Carenza di vitamina D e patologie ad essa correlate

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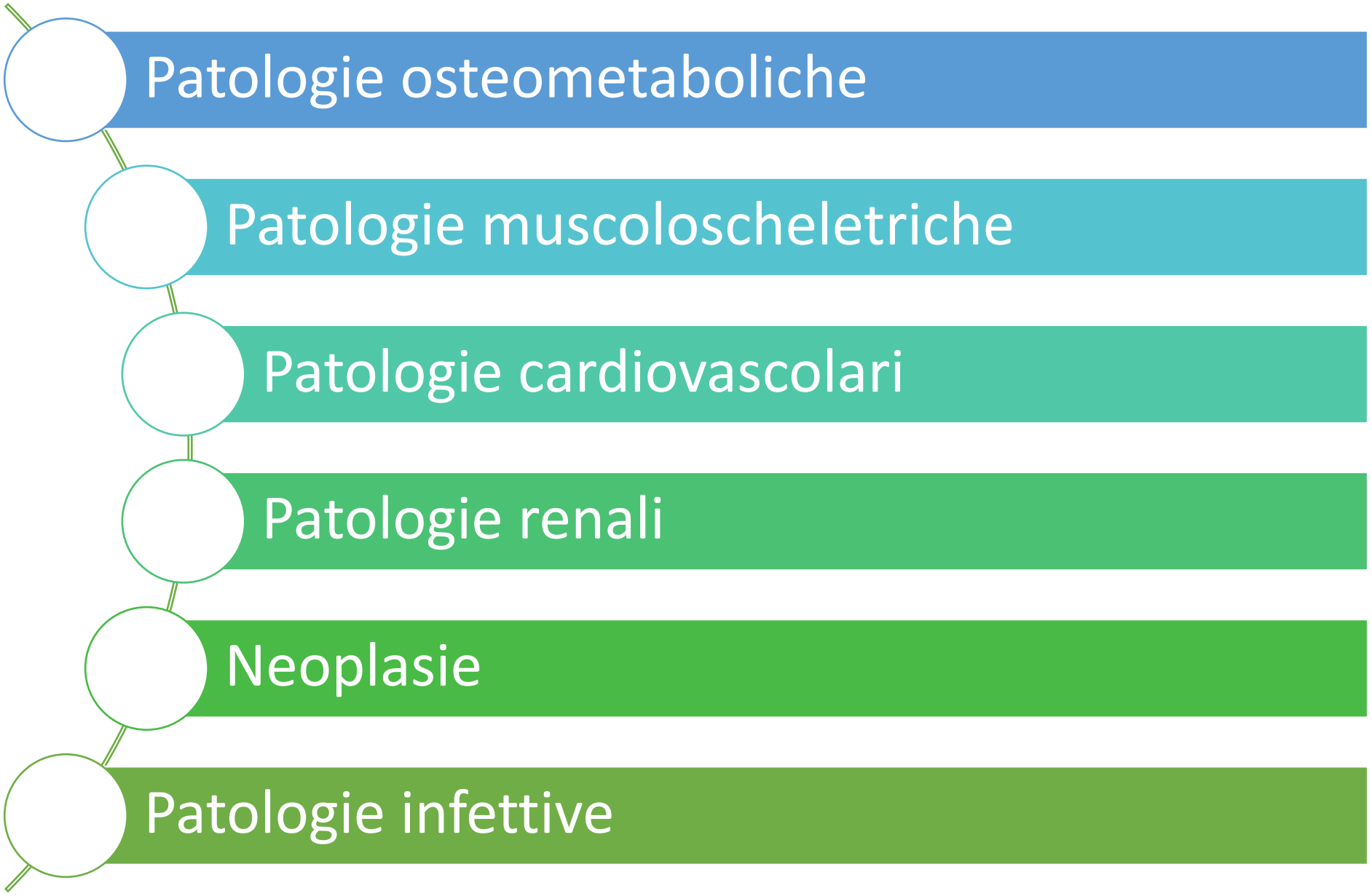
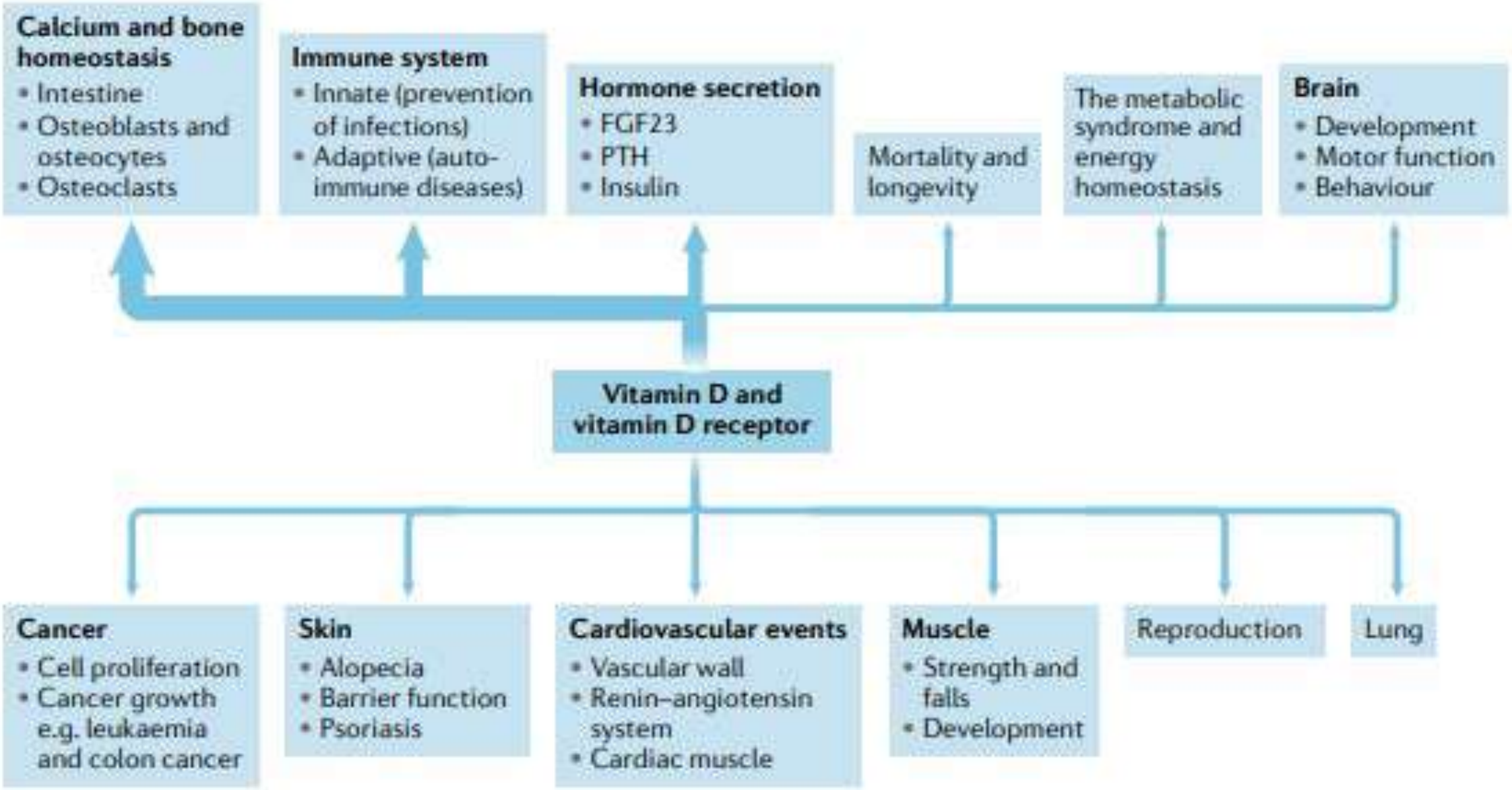
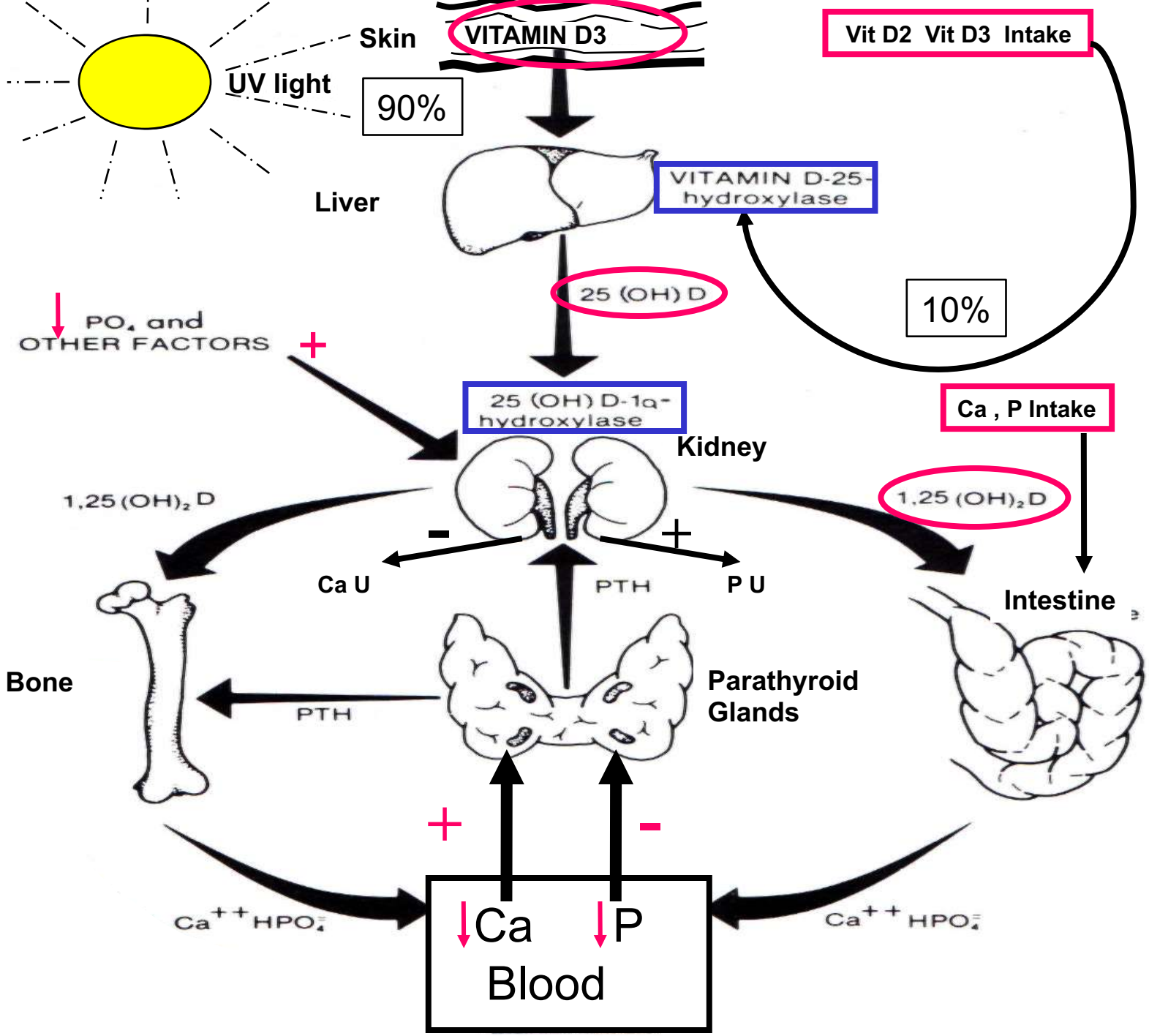

Patologie osteometaboliche
Patologie muscoloscheletriche
Patologie cardiovascolari
Patologie renali
Neoplasie
Patologie infettive

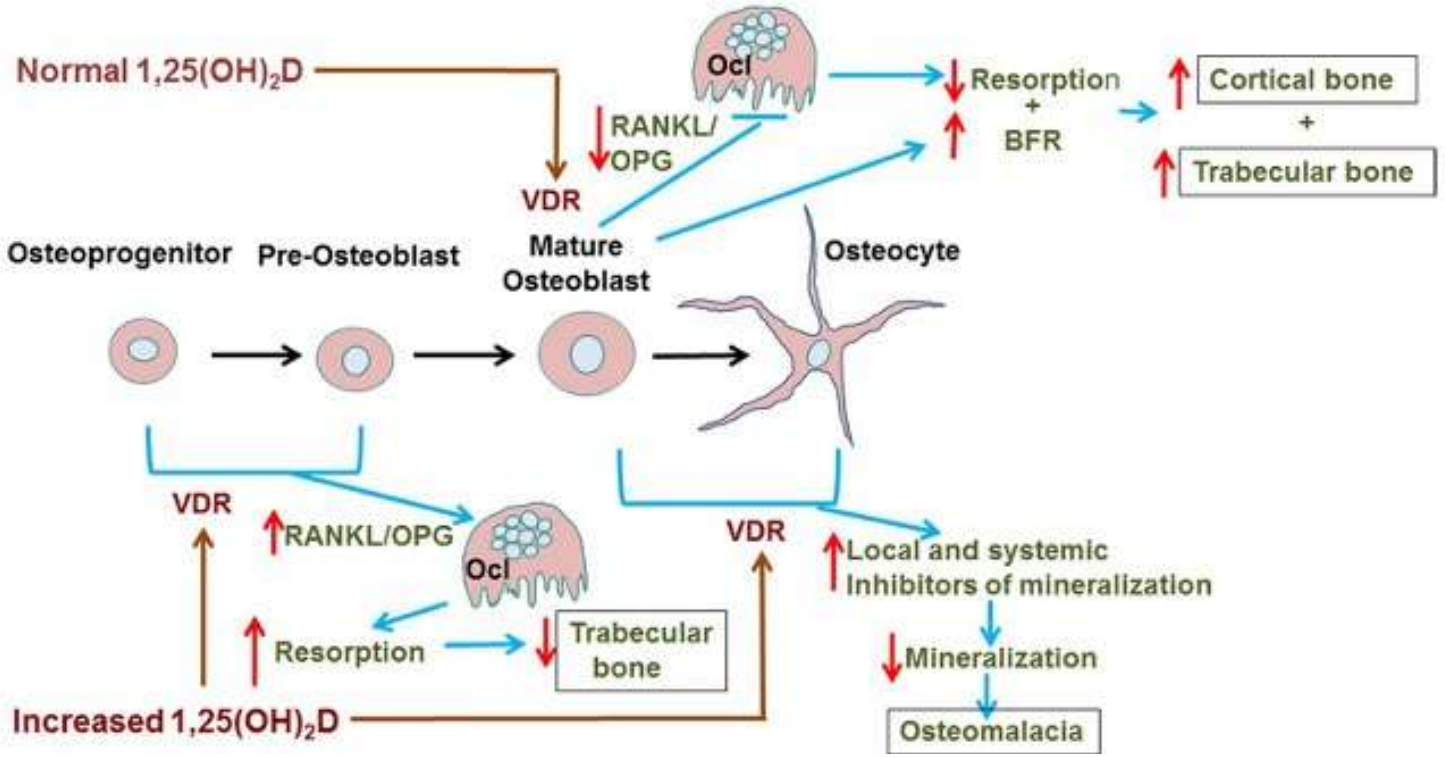


Bouillon et al., *Nature Reviews Endocrinology*, 2022


Skin
UV light
90%
VITAMIN D3
Vit D2 Vit D3 Intake
Liver
VITAMIN D-25-hydroxylase
25 (OH) D
10%
PO4 and OTHER FACTORS
+
25 (OH) D-1α-hydroxylase
Kidney
Ca , P Intake
1,25 (OH)2 D
1,25 (OH)2 D
-
+
Ca U
PTH
P U
Intestine
Bone
PTH
Parathyroid Glands
+
-
Ca++ HPO4=
Ca++ HPO4=
Ca
P
Blood

Normali livelli di $1,25(OH)_2D$ agiscono tramite il recettore della vitamina D (VDR) espresso sulla superficie degli osteoblasti maturi nel ridurre il rapporto RANKL/OPG e il riassorbimento osseo.

Al tