above 50 nmol/L. There were no significant changes in phosphate, PTH, alkaline phosphatase, and FGF23 levels before and after supplementation. Calcium levels increased from 2.39 to 2.44 mmol/L ($p = 0.017$), but no differences in calciuria and urinary calcium/creatinine ratio were observed.

Conclusion: This vitamin D supplementation protocol using intermittent moderate doses of cholecalciferol seems efficient in 54% of cases, with neither significant overdose nor hypercalciuria.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Déficit de Vitamina D y la COVID

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SHORT COMMUNICATION

The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality

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Abstract
WHO declared SARS-CoV-2 a global pandemic. The present aim was to propose an hypothesis that there is a potential association between mean levels of vitamin D in various countries with cases and mortality caused by COVID-19. The mean levels of vitamin D for 20 European countries and morbidity and mortality caused by COVID-19 were acquired. Negative correlations between mean levels of vitamin D (average 56 mmol/L, STDEV 10.61) in each country and the number of COVID-19 cases/1 M (mean 295.95, STDEV 298.7, and mortality/1 M (mean 5.96, STDEV 15.13) were observed. Vitamin D levels are severely low in the aging population especially in Spain, Italy and Switzerland. This is also the most vulnerable group of the population in relation to COVID-19. It should be advisable to perform dedicated studies about vitamin D levels in COVID-19 patients with different degrees of disease severity.

Keywords COVID-19 · SARS-CoV2 · Vitamin D · Cholecalciferol · Calcitriol

Background/aims

WHO declared COVID-19 caused by the virus SARS-CoV-2 a global pandemic. Little is known about the potential protective factors. In the case of COVID-19 we should delineate the protective factors in anti-infective agents that might protect against infection and factors that improve the outcome once the infection has been produced.

Previous observational studies report independent associations between low serum concentration of 25-hydroxy-vitamin D and susceptibility to acute respiratory tract infections [1]. In a systematic review and meta-analysis of 25 randomised controlled studies, Martineau et al. has described that vitamin D protected against acute respiratory tract infection overall [2]. In a review of the literature, regarding the possible role of vitamin D in the prevention of influenza virus infection, Gruber-Bzura noticed that the data generate controversies and doubts [3].

Calcitriol (1,25-dihydroxyvitamin D3) exerts pronounced impacts on ACE2/Ang(1–7)/MasR axis with enhanced expression of ACE2 [4]. ACE-2 is the host cell receptor responsible for mediating infection by SARS-CoV-2. Starting from this, it might suggest a higher risk of infection. However, this has not been shown to date and previous studies identified associations between higher levels of ACE2 and better coronavirus disease health outcomes. In the lung, ACE2 was shown to protect against acute lung injury [5].

We hypothesize that vitamin D may play a protective role for COVID-19.

The primary aims of this study are to assess if there is any association between the mean levels of vitamin D in various countries and the mortality caused by COVID-19. The secondary aim was to identify if there is any association between the mean vitamin D levels in various countries and the number of cases of COVID-19.

Materials and methods

To test this hypothesis and to limit confounding bias (latitude, etc.), we focused on European countries only. We searched the literature for the mean levels of vitamin D

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INVITED EDITORIAL

APT Alimentary Pharmacology & Therapeutics WILEY

Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity

The excellent review by Al-Ani et al reflects a consensus approach to management of inflammatory bowel disease during the SARS-CoV-2 pandemic that has been established remarkably rapidly by very effective international collaboration.[1] Much of the focus has appropriately been on the potential impact of immuno-modulating therapies. We would also like to highlight the potential importance of nutrition and particularly vitamin D as raised by Panarese and Shahini.[2]

There are marked variations in mortality from COVID-19 between different countries. It is becoming clear that countries in the Southern Hemisphere are seeing a relatively low mortality (Figure 1 and Table 1).[2,3] It could be argued that the virus spread later to the Southern Hemisphere and that countries there are simply behind those in the Northern Hemisphere but as time goes by this argument looks increasingly weak. In Australia, 100 cases were reported by 10th March, 1000 by 21st March; in the UK, the first 100 had been reported by 5th March and the first 1000 by 14th March, just 1 week earlier. If one compares the mortality (68 per million) in the UK by 3rd April with the mortality (2 per million) in Australia by 10th April, there is still a huge discrepancy.

When mortality per million is plotted against latitude, it can be seen that all countries that lie below 35 degrees North have relatively low mortality. Thirty-five degrees North also happens to be the latitude above which people do not receive sufficient sunlight to retain adequate vitamin D levels during winter. This suggests a possible role for vitamin D in determining outcomes from COVID-19. There are outliers of course—mortality is relatively low in Nordic countries—but there vitamin D deficiency is relatively uncommon, probably due to widespread use of supplements.[4] Italy and Spain, perhaps surprisingly, have relatively high prevalences of vitamin D deficiency. Vitamin D deficiency has also been shown to correlate with hypertension,[5] diabetes,[6] obesity[7] and ethnicity[8]—all features associated with increased risk of severe COVID-19.

There are considerable experimental data showing that vitamin D is important in regulating and suppressing the inflammatory cytokine response of respiratory epithelial cells and macrophages to various pathogens including respiratory viruses.[9] Evidence that vitamin D might protect against infection is modest but it is important to note that the hypothesis is not that vitamin D would protect against SARS-CoV-2 infection but that it could be very important in preventing the cytokine storm and subsequent acute respiratory distress syndrome that is commonly the cause of mortality.[10]

Research is urgently needed to assess whether there may be a correlation between vitamin D status and severity of COVID-19 disease. Meanwhile, the evidence supporting a protective effect of vitamin D against severe COVID-19 disease is very suggestive, a substantial proportion of the population in the Northern Hemisphere will currently be vitamin D deficient, and supplements, for example, 1000 international units (25 micrograms) per day are very safe. It is time for governments to strengthen recommendations for vitamin D intake and supplementation, particularly when under lock-down.

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Declaration of personal interests: JMR is Co-Editor of Alimentary Pharmacology and Therapeutics and with the University of Liverpool and Provexis UK, holds a patent for use of a soluble fibre preparation as maintenance therapy for Crohn's disease plus a patent for its use in antibiotic-associated diarrhoea. Patent also held with the University of Liverpool and others in relation to use of modified heparins in cancer therapy. SS has received speaker fees from MSD, Actavis, Abbvie, Dr Falk pharmaceuticals, Shire and received educational grants from MSD, Abbvie, Actavis and is an advisory board member for Abbvie, Dr Falk pharmaceutics and Vifor pharmaceuticals. EL and RAK have no conflicts to declare.

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AP&T invited editorial columns are restricted to discussing papers that have been published in the journal. An editorial must have a maximum of 500 words, may contain one table or figure, and should have no more than 10 references. It should be submitted electronically to the Editors via http://mc.manuscriptcentral.com/apt.

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nutrients MDPI

Review

Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths

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check for updates

Abstract: The world is in the grip of the COVID-19 pandemic. Public health measures that can reduce the risk of infection and death in addition to quarantines are desperately needed. This article reviews the roles of vitamin D in reducing the risk of respiratory tract infections, knowledge about the epidemiology of influenza and COVID-19, and how vitamin D supplementation might be a useful measure to reduce risk. Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines. Several observational studies and clinical trials reported that vitamin D supplementation reduced the risk of influenza, whereas others did not. Evidence supporting the role of vitamin D in reducing risk of COVID-19 includes that the outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that the number of cases in the Southern Hemisphere near the end of summer are low; that vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration. To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D_3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40–60 ng/mL (100–150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D_3 doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations.

Keywords: acute respiratory distress syndrome (ARDS); ascorbic acid; cathelicidin; coronavirus; COVID-19; cytokine storm; influenza; observational; pneumonia; prevention; respiratory tract infection; solar radiation; treatment; UVB; vitamin C; vitamin D

1. Introduction

The world is now experiencing its third major epidemic of coronavirus (CoV) infections. A new CoV infection epidemic began in Wuhan, Hubei, China, in late 2019, originally called 2019-nCoV [1]

Journal Pre-proofs

Vitamin D: A simpler alternative to tocilizumab for trial in COVID-19?

M. Silberstein

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Review

Modulation of the Immune Response to Respiratory Viruses b Vitamin D

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Abstract: Background: Vitamin D deficiency has been shown to be independently associated with increased risk of viral acute respiratory infection (ARI) in a number of observational studies, and meta-analysis of clinical trials of vitamin D supplementation for prevention of ARI has demonstrated protective effects. Several cellular studies have investigated the effects of vitamin D metabolites on immune responses to respiratory viruses, but syntheses of these reports are lacking. Scope: In this article, we review the literature reporting results of *in vitro* experiments investigating immunomodulatory actions of vitamin D metabolites in human respiratory epithelial cells infected with respiratory viruses. Key findings: Vitamin D metabolites do not consistently influence replication or clearance of rhinovirus, respiratory syncytial virus (RSV) or influenza A virus in human respiratory epithelial cell culture, although they do modulate expression and secretion of type 1 interferon, chemokines including CXCL8 and CXCL10 and pro-inflammatory cytokines, such as TNF and IL-6. Future research: More studies are needed to clarify the effects of vitamin D metabolites on respiratory virus-induced expression of cell surface markers mediating viral entry and bacterial adhesion to respiratory epithelial cells.

Keywords: vitamin D; respiratory viruses; antiviral immunity

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Vitamin D deficiency and co-morbidities in COVID-19 patients – A fatal relationship?

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1. Introduction

Infections of the respiratory tract are more frequent in the winter months and especially in the northern latitudes than they are in summer [1]. This obviously also applies to the COVID-19 infectious disease that briefly spread all over the world in the winter months and became a pandemic [2,3]. A common feature of the winter months and the inhabitants of all countries north of the 42nd parallel is a hypovitaminosis D that frequently occurs during this period [4]. In addition during cold temperature the virus will be more easily transmitted. This raises the question of whether an inadequate vitamin D supply has an influence on the progression and severity of COVID-19 disease.

A low vitamin D status, measured as the plasma level of the transport form of vitamin D, 25(OH)D, is widespread worldwide and is mainly found in regions of northern latitudes, but also in southern countries [5]. In Europe, vitamin D deficiency is widely prevalent during the winter months and affects mainly elderly people and migrants. In Scandinavia only 5% of the population is affected by a low vitamin D status, in Germany, France and Italy more than 25%, particularly older people e.g. in Austria up to 90% of senior citizens [6,7]. In Scandinavian countries, the low incidence of vitamin D deficiency may be due to the traditional consumption of cod liver oil rich in vitamin D and A or to genetic factors resulting in higher synthesis of vitamin D in the epidermal layer [8]. Taken together, low vitamin D status is common in Europe with the exception of the Scandinavian countries. The calculated COVID-19 mortality rate from 12 European countries shows a significant ($P = .046$) inverse correlation with the mean 25(OH)D plasma concentration [9].

This raises the question whether insufficient vitamin D supply has an influence on the course of COVID-19 disease? An analysis of the distribution of Covid-19 infections showed a correlation between geographical location (30–50° N+), mean temperature between 5–11 °C and low humidity [10]. In a retrospective cohort study (1382 hospitalized patients) 326 died, Among them 70.6% were black patients. However, black race was not independently associated with higher mortality [11]. An excess mortality (2 to sixfold have been described in African-Americans with average latitudes of their state of residence in higher latitudes (> 40) [12]. The mortality of COVID-19 (cases/ million population) shows a clear dependence on latitude. Below latitude 35, mortality decreases markedly [13]. Indeed, there are exceptions e.g. Brazil (tenfold higher than all other latin American countries – except mexico), however, the management of the pandemic may increase infection risk.

1.1. Vitamin D effects

The skeletal and extra skeletal effects of vitamin D have recently been described in an extensive review [14]. Vitamin D exerts a genomic and non-genomic effect on gene expression. The genomic effect is mediated by the nuclear vitamin D receptor (VDR), which acts as a ligand activated transcription factor. The active form $1,25(OH)_2D$ binds to the VDR and in most cases heterodimerizes with the retinoid X receptor (RXR), whose ligand is one of the active metabolites of vitamin A, 9-cis retinoic acid. The interaction of this complex with the vitamin D responsive element can regulate the expression of target genes either positively or negatively [15]. The non-genomic effects involve the activation of a variety of signaling molecules that interact with Vitamin D responsive element (VDRE) in the promoter regions of vitamin D dependent genes [16]. Vitamins A and D are also of particular importance for the barrier function of mucous membranes in the respiratory tract [17,18].

1.2. Vitamin D and immune system

Vitamin D plays an essential role in the immune system [19]. Vitamin D interferes with the majority of the immune systems cells such as macrophages, B and T lymphocytes, neutrophils and dendritic cells, which express VDR (for details [20] and Fig. 3). Cathelicidin, a peptide formed by vitamin D stimulated expression, has shown antimicrobial activity against bacteria, fungi and enveloped viruses, such as corona viruses [21,22]. Furthermore Vitamin D inhibits the production of pro-inflammatory cytokines and increases the production of anti-inflammatory cytokines [23].

The active metabolite of vitamin D in macrophages and dendritic cells, derived from the precursor 25(OH)D, leads to the activation of VDR, which, after RXR heterodimerization, results in the expression of various proteins of the innate and adaptive immune system (Treg cells, cytokines, defensins, pattern recognition receptors etc.) [24]. Vitamin D

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Short communication

Vitamin D receptor stimulation to reduce acute respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections Revised Ms SBMB 2020_166

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Cytokine storm
Lung disease
Renin-angiotensin system
Hypercoagulability

ABSTRACT

Coronavirus infection is a serious health problem awaiting an effective vaccine and/or antiviral treatment. The major complication of coronavirus disease 2019 (COVID-19), the Acute Respiratory Distress syndrome (ARDS), is due to a variety of mechanisms including cytokine storm, dysregulation of the renin-angiotensin system, neutrophil activation and increased (micro)coagulation. Based on many preclinical studies and observational data in humans, ARDS may be aggravated by vitamin D deficiency and tapered down by activation of the vitamin D receptor. Several randomized clinical trials using either oral vitamin D or oral Calcifediol (25OHD) are ongoing. Based on a pilot study, oral calcifediol may be the most promising approach. These studies are expected to provide guidelines within a few months.

1. Introduction

The coronavirus disease 2019 (COVID-19) is rapidly causing worldwide morbidity and mortality. While most infected people will recover after a mild to modest course of the disease, some patients, especially older people or those with other major diseases, will suffer serious morbidity and a high mortality risk. In the absence of vaccines, some therapeutic interventions have some proven benefits (such as convalescent plasma [1] and remdesivir [2], whereas other approaches (including vitamin D) that may influence the course of the disease deserve special attention.

The vitamin D endocrine system is well known for its beneficial effects on calcium and bone homeostasis, especially in children and elderly subjects. Moreover, it may have several extra-skeletal effects [3] especially on the immune system and lung function. All cells of the immune cells can express the vitamin D receptor (VDR) and most cytokines, produced by or regulating these immune cells are under the coherent control of the active vitamin D hormone, 1,25(OH)2D. Indeed, in essence, 1α,25(OH)2D activates the native immune defense system while tapering down the acquired immune system [3–5]. In addition, antigen-presenting cells and monocytic cells can express CYP27B1, the essential enzyme for the local, auto/paracrine production of 1α,25(OH) 2D in the immune system. Vitamin D deficiency may predispose to increased risk of infections, and vitamin D supplementation may decrease the risk of upper respiratory infections [6]. The lung epithelium also expresses the VDR and CYP27B1 and may be an important target tissue for the vitamin D endocrine system [7]. Therefore, there may be many potential links between viral infections such as COVID19 and vitamin D status.

In this Viewpoint, we summarize how activation of the vitamin D Receptor (VDR) may be able to decrease acute lung injury (ALI) and Acute Respiratory Distress Syndrome (ARDS). We therefore will first review the major mechanisms underlying ALI and ARDS in patients with viral (including Coronavirus) infections. Thereafter, we present an

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Brief Report

25-Hydroxyvitamin D Concentrations Are Lower in Patients with Positive PCR for SARS-CoV-2

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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), with a clinical outcome ranging from mild to severe, including death. To date, it is unclear why some patients develop severe symptoms. Many authors have suggested the involvement of vitamin D in reducing the risk of infections; thus, we retrospectively investigated the 25-hydroxyvitamin D (25(OH)D) concentrations in plasma obtained from a cohort of patients from Switzerland. In this cohort, significantly lower 25(OH)D levels ($p = 0.004$) were found in PCR-positive for SARS-CoV-2 (median value 11.1 ng/mL) patients compared with negative patients (24.6 ng/mL); this was also confirmed by stratifying patients according to age >70 years. On the basis of this preliminary observation, vitamin D supplementation might be a useful measure to reduce the risk of infection. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations and to confirm our preliminary observation.

Keywords: vitamin D; SARS-CoV-2; concentrations; COVID-19; coronavirus; deficiency

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), with clinical outcomes ranging from mild to severe, including death. To date, there is no specific recommended treatment, with COVID-19- and SARS-COV-2-affected patients targeted to receive supportive care to help relieve symptoms.

However, only a fraction of infected people show clinical symptoms, and an even lower percentage require medical attention [1,2]. To date, it is not yet known why some patients develop more severe symptoms.

Recently, some articles have suggested the possible involvement of vitamin D in reducing the risk of respiratory tract infections, especially in the influenza and COVID-19 context. Furthermore, the role of vitamin D supplementation in reducing the risk of infection [3–6] is still under investigation, however, no clinical evidence has been reported yet.

For these reasons, we retrospectively described the 25-hydroxyvitamin D (25(OH)D) plasma concentrations in a cohort of patients from Switzerland.

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ARTÍCULOS DE REVISIÓN

Efectos inmunológicos de la vitamina D en COVID-19

Immunological effects of vitamin D on COVID-19

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Resumen

El síndrome respiratorio severo o grave causado por el nuevo coronavirus (SARS-CoV-2) es una enfermedad de gran auge en la actualidad, que se ha propagado vertiginosamente a lo largo de los 5 continentes, siendo Norteamérica y algunos países europeos como Italia, España y Francia los más afectados por esta pandemia. En la actualidad, no se cuenta con una estrategia de prevención o tratamiento que logre mitigar de forma contundente las cifras de infectados y muertos a nivel mundial; sin embargo, se están estudiando alternativas que podrían impactar de forma positiva en el curso de la enfermedad.

El déficit de 25 hidroxivitamina D (25OH D) ha mostrado ser un factor independiente de mortalidad por todas las causas, principalmente en enfermedades cardiovasculares y cáncer. La suplementación de esta también se ha asociado a beneficios en la prevención de enfermedades respiratorias; para el caso de la COVID-19, los mecanismos por los cuales la vitamina D podría ser útil para el tratamiento y la prevención se resumen en la actividad sobre las barreras físicas y la inmunidad natural celular y adaptativa, que disminuye la probabilidad de tormenta de citocinas.

Algunos estudios realizados concluyeron que el pico de la infección por SARS-CoV-2 se presentó durante el invierno, tiempo donde los niveles de 25OH D son más bajos; además, estos niveles subóptimos se han relacionado con aumento en la incidencia de complicaciones tales como falla cardíaca, sepsis y progresión a síndrome de dificultad respiratoria del adulto (SDRA); y, por consiguiente, con un aumento en las tasas de mortalidad, lo cual respalda el papel de la vitamina D en la modificación del curso natural de la enfermedad. Sin embargo, también se prendieron las alarmas, ya que se ha demostrado una prevalencia alta de hipovitaminosis D en Bogotá, Villavicencio, Neiva, Barranquilla y Medellín, que podría exponer a la población colombiana a resultados adversos.

La evidencia indica que la suplementación con vitamina D modula y reduce el riesgo de infección por SARS-CoV-2, pero se precisan más estudios para corroborar los efectos benéficos en la población.

Palabras claves: síndrome de dificultad respiratoria aguda (SDRA), enfermedades crónicas, mortalidad, coronavirus, COVID-19, tormenta de citocinas, influenza, observacional, neumonía, prevención, infección del tracto respiratorio, radiación solar, tratamiento, UVB, vitamina D.

Abstract

The severe respiratory syndrome, caused by the new coronavirus (SARS-CoV-2), is a currently booming disease that has spread rapidly throughout the 5 continents. North America and some European countries such as Italy, Spain and France have been the most affected by this pandemic. Currently, there is no prevention or treatment strategy that can conclusively mitigate the numbers of infected and dead worldwide; however, alternatives are being studied that could positively impact the course of the disease. The deficiency of 25 hydroxy-vitamin D (25OH D) has shown to be an independent factor in all-cause mortality, mainly in cardiovascular disease and cancer. Supplementation of it has also been associated with benefits in the prevention of respiratory diseases. In the case of COVID-19, the mechanisms by which vitamin D could be useful for treatment and prevention are summarized in activity on physical barriers, and by natural cellular and adaptive immunity, reducing the probability of cytokine storm. Some studies concluded that the peak of SARS-CoV-2 infection occurred during the winter, when the levels of 25OH D are lower. In addition, these suboptimal levels have been related to an increase in the incidence of complications such as heart failure, sepsis, and progression to adult respiratory distress syndrome (ARDS), and consequently an increase in mortality rates. This supports the role of vitamin D in modifying the natural course of the disease. However, the alarms are

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LETTER TO THE EDITOR

COVID-19 and vitamin D—Is there a link and an opportunity for intervention?

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Submitted 6 April 2020; accepted in final form 7 April 2020

TO THE EDITOR: The recent outbreak and rapid spreading of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are a global threat and primary concern worldwide, with a still uncertain outcome. With the lack of effective therapy, chemoprevention, and vaccination, focusing on the immediate repurposing of existing drugs gives hope of curbing the pandemic. Here, I underline that so far there are no reports on the vitamin D status among affected persons. On the other hand, a large number of well-established data showed antiviral effects of vitamin D, which can interfere directly with viral replication, but also can act in an immunomodulatory and anti-inflammatory way (7). The latter effects could be crucial for their assumptive beneficial effects during SARS-CoV-2 infection, since it seems that SARS-CoV-2 initially uses immune evasion mechanisms, which in some patients is followed by immune hyperreaction and cytokine storm (1), as a common pathogenic mechanism of acute respiratory disease syndrome (ARDS) and systemic inflammatory response syndrome (SIRS) development, regardless of the etiological factor. In that sense, the protective effect of vitamin D has been reported in many conditions associated with pneumonia, cytokine hyperproduction, and ARDS (2, 8, 10), and vitamin D was recently proposed as a repurposed drug for influenza A H5N1 virus-induced lung injury (3). Additionally, some studies suggest the effectiveness of vitamin D as an adjuvant therapy along with antiretroviral agents in HIV-infected patients (5). Furthermore, vitamin D pretreatment was beneficial in animal models of ARDS, reducing lung permeability by modulation of renin-angiotensin system activity and ACE2 expression (9). The role of vitamin D in the context of viral infections is also supported by findings of certain vitamin D receptor gene (*VDR*) alleles that are associated with increased susceptibility to respiratory infections (6), as well as with the progression of HIV infection (4).

Owing to the lack of specific treatment and urgency to act, these findings could be tentatively extrapolated to SARS-CoV-2 infection, justifying the use of vitamin D as a possible adjuvant therapy. From the public health aspect, the recommendation of intensive supplementation as possible prophylaxis also could be considered. Given the good tolerability and safety of even high doses of vitamin D, this approach complies primum non nocere principle.

Investigations on vitamin D status and *VDR* polymorphisms of affected subjects could contribute to explain "unusual behavior" of SARS-CoV-2 spreading and a tremendous variety of COVID-19 clinical presentations and outcomes.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

H.J. drafted manuscript; edited and revised manuscript; approved final version of manuscript.

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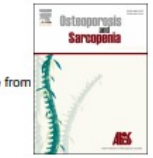

Vitamin D in COVID - 19: Dousing the fire or averting the storm? – A perspective from the Asia-Pacific

Manju Chandran, Aye Chan Maung, Ambrish Mithal, Rajeev Parameswaran

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brain sciences

MDPI

Review

Potential Role of Vitamin D in the Elderly to Resist COVID-19 and to Slow Progression of Parkinson's Disease

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Abstract: While we are still learning more about COVID-19, caused by the novel SARS-CoV-2 virus, finding alternative and already available methods to reduce the risk and severity of the disease is paramount. One such option is vitamin D, in the form of vitamin D_3 (cholecalciferol) supplementation, due to its potential antiviral properties. It has become apparent that older individuals have a greater risk of developing severe COVID-19, and compared to younger adults, the elderly have lower levels of vitamin D due to a variety of biological and behavioral factors. Older adults are also more likely to be diagnosed with Parkinson's disease (PD), with advanced age being the single greatest risk factor. In addition to its immune-system-modulating effects, it has been suggested that vitamin D supplementation plays a role in slowing PD progression and improving PD-related quality of life. We completed a review of the literature to determine the relationship between vitamin D, PD, and COVID-19. We concluded that the daily supplementation of 2000–5000 IU/day of vitamin D_3 in older adults with PD has the potential to slow the progression of PD while also potentially offering additional protection against COVID-19.

Keywords: Parkinson's disease; COVID-19; vitamin D; cholecalciferol; therapeutics; antiviral; neurodegeneration; SARS-CoV-2; elderly

1. Introduction

1.1. COVID-19

In late 2019, a novel coronavirus, originally named 2019-nCoV, began circulating around the world. It was later renamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), after similarities to SARS were noted [1]. The resulting disease caused by SARS-CoV-2 was termed coronavirus disease 2019 (COVID-19) [1]. SARS-CoV-2, like SARS and Middle East Respiratory Syndrome (MERS), is a beta coronavirus that is thought to have originated in bats.

Like other coronaviruses, SARS-CoV-2 is a non-segmented, positive sense, enveloped, single-stranded RNA virus. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor on type I and type II pneumocytes [1]. Unsurprisingly, the most common symptoms of COVID-19 include fever, cough, and dyspnea, with progression to pneumonia and/or sepsis in more critical cases [2,3]. The most severe cases can lead to marked hypoxemia and a need for mechanical ventilation. This pro-inflammatory state can lead to acute respiratory distress syndrome and cytokine storm syndrome (CSS), likely mediated by a dysregulated immune response involving interleukin-6

1.*Revista Colombiana de Endocrinología, Diabetes y Metabolismo Volumen 7, Suplemento 2, junio de 2020.* ***2***. *Am J Physiol Endocrinol Metab* 318: E589, 2020. **3**. Osteoporosis and Sarcopenia (2020), **4**. Brain Sci. 2020, 10, 284.

Requerimientos e Ingesta Diaria Recomendada de Vitamina K

Etapa de la vida	
Bebés hasta los 6 meses de edad	2.0 mcg
7 a 12 meses de edad	2.5 mcg
1 a 3 años de edad	30 mcg
4 a 8 años de edad	55 mcg
9 a 13 años de edad	60 mcg
14 a 18 años de edad	75 mcg
Hombres adultos mayores de 19 años de edad	120 mcg
Mujeres adultas mayores de 19 años de edad	90 mcg
Adolescentes embarazadas o en período de lactancia	75 mcg
Mujeres embarazadas o en período de lactancia	90 mcg

Microgramos de vitamina K por 100 gr

Alimento	Contenido mcg	Alimento	Contenido mcg
Apio	100	Maíz	40-150
Col	130	Papa	50
Coliflor	300	Salvado	80
Champiñones	17	Carne	21
Espárragos	40	Hígado	150
Espinaca	350	Queso blanco	25-50
Lechuga	200	Huevo	45
Perejil	790	Aguacate	8
Zanahoria	86	Mantequilla	60

Int J Mol Sci. 2019 Feb; 20(4): 896.

Nutrients 2020 Jan; 12(1): 138.

Abordaje Integral del Déficit de Vitamina D

nutrients

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Article

Combined Treatment with Omega-3 Fatty Acid and Cholecalciferol Increases 1,25-Dihydroxyvitamin D Levels by Modulating Dysregulation of Vitamin D Metabolism in 5/6 Nephrectomy Rats

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Abstract: The protein 1α-hydroxylase (CYP27B1) was expressed in liver and omega-3 fatty acid (FA) elevated 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] levels in dialysis patients. The aim of this study was to determine whether omega-3 FA and cholecalciferol have effects on vitamin D metabolism related to CYP27B1 and 24-hydroxylase (CYP24) activities in the kidney and liver of 5/6 nephrectomy (Nx) rats. Male Sprague–Dawley rats were divided into the following groups: sham control, 5/6 Nx, 5/6 Nx treated with cholecalciferol, 5/6 Nx treated with omega-3 FA, and 5/6 Nx treated with cholecalciferol/omega-3 FA. CYP27B1 and CYP24 expression were measured in the liver and kidney. Further, 1,25$(OH)_2$D and 25-hydroxyvitamin D [25(OH)D] levels were measured in serum. Among Nx groups, 1,25$(OH)_2$D and 25(OH)D levels were lowest in the 5/6 Nx group. CYP24 expression was increased in the kidney of the 5/6 Nx rat model, which was found to be reversed by omega-3 FA or cholecalciferol/omega-3 FA supplementation. Decreased CYP27B1 expression was observed in the liver of the 5/6 Nx rats and its expression was recovered by supplementation with cholecalciferol/omega-3 FA. In conclusion, omega-3 FA and cholecalciferol may synergistically increase 1,25$(OH)_2$D levels by inhibiting CYP24 expression in the kidney and liver and activating CYP27B1 expression in the liver of 5/6 Nx rats.

Keywords: 1α-hydroxylase (CYP27B1); 24-hydroxylase (CYP24); 1,25-dihydroxyvitamin D; 25-hydroxyvitamin D; cholecalciferol; omega-3 fatty acid

1. Introduction

Vitamin D deficiency is very frequent among chronic kidney disease (CKD) patients and has been associated with increased mortality as well as faster progression of CKD [1,2]. Decreased renal 1α-hydroxylase (CYP27B1) activity with reduced kidney function in CKD contributes to a gradual decrease in 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] levels [3]. In addition, increased capacity of 24-hydroxylase (CYP24) is associated with vitamin D catabolism in CKD [3]. Therefore, CYP27B1 and CYP24 in proximal tubules of kidney play an important role in vitamin D metabolism in CKD [4].

One study reported that CYP27B1 was strongly presented in monocytes that develop into Kupffer cells [5]. Recent studies reported that CYP24 is expressed in hepatocytes [6,7]. In addition, rat models of ageing and long-term diabetes mellitus showed significantly increased expression of CYP24 in hepatocytes, as well as in non-hepatocytes including Kupffer cells, hepatic stellate cells, and sinusoidal endothelial cells [7]. Extrarenal 1,25$(OH)_2$D production has previously been reported in anephric

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Review Article

Crosstalk between Vitamins A, B12, D, K, C, and E Status and Arterial Stiffness

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Arterial stiffness is associated with cardiovascular risk, morbidity, and mortality. The present paper reviews the main vitamins related to arterial stiffness and enabling destiffening, their mechanisms of action, providing a brief description of the latest studies in the area, and their implications for primary cardiovascular prevention, clinical practice, and therapy. Despite inconsistent evidence for destiffening induced by vitamin supplementation in several randomized clinical trials, positive results were obtained in specific populations. The main mechanisms are related to antiatherogenic effects, improvement of endothelial function (vitamins A, C, D, and E) and metabolic profile (vitamins A, B12, C, D, and K), inhibition of the renin-angiotensin-aldosterone system (vitamin D), anti-inflammatory (vitamins A, D, E, and K) and antioxidant effects (vitamins A, C, and E), decrease of homocysteine level (vitamin B12), and reversing calcification of arteries (vitamin K). Vitamins A, B12, C, D, E, and K status is important in evaluating cardiovascular risk, and vitamin supplementation may be an effective, individualized, and inexpensive destiffening therapy.

1. Introduction

Cardiovascular diseases are the main cause of mortality worldwide and prophylactic measures deserve special attention. Arterial stiffness, one of the earliest detectable signs of structural and functional changes of the vessel wall [1], is associated with cardiovascular risk, morbidity and mortality, atherosclerosis and arteriosclerosis, aging, and several chronic disorders. Measurement of pulse wave velocity (PWV) is a simple, noninvasive, validated, the most used, and reproducible method to assess arterial stiffness [2]. A recently published meta-analysis, including 17,635 participants, demonstrated that an increase of PWV of 1 m/s is associated with a 7% increased risk of subsequent cardiovascular events, concluding that aortic PWV enables identification of high cardiovascular risk subjects, that might benefit from more aggressive risk factor management [3]. Augmentation index, a measure of peripheral arterial reflective properties, is also a complex and indirect marker of arterial stiffening [4, 5]. A 10% increase in the augmentation index was associated with 31.8% increased risk of cardiac events [6].

Aging and several disorders cause degenerative changes of the vessel wall of large arteries, related to the rupture of the elastic fibers, impaired cross-linking of extracellular matrix components, accumulation of collagen, fibrosis and necrosis of muscle fibers, inflammation, and calcification, leading to their stiffening [7, 8]. Vascular calcification, calcium phosphate complexes deposition in the arterial wall, is an active process, enabled by several mechanisms, and leads also to loss of arterial wall elasticity and an increased PWV, related to vascular remodeling, organ damage, and overall morbidity and mortality [9, 10]. It can be present as medial calcification (Monckeberg's medial sclerosis, prevalent among patients with diabetes and renal and hyperparathyroid disorders) or intimal calcification (on the surface of the atherosclerotic plaque) [11]. Hypertension, inflammation, oxidized low density lipoproteins, and a high calcium-phosphorus ion product enable transformation of vascular smooth muscle

Improving the Vitamin D Status of Vitamin D Deficient Adults Is Associated With Improved Mitochondrial Oxidative Function in Skeletal Muscle

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Objective: Suboptimal mitochondrial function has been implicated in several disorders in which fatigue is a prominent feature. Vitamin D deficiency is a well-recognized cause of fatigue and myopathy. The aim of this study was to examine the effects of cholecalciferol therapy on skeletal mitochondrial oxidative function in symptomatic, vitamin D-deficient individuals.

Design: This longitudinal study assessed mitochondrial oxidative phosphorylation in the gastrosoleus compartment using phosphorus-31 magnetic resonance spectroscopy measurements of phosphocreatine recovery kinetics in 12 symptomatic, severely vitamin D-deficient subjects before and after treatment with cholecalciferol. All subjects had serum assays before and after cholecalciferol therapy to document serum 25-hydroxyvitamin D (25OHD) and bone profiles. Fifteen healthy controls also underwent ^{31}P-magnetic resonance spectroscopy and serum 25OHD assessment.

Results: The phosphocreatine recovery half-time ($\tau_{1/2}$PCr) was significantly reduced after cholecalciferol therapy in the subjects indicating an improvement in maximal oxidative phosphorylation (34.44 ± 8.18 sec to 27.84 ± 9.54 sec, $P < .001$). This was associated with an improvement in mean serum 25OHD levels (8.8 ± 4.2 nmol/L to 113.8 ± 51.5 nmol/L, $P < .001$). There was no difference in phosphate metabolites at rest. A linear regression model showed that decreasing serum 25OHD levels was associated with increasing $\tau_{1/2}$PCr ($r = -0.41$, $P = .009$). All patients reported an improvement in fatigue after cholecalciferol therapy.

Conclusions: Cholecalciferol therapy augments muscle mitochondrial maximal oxidative phosphorylation after exercise in symptomatic, vitamin D-deficient individuals. This finding suggests that changes in mitochondrial oxidative phosphorylation in skeletal muscle could at least be partly responsible for the fatigue experienced by these patients. For the first time, we demonstrate a link between vitamin D and the mitochondria in human skeletal muscle. *J Clin Endocrinol Metab* 98: E509–E513, 2013)

Mitochondrial oxidative phosphorylation is the primary source of cellular ATP with suboptimal mitochondrial function implicated in disorders in which fatigue is a feature (1–3). Fatigue and myopathy are well recognized in the context of vitamin D deficiency and muscle symptoms may arise independent of derangements in bone biochemistry (4). Phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) is a noninvasive tool used to assess mitochondrial function in vivo by measuring the kinetics of high energy phosphate metabolites involved in

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For editorial see page 961

Abbreviations: CV, coefficient of variation; 25OHD, 25-hydroxyvitamin D; PCr, phosphocreatine; $\tau_{1/2}$PCr, phosphocreatine recovery half-time; Pi, inorganic phosphate; ^{31}P-MRS, phosphorus-31 magnetic resonance spectroscopy.

Abordaje Integral

Vitamina D

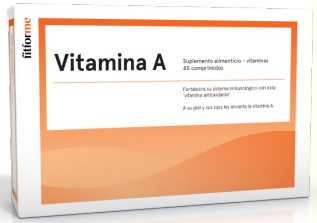
+

Vitamina E

+

Vitamina K dietaria

+



Vitamina A

Vitamina B12

+

Vitamina C

+

Calcio citrato

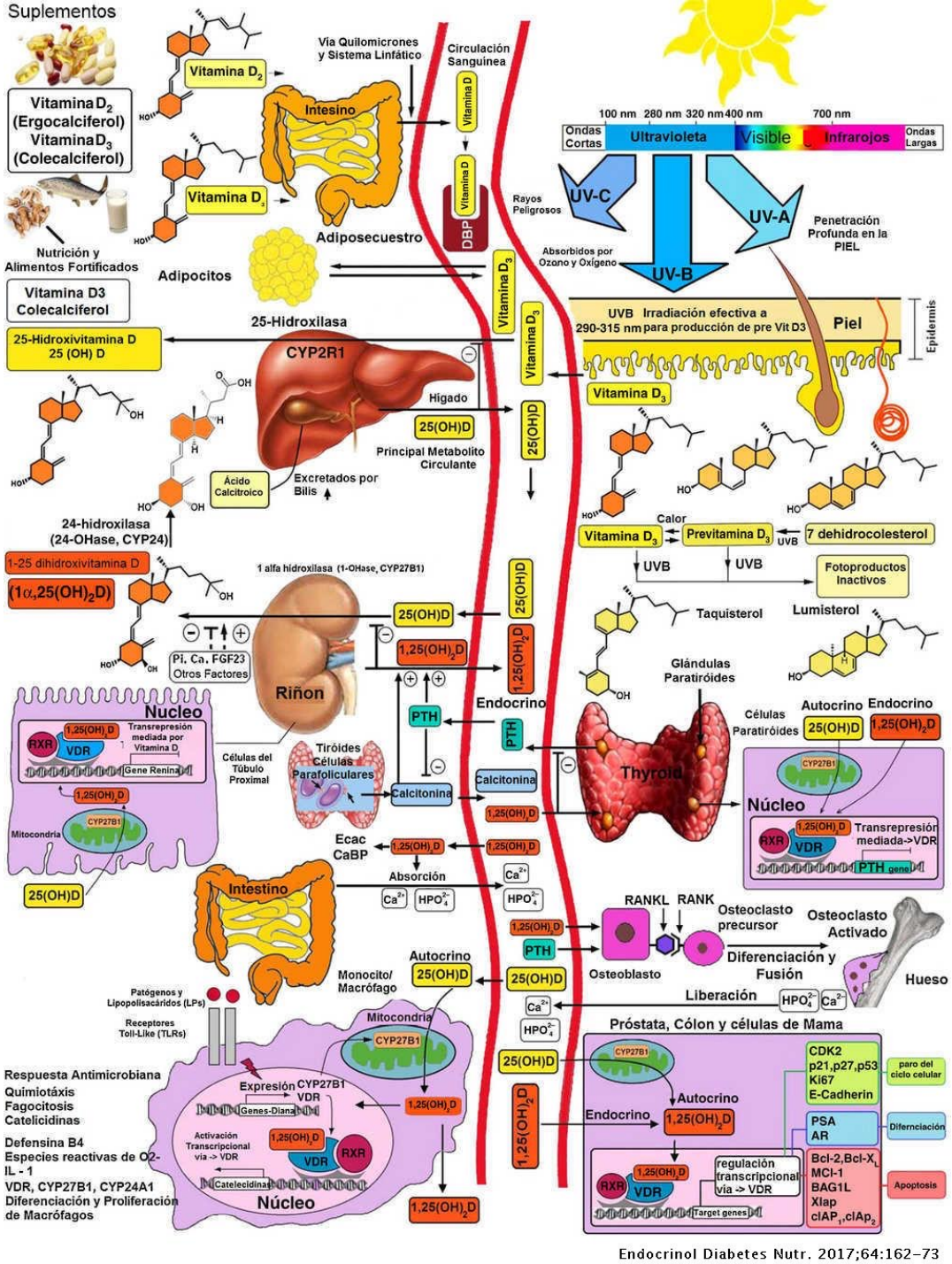
DEKA

+

BCC

+

Ω3



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!Muchas gracias!

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