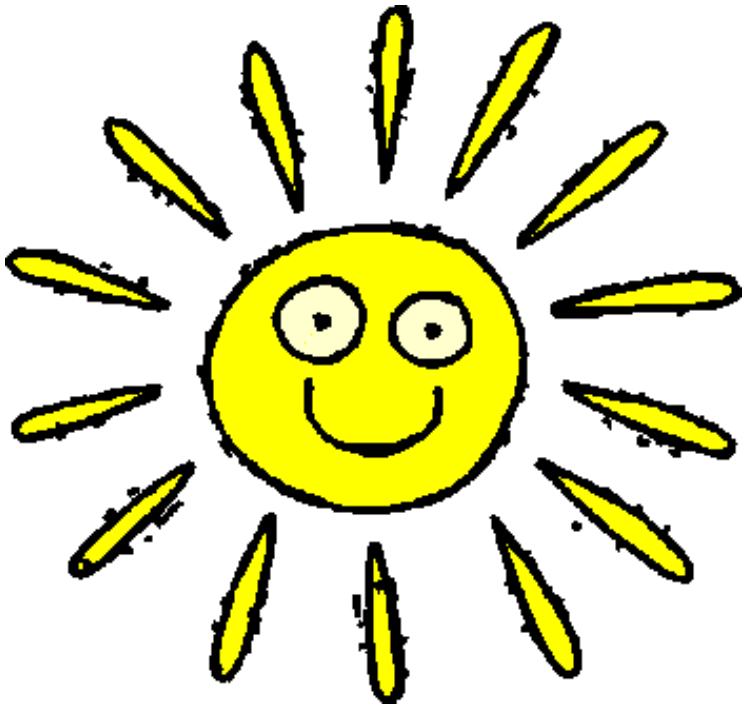
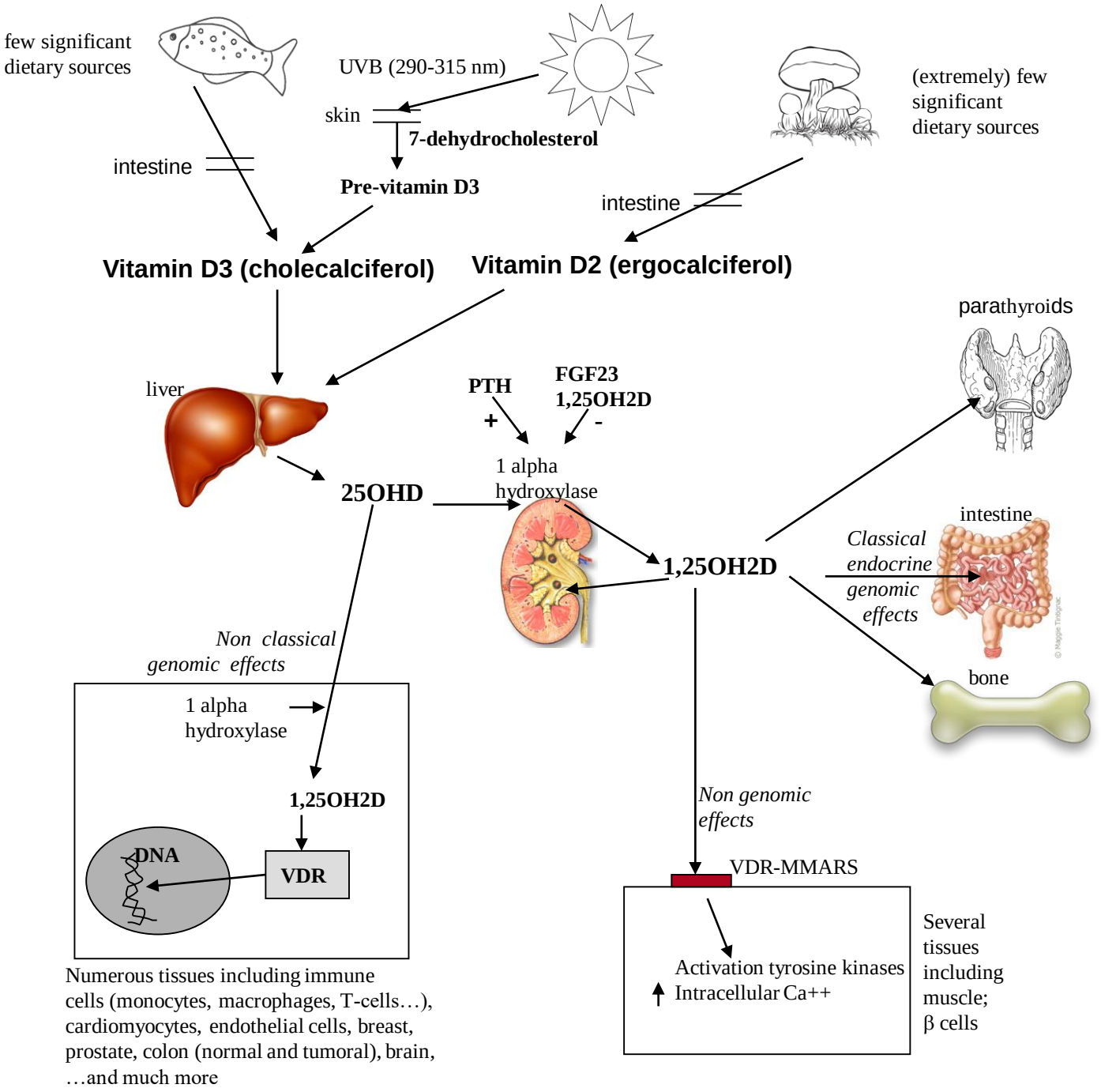
Bénéfices extra-osseux de la supplémentation en vitamine D : mythes ou réalité ?

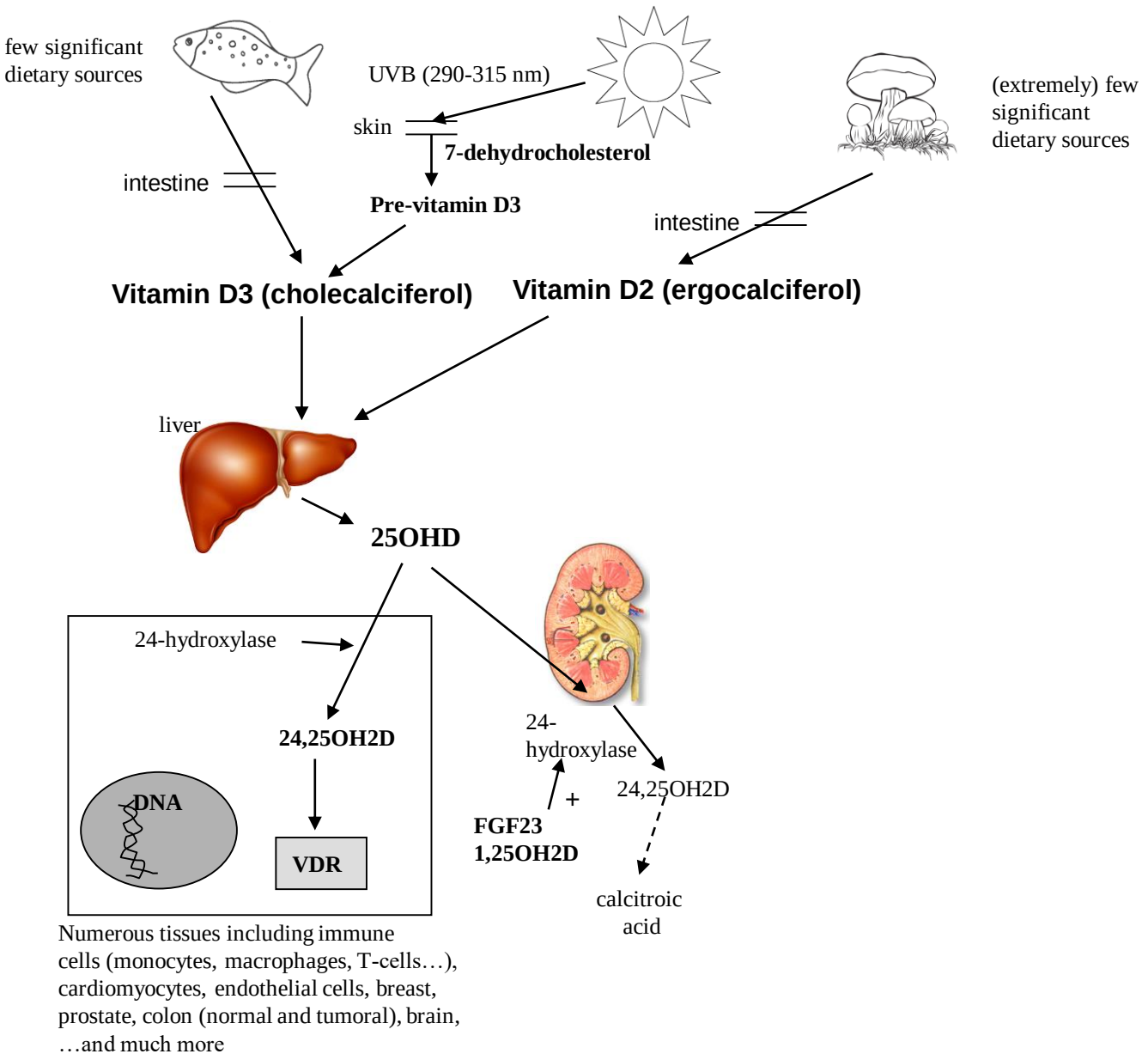
Jean-Claude Souberbielle



Liens d'intérêt en rapport avec le sujet dans les 3 années précédentes:

Interventions ponctuelles Effik, Mylan/Viatris, DiaSorin, Crinex


few significant dietary sources
UVB (290-315 nm)
skin
7-dehydrocholesterol
intestine
Pre-vitamin D3
(extremely) few significant dietary sources
intestine
Vitamin D3 (cholecalciferol)
Vitamin D2 (ergocalciferol)
parathyroids
liver
PTH
+
FGF23
1,25OH2D
-
1 alpha hydroxylase
25OHD
1,25OH2D
intestine
Classical endocrine genomic effects
bone
Non classical genomic effects
1 alpha hydroxylase
1,25OH2D
DNA
VDR
Non genomic effects
VDR-MMARS
Activation tyrosine kinases
Intracellular Ca++
Several tissues including muscle; β cells
Numerous tissues including immune cells (monocytes, macrophages, T-cells…), cardiomyocytes, endothelial cells, breast, prostate, colon (normal and tumoral), brain, …and much more


few significant dietary sources
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Vitamin D3 (cholecalciferol)
Vitamin D2 (ergocalciferol)
liver
25OHD
24-hydroxylase
24,25OH2D
DNA
VDR
24-hydroxylase
+
FGF23
1,25OH2D
24,25OH2D
calcitroic acid
Numerous tissues including immune cells (monocytes, macrophages, T-cells…), cardiomyocytes, endothelial cells, breast, prostate, colon (normal and tumoral), brain, …and much more

La concentration sérique de 25OHD est le marqueur consensuel du statut vitaminique D

- **Quelle que soit la population :**
  - **concentration de 25OHD < 12 ng/mL (30 nmol/L) = *déficit profond* ou *carence* en vitamine D (*présente chez environ 10-15% de la population générale*)**

- **En population générale :**
  - **concentration de 25OHD entre 20 et 60 ng/mL (50-150 nmol/L) = *statut vitaminique D optimal, en particulier pour la santé osseuse* (*présente chez environ 45-55% de la population générale*)**

- **Chez certains patients : ostéoporotiques (ou à risque d'ostéoporose), insuffisants rénaux chroniques à partir du stade 3b (DFGe<45 mL/mn), porteurs d'une malabsorption, âgés à fort risque de chute, cibler une concentration de 25OHD entre 30 et 60 ng/mL *(75-150 nmol/L) (présente chez environ 20-25% de la population générale*).**

- **Les études épidémiologiques ont permis de définir, dans la population générale, des individus à risque d'hypovitaminose D chez qui la fréquence des carences (25OHD <12 ng/mL) ou des déficits modérés (25OHD entre 12 et 20 ng/mL) est beaucoup plus importante en moyenne que dans le reste de la population:**
  - **sujets en surpoids ou obèses**
  - **sujets à peau foncée**
  - **personnes sédentaires et/ou avec très peu d'activité en extérieur**
  - **personnes qui portent des vêtements couvrants**
  - **sujets âgés « fragiles »**
  - **patients avec maladie(s) chronique(s)**

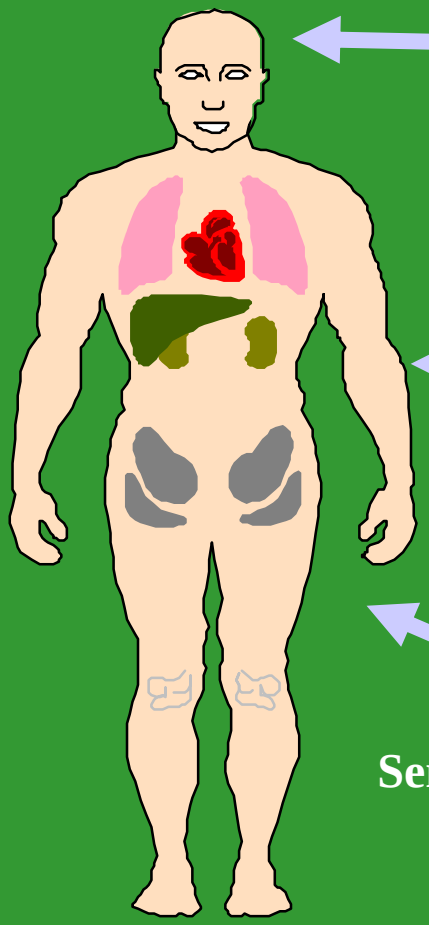
  ET, d'une façon générale, la concentration de 25OHD de l'ensemble de la population est très significativement plus basse entre novembre et Mars (versus Avril-octobre)

Bénéfices extra-osseux de la supplémentation en vitamine D : mythe ou réalité ?

Quid du niveau de preuves?

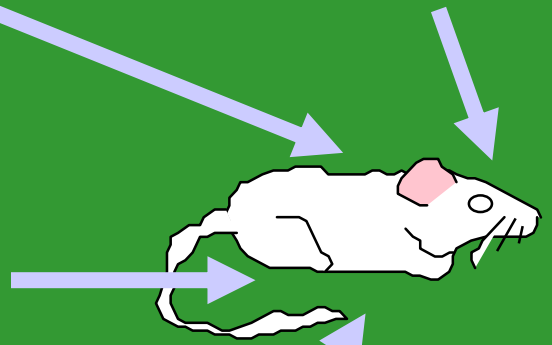
Conséquences d'une altération du gène codant le VDR chez l'homme et la souris transgénique (Exon 2 ou 3)

Vitamin D in human health: lessons from VDR null mice. Bouillon et al Endocr Rev 2008; 29: 726-776



Alopécie

Dysmorphie faciale



- Défaut d'absorption intestinale de calcium
- Rachitisme hypocalcémique
- Retard de croissance
- HTA rénine élevée
- Hypertrophie cardiaque
- Sensibilité accrue à l'autoimmunité et aux tumeurs induites par oncogènes et chemocarcinogènes
- Altération de l'immunité adaptative

Sensibilité aux infections

hypofertilité

certaines des anomalies peuvent être améliorées par un régime riche en calcium, d'autres sont indépendantes du régime calcique

Question du « niveau de preuves »
(Evidence-based Medicine)

-Etudes « écologiques »

-Etudes « observationnelles » et meta-analyses d'études observationnelles

-Etudes expérimentales (ou mécanistiques)

-Etudes interventionnelles (RCTs)

-Meta-analyses de RCTs, « classiques » ou « IPD » ou en « parapluie »

-Etudes de « randomisation mendéliennes »

Explications possibles pour les discordances dans les résultats des RCTs « vitamin D » (vs RCTs médicaments « traditionnels »):

-taille de l'échantillon et durée de l'essai
-adhérence/observance
-dose de vitamine D
-D2 ou D3
-association avec calcium
-possibilité de prendre des suppléments en plus de la randomisation
-mode d'administration (journalier, « espacé »)
-niveau de base de 25OHD
-niveau de 25OHD atteint dans le groupe « vitamine D »
-état (clinique, biologique) de base

-analyse en IT ou analyse secondaire (préspécifiée) en sous-groupes ou « post-hoc »

Recent « mega-trials »

-Vital : 25,871 subjects aged 67 yrs in mean. 2000 IU/day D3 for a mean 5.3 yrs. Mean 25OHD : 77 nmol/L

-Do-health : 2157 ; 75 yrs in mean ; 2000 IU/day D3 for 3yrs ; Mean 25OHD : 56 nmol/L

-D2D : 2423 patients with prediabetes ; 60 yrs in mean ; 4000 IU/day D3 for 2 yrs; mean 25OHD : 70 nmol/L

-D-health : 21,315 persons aged 60-84 yrs ; 60 000 IU/month D3 ; 76% had a predicted 25OHD ≥50 nmol/L

-VIDA : 5,018 subjects aged 66 yrs in mean ; 200,000 IU D3 start followed by 100,000 IU/mo for a median of 3.6 yrs ; mean 25OHD : 63 nmol/L

-TIPS-3 : 5,713 subjects aged 63.9 yrs in mean ; 60,000 IU/mo D3 for a median of 4.6 yrs

Vitamine D et infections (en particulier respiratoires)

SPECIAL ISSUE

JBMR PLUS Open Access ASBMR

Vitamin D and Immune Regulation: Antibacterial, Antiviral, Anti-Inflammatory

Emma L Bishop,[1†] Aiten Ismailova,[2†] Sarah Dimeloe,[1,3] Martin Hewison,[3] and John H White[2,4]

JBMR® Plus (WOA), Vol. 5, No. 1, January 2021, e10405.
DOI: 10.1002/jbm4.10405

1,25D Induces Antimicrobial Innate Immunity

1,25D Regulates Expression of Cytokines Important in Innate Immunity

Direct Effects of 1,25D on T Cells

Indirect Effects of Vitamin D on T Cells

Anti-Inflammatory Effects of Vitamin D and Autoimmune Disease

Activation of human TLR2/1 triggers a vitamin D receptor-dependent antimicrobial response

Philip T. Liu*[1], Steffen Stenger*[2], Huiying Li[3], Linda Wenzel[2], Belinda H. Tan[1], Stephan Krutzik[1], Maria Teresa Ochoa[1], Jürgen Schauber[4], Kent Wu[1], Christoph Meinken[2], Manfred Wagner[5], Robert Bals[6], Andreas Steinmeyer[7], Ulrich Zügel[8], Richard L. Gallo[4], David Eisenberg[3], Martin Hewison[9], Bruce W. Hollis[10], John S. Adams[7], Barry R. Bloom[9] and Robert L. Modlin[1,11].

(*Science 2006 ; 311 : 1770-1773*)

Activation of Toll-like receptor 2/1 in monocytes/macrophages by specific proteins of *Mycobacterium Tuberculosis* induces the transcription of the VDR and CYP27B1 genes and expression of the proteins in the cytosol and ER respectively.

If the extracellular 25OHD concentration is sufficient (>70 nmol/L), 25OHD enters the cells and is locally activated into 1,25OH2D which binds to the VDR. VDR associates with RXR, and the trimeric complex activates the gene coding for cathelicidin (LL37), an antimicrobial peptide able to induce bacterial destruction.

Vitamin D and respiratory infections (including TB)
Observational data

« Poor vitamin D status is significantly associated with an increased risk of both upper and lower respiratory tract infections as reviewed in a recent meta-analysis (4 cross-sectional, 8 case-control, and 13 cohort studies of overall good quality); This was the case in adults as well as in children »

Jolliffe D et al. Vitamin D in the prevention of acute respiratory infection: Systematic review of clinical studies
J Steroid Biochem Mol Biol 2013; 136: 321-329

Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data

Adrian R Martineau, David A Jolliffe, Richard L Hooper, Lauren Greenberg, John F Aloia, Peter Bergman, Gal Dubnov-Raz, Susanna Esposito, Davaasambuu Ganmaa, Adit A Ginde, Emma C Goodall, Cameron C Grant, Christopher J Griffiths, Wim Janssens, Ilkka Laaksi, Semira Manaseki-Holland, David Mauger, David R Murdoch, Rachel Neale, Judy R Rees, Steve Simpson, Iwona Stelmach, Geeta Trilok Kumar, Mitsuyoshi Urashima, Carlos A Camargo Jr

BMJ 2017;356:i6583

WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised controlled trials of vitamin D supplementation for the prevention of acute respiratory tract infection have yielded conflicting results

Individual participant data (IPD) meta-analysis has the potential to identify factors that may explain this heterogeneity, but this has not previously been performed

WHAT THIS STUDY ADDS

Meta-analysis of IPD from 10 933 participants in 25 randomised controlled trials showed an overall protective effect of vitamin D supplementation against acute respiratory tract infection (number needed to treat (NNT)=33)

Benefit was greater in those receiving daily or weekly vitamin D without additional bolus doses (NNT=20), and the protective effects against acute respiratory tract infection in this group were strongest in those with profound vitamin D deficiency at baseline (NNT=4)

These findings support the introduction of public health measures such as food fortification to improve vitamin D status, particularly in settings where profound vitamin D deficiency is common

MAIS…

Vitamin D supplementation to prevent acute respiratory Infections (ARI): systematic review and meta-analysis of stratified aggregate data

David A Jolliffe, Carlos A Camargo Jr, et al

***Lancet Diabetes Endocrinol* 2025** Published **Online** February 21, 2025

Trial-level (not IPD!) meta-analysis of 46 RCTs
No/borderline significant (OR : 0.94 ; 95%CI : 0.88-1.00) effect of vitamin D supplementation on ARI prevention in the ITT analysis

The only secondary sub-group analyses that concluded to a beneficial effect of vitamin D on ARI concerned
1) dosing frequency :
daily dosing (21552 participants, 21 studies) was beneficial (OR: 0.84 [0.73-0.97])
but not weekly or monthly or longer interval
2) Age
Vitamin D reduced ARI in children aged 1-15 yrs
(11944 participants; 16 studies ; OR: 0.74 [0.60-0.92])

Effects of **vitamin D** supplementation on acute respiratory tract infections in 6-8-year-old children: a randomized clinical trial. Clerico JW, Thams L, Stounbjerg NG, Hauger H, Damsgaard CT, Mølgaard C. Eur J Nutr. 2025 May 1;64(4):170.

-Secondary analyses from a double-blinded, randomized, clinical 24-week trial, which investigated effects of vitamin D supplementation on children's growth and health.

-Copenhagen, Denmark (55ºN) from August-October 2019 and endpoint visits February-April 2020. 200 healthy, white 6-8-y-old children were included and randomized to 20 µg/day (800 IU/day) vitamin D_3 or placebo.

-Baseline serum 25-hydroxyvitamin D was 79.8 (17.2) nmol/L, which increased by 9.4 (17.0) nmol/L in the vitamin D group and decreased by 32.7(17.4) nmol/L in the placebo group.

-The vitamin D-supplemented children had 17% fewer sick days due to ARTI (risk ratio (RR), 0.83; 95% CI, 0.76-0.90; $P < 0.001$) compared with placebo. Children also had 43% fewer days with ARTI with fever (RR, 0.57; 95% CI, 0.48-0.67; $P < 0.001$), vitamin D group compared with placebo.

Conclusion: Vitamin D supplementation reduced the number of days with ARTI. This supports a recommendation of vitamin D supplementation during extended winter at northern latitudes.

The impact of supplementing vitamin D through different methods on the prognosis of COVID-19 patients: a systematic review and meta-analysis, Xiangqun Zhang, Junyuan Wu , Hongmeng Dong, et al, Front. Nutr. 11:1441847.doi: 10.3389/fnut.2024.1441847 (published sept 25. 2024)

A total of 21 studies involving 4,553 participants were included. Vitamin D supplementation significantly reduced the mortality rate (RR = 0.72, 95% CI: 0.54–0.94, p = 0.02), with continuous dosing being more effective (RR = 0.53, 95% CI: 0.34–0.83, p = 0.006) compared to single-dose (RR = 0.88, 95% CI: 0.69–1.12, p = 0.3). Mortality was significantly reduced in the Vitamin D-deficient group (25OHD < 30 ng/mL) (RR = 0.73, 95% CI: 0.59–0.89, p = 0.002) but not in the non-restricted group. Regarding ICU admission, supplementation reduced ICU admission rates (RR = 0.58, 95% CI: 0.38–0.88, p = 0.01), with continuous dosing (RR = 0.44, 95% CI: 0.22–0.90, p = 0.02) being more effective than single-dose (RR = 0.79, 95% CI: 0.61–1.03, p = 0.08). ICU admission rates were significantly reduced in the Vitamin D-deficient group (RR = 0.63, 95% CI: 0.42–0.93, p = 0.02) but not in the non-restricted group (RR = 0.59, 95% CI:0.32–1.11, p = 0.1).

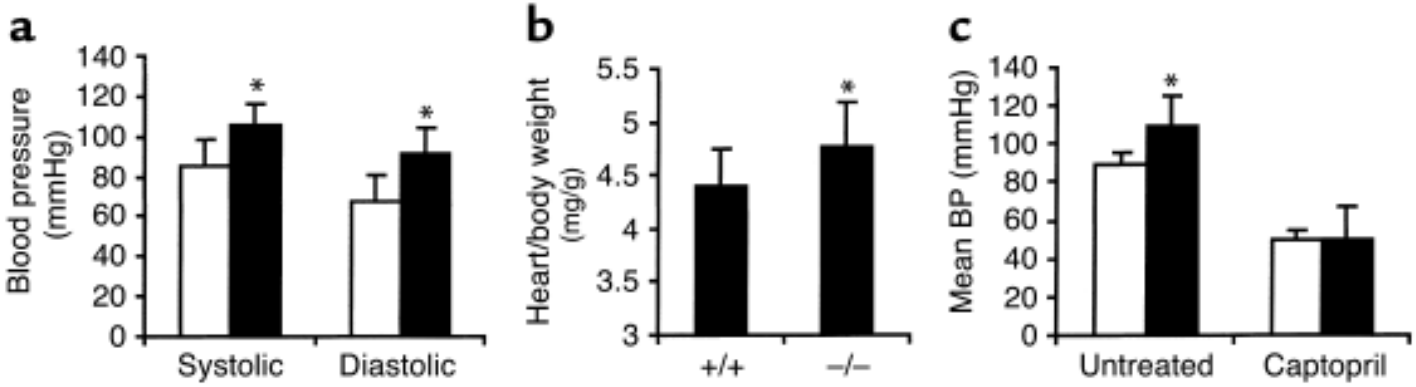
Vitamine D et hypertension

1,25-Dihydroxyvitamin D_3 is a negative endocrine regulator of the renin-angiotensin system

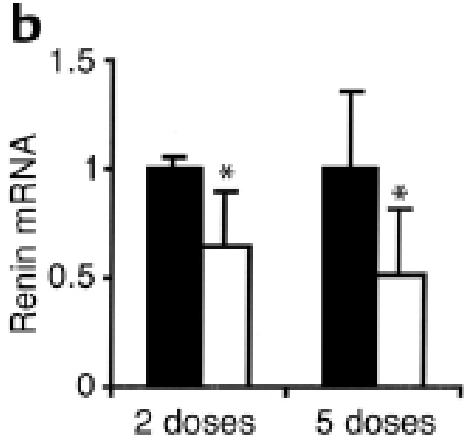
See related Commentary on pages 155–156.

Yan Chun Li,[1] Juan Kong,[1] Minjie Wei,[1] Zhou-Feng Chen,[2] Shu Q. Liu,[3] and Li-Ping Cao[1]

J. Clin. Invest. 110:229–238 (2002). doi:10.1172/JCI200215219.



Effect independent of calcium



Eur J Epidemiol
DOI 10.1007/s10654-013-9790-2

META-ANALYSIS

Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants

Setor Kwadzo Kunutsor · Tanefa Antoinette Apekey · Marinka Steur

Published online: 02 March 2013

The pooled RR of incident hypertension per 10 ng/mL increment in baseline 25(OH)D levels was 0.88 (0.81, 0.97) in dose–response analysis.

Studies are needed to determine whether the association of vitamin D with hypertension represents a causal association and also to determine whether vitamin D therapy may be beneficial in the prevention or the treatment of hypertension.

However, RCTs testing the effect of vitamin D supplementation on blood pessure did not show positive effect in most of the ITT analysis [Beveridge LA, Struthers AD et al. JAMA Intern Med 2015 ; 175 : 745-754]. In some studies however, secondary/post-hoc analyses showed that cholecalciferol supplementation may slightly but significantly decrease systolic blood pressure in moderatly hypertensive patients with vitamin D deficiency.

Current Hypertension Reports
https://doi.org/10.1007/s11906-022-01204-6

NUTRITION AND HYPERTENSION (T MORI, SECTION EDITOR)

Is Vitamin D Supplementation an Effective Treatment for Hypertension?

Songcang Chen[1] · Gio Gemelga[1] · Yerem Yeghiazarians[1]

Recent Findings HTN is caused by multiple factors. VDD may be one of the factors contributing to the development of this disorder. There are more than 70 RCTs that examined the impact of VD supplementation on BP. These RCTs can be classified into four groups based on their respective study populations, including participants who are (1) VD-sufficient and normotensive, (2) VD-deficient and normotensive, (3) VD-sufficient and hypertensive, and (4) VD-deficient and hypertensive.

Summary Our evaluation of these studies demonstrates that VD supplementation is ineffective when used to reduce BP in VD-sufficient normotensive subjects. VD supplementation for five years or more may reduce the risk of developing HTN specifically among those with VDD. Interestingly, findings from 12 RCTs indicate that daily or weekly supplementation, as opposed to large bolus dosing, results in the reduction of BP in VD-deficient hypertensive patients. Our ongoing research

Current Hypertension Reports
https://doi.org/10.1007/s11906-022-01204-6

NUTRITION AND HYPERTENSION (T MORI, SECTION EDITOR)

Résultat confirmé fin décembre 2023

Is Vitamin D Supplementation an Effective Treatment for Hypertension?

Songcang Chen[1] · Gio Gemelga[1] · Yerem Yeghiazarians[1]

Mais aussi……

Vitamine et pathologies gravidiques :Méta-analyse COCHRANE

Cochrane Library
Cochrane Database of Systematic Reviews

Palacios C, Kostiuk LK, Peña-Rosas JP.
Vitamin D supplementation for women during pregnancy.
Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD008873.
DOI: 10.1002/14651858.CD008873.pub4.

Vitamin D supplementation for women during pregnancy (Review)

Palacios C, Kostiuk LK, Peña-Rosas JP

Supplementation with vitamin D alone versus placebo/no intervention. A total of 22 trials involving 3725 pregnant women were included in this comparison; 19 trials were assessed as having low-to-moderate risk of bias for most domains and three trials were assessed as having high risk of bias for most domains

Vitamin D supplementation during pregnancy significantly decreased the risk of preeclampsia and gestational diabetes

Vitamin D supplementation and total cancer incidence and mortality by daily vs. infrequent large-bolus dosing strategies: a meta-analysis of randomised controlled trials

N. Keum[1,2], Q-Y. Chen[1], D. H. Lee[2], J. E. Manson[3,4] and E. Giovannucci[2,4]

British Journal of Cancer; https://doi.org/10.1038/s41416-022-01850-2

12 essais pour incidence des cancers (tous cancers)

6 essais pour mortalité chez des patients ayant développé un cancer

CONCLUSIONS: For vitamin D supplementation, daily dosing, but not infrequent large-bolus dosing, reduced total cancer mortality. For total cancer incidence, bolus dosing did not reduce the risk and the benefits of daily dosing were limited to normal-weight individuals.

La supplémentation en vitamine D chez des patients dans un état de "prédiabète" améliore le profil glucidique (*Zhang et al. Effect of vitamin D supplementation on glycemic control in prediabetes: a meta-analysis. Nutrients 2021, 4464*) et réduit (vs placebo) l'incidence du diabète de type 2 chez ceux qui avaient une 25OHD<12 ng/mL en début d'étude ainsi que chez ceux qui avaient un IMC<30 kg/m² (*Pittas et al. Vitamin D supplementation and prevention of type 2 diabetes. The D2D study. N Engl J Med 2019*) et chez ceux qui ont maintenu une concentration de 25OHD >100 nmol/L (soit 40 ng/mL) pendant l'étude (*Dawson-Hughes B et al. Intratrial exposure to vitamin D and new-onset diabetes in adults with prediabetes: a secondary analysis of the D2D study. Diabetes Care 2020*)

Role of vitamin D in prevention of type 2 diabetes mellitus:
A systematic review and meta-analysis

GYURI SIM, YUNJUNG KIM, SUN MIN LEE, JONGSUNG HAHN and JONGYOON KIM

Accepted September 4, 2024

This meta-analysis of 11 RCTs (5221 patients) shows that vitamin D supplementation in prediabetic patients lowers the risk of T2DM and promotes regression to normoglycemia, with no significant differences in subgroup analyses or interaction with baseline vitamin D levels, ethnicity, or body mass index (BMI).

Incidence des maladies auto-immunes

Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial

Jill Hahn,[1,2,3] Nancy R Cook,[1,4] Erik K Alexander,[5] Sonia Friedman,[6] Joseph Walter,[4] Vadim Bubes,[4] Gregory Kotler,[4] I-Min Lee,[1,4] JoAnn E Manson,[1,4] Karen H Costenbader[2]

BMJ 2022;376:e066452 | doi: 10.1136/bmj-2021-066452

CONCLUSIONS

Vitamin D supplementation for five years, with or without omega 3 fatty acids, reduced autoimmune disease by 22%, while omega 3 fatty acid supplementation with or without vitamin D reduced the autoimmune disease rate by 15% (not statistically significant). Both treatment arms showed larger effects than the reference arm (vitamin D placebo and omega 3 fatty acid placebo).

Progression/Evolution des maladies auto-immunes

- Efficacy of vitamin D in treatment of inflammatory bowel disease: A meta-analysis

Li J et al **Medicine (Baltimore)** 2018 Nov;97(46):e12662.

Eighteen RCTs involving 908 patients were included.

Conclusions: The treatment of VitD in patients with IBD can improve the level of 25(OH)D3 and control the relapse rate of the disease, whose clinical curative effect is more accurate.

Thus, VitD should be recommended for the treatment of IBD, at least as an adjunctive treatment.

- The Effect of Vitamin D Supplementation on Rheumatoid Arthritis Patients: A Systematic Review and Meta-Analysis

Guan Y et al. **Front Med (Lausanne)** 2020 Oct 30;7:596007.

Six studies (*n* = 438 patients) were included in the meta-analysis.

Conclusions: Compared with placebo control interventions, vitamin D supplementation seemed to be an effective intervention for patients with rheumatoid arthritis. Different doses of vitamin D and durations of intervention produce different effects.

- The effect of vitamin D supplementation on thyroid autoantibody levels in the treatment of autoimmune thyroiditis: a systematic review and a meta-analysis

Wang S et al. **Endocrine**. 2018 Mar;59(3):499-505.

Six randomized controlled trials (RCTs) were included representing a total of 344 patients with AIT

Conclusions: The current evidence suggests that vitamin D supplementation could decrease serum PO-Ab and Tg-Ab titers of patients with AIT in the short-term (about six months). More high-quality studies are needed to further confirm the effects, especially the long-term effects of Vitamin D supplementation on thyroid autoantibodies levels in the treatment of AIT.

….

Diabète de type 1

Gregoriou et al. Rev Diabet Stud 2017

7 RCTs (2 cholecalciferol; 2 alphacalcidol; 3 calcitriol**)**, **287 individuals**

Results: Significant positive effects on DID (daily insulin dose), FCP (fasting C-Peptide), and SCP (stimulated C-Peptide) levels were observed after supplementation with alphacalcidol and cholecalciferol, whereas supplementation with calcitriol showed no effect.
Conclusions: Vitamin D supplementation in the form of alphacalcidol
and cholecalciferol appears to be beneficial in the treatment of T1D patients by attenuating the natural history of the disease.

Cholecalciferol in relapsing-remitting MS: A randomized clinical trial (CHOLINE)

William Camu, Philippe Lehert, Charles Pierrot-Deseilligny, Patrick Hautecoeur, Anne Besserve, Anne-Sophie Jean Deleglise, Marianne Payet, Eric Thouvenot, Jean Claude Souberbielle

Neurol Neuroimmunol Neuroinflamm 2019 Aug 6;6(5):e597

Results: The primary end point was not met. In patients who completed the 2-year follow-up (45 with cholecalciferol and 45 with placebo), all efficacy parameters favored cholecalciferol with an ARR reduction : rR 0,4 (p = 0.012), less new hypointense T1-weighted lesions (p = 0.025), a lower volume of hypointense T1-weighted lesions (p = 0.031), and a lower progression of EDSS (p = 0.026). The overall rate of adverse events was well balanced between groups.
Conclusions: Although the primary end point was not met, these data suggest a potential treatment effect of cholecalciferol in patients with RRMS already treated with interferon beta-1a and low serum 25OHD concentration. Together with the good safety profile, these data support the exploration of cholecalciferol treatment in such patients with RRMS.

High-Dose Vitamin D in Clinically Isolated Syndrome Typical of Multiple Sclerosis: The D-Lay MS Randomized Clinical Trial. D-LAY-MS Trial

Thouvenot E, et al.JAMA. 2025 Mar 10:e251604. doi: 10.1001/jama.2025.1604.

316 participants untreated with CIS; 303 included in the ITT analysis, Duration : 24 months

Disease activity was observed in 94 patients (60.3%) in the vitamin D group and 109 patients (74.1%) in the placebo group (hazard ratio [HR], 0.66 [95% CI, 0.50-0.87]; P = .004), and median time to disease activity was longer in the vitamin D group (432 vs 224 days; log-rank P = .003). All 3 secondary MRI outcomes reported significant differences favoring the vitamin D group vs the placebo group: MRI activity (89 patients [57.1%] vs 96 patients [65.3%]; HR, 0.71 [95% CI, 0.53-0.95]; P = .02), new lesions (72 patients [46.2%] vs 87 patients [59.2%]; HR, 0.61 [95% CI, 0.44-0.84]; P = .003), and contrast-enhancing lesions (29 patients [18.6%] vs 50 patients [34.0%]; HR, 0.47 [95% CI, 0.30-0.75]; P = .001).

Conclusions and relevance: Oral cholecalciferol 100 000 IU every 2 weeks significantly reduced disease activity in CIS and early relapsing-remitting MS. These results warrant further investigation, including the potential role of pulse high-dose vitamin D as add-on therapy

Smith H, Anderson F, Raphael P, et al. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women – A population-based, randomized,double-blind, placebo-controlled trial. Rheumatology 2007;46:1852–7.

In 9440 men and women older than 75 years a higher hip fracture rate was found in those given annual intramuscular injections of 300,000 IU of vitamin D2 instead of a placebo

Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 2010;303:1815–22.

In 2256 women older than 80 years, a single annual dose of 500,000 IU of vitamin D3 given for 4 consecutive years increased the risk of both fractures and falls compared to a placebo

Välimäki VV, Löyttyniemi E, Pekkarinen T, et al. How well are the optimal serum 25OHD concentrations reached in high-dose inermittent vitamin D therapy? a placebo-controlled study on comparison between 100,000 IU and 200,000 IU of oral D3 every 3 months in elderly women. Clin Endocrinol (Oxf)2016;84:837–44.

Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinicaltrial. JAMA Intern Med 2016;176:175–83.
200 community-dwelling men and women 70 years and older with a prior fall who received 2400 0 IU D3, 60000 IU D3, or 24000 IU D3 +300 μ g calcifediol per month, "Although higher monthly doses of vitamin D were effective in reaching a threshold of at least 30 ng/mL of 25-hydroxyvitamin D, they had no benefit on lower extremity function and were associated with increased risk of falls compared with 24,000 IU".

Waterhouse M, Sanguineti E, Baxter C, et al. Vitamin D supplementation andrisk of falling: outcomes from the randomized, placebo-controlled D-HealthTrial. J Cachexia Sarcopenia Muscle 2021;12:1428–39.
D-health trial ; 21 315 persons (60–84 years) ; 60 000 IU/month D3 for a median of 5 years; 76% had a predicted 25(OH)D ≥50 nmol/L
Significant higher risk of falls in the vitamin D group

Myung SK, Cho H. Effects of intermittent or single high-dose vitamin D supple-mentation on risk of falls and fractures: a systematic review and meta-analysis. Osteoporos Int 2023;34:1355–67.
"Intermittent or single high-dose vitamin D supplementation had no preventive effect on the risk of falls and fractures and might even increase the risk of falls"

Thompson B, Waterhouse M, English DR, et al. Vitamin D supplementation and major cardiovascular events: D-Health randomised controlled trial. BMJ 2023;381:e075230. D-health trial
As a secondary objective, vitamin D did not reduce all-cause mortality, and exploratory analyses excluding the early
follow-up period were consistent with an increased risk of death from cancer in the vitamin D group

Joseph P, Pais P, Gao P,et al. Vitamin D supplementation and adverse skeletal and non- skeletal outcomes in individuals at increased cardiovascular risk: results from the International Polycap Study (TIPS)-3 randomized controlled trial. Nutr Metab Cardiovasc Dis 2023;33:434–40. 5713 subjects (63.9 years) ; 60 000 IU/months D3 for a median of 4.6 years Vitamin D did not reduce fracture, the primary outcome, and the composite of CV death, myocardial infarction stroke, cancer, fracture, or fall, the secondary outcome. Higher total mortality, a prespecified outcome was observed in the vitamin D group (P = 0.03).

Daily or intermittent vitamin D supplementation in patients with or at risk of osteoporosis : Position statement from the GRIO

Pickering M-E, Souberbielle J-C, Boutten A, Breuil V, Briot, Chapurlat R, Fardellone P, Javier R-M, Koumakis E, Cortet B,
in name of Groupe de Recherche et d'Information sur les Ostéoporoses (GRIO)

Joint Bone Spine 2025

-Effets bénéfiques d'une supplémentation quotidienne mais (généralement) pas d'une supplémentation intermittente chez les insuffisants/carencés en vitamine D

-Quelques études récentes (« Mega-trials » comme TIPS-3 ou D-Health) ont rapporté un excès de chutes, mais aussi de mortalité dans les groupes « vitamine D » (par rapport aux groupes « placebo ») qui recevaient une supplémentation considérée à ce jour comme modérée (60 000 UI/mois).

-Explication probable : une forte dose administrée de manière intermittente stimule durablement des voies d'inactivation de la vitamine D (CYP24A1; FGF23…) ce qui n'est pas le cas lors d'une supplémentation quotidienne à dose « modérée »

-Pas de preuve d'une meilleure observance/adhérence avec supplémentation intermittente vs quotidienne

Conclusions

Les essais randomisés Vitamine D vs Placebo rapportent (le plus souvent) des effets bénéfiques de la vitamine D chez des patients initialement déficitaires ou carencés en vitamine D qui reçoivent une supplémentation quotidienne mais pas « espacée » (sauf rares exceptions), mais pas d'effet chez les non déficitaires (là encore, en dehors de rares situations à confirmer).

=>

Ceci suggère que l'hypovitaminose D est un facteur de risque indépendant pour différentes pathologies et incite avant tout à éviter l'hypovitaminose D plutôt qu'espérer (aujourd'hui) des bénéfices d'une supplémentation chez des sujets non déficitaires en vitamine D (en dehors de quelques situations à confirmer).

Les bénéfices observés très majoritairement avec une supplémentation quotidienne et les quelques effets « indésirables » avec une supplémentation intermittente devraient nous inciter à revoir notre façon de supplémenter.

Merci pour votre attention

Quelques suggestions de questions « pratico/cliniques » pour la table ronde

-Quels apports de vitamine D pour que la majorité de la population générale ait une 25OHD sérique entre 20 et 60 ng/mL?
Place du dosage de 25OHD ?

-Idem pour avoir entre 30 et 60 ng/ml (ostéoporoses, IRC…)?
Place du dosage de 25OHD ?

-Qui/quand supplémenter ?

-Place du calcifediol ?

-Si on prescrit de la vitamine D sans faire de dosage est-ce qu'il y a un risque de lithiase rénale ?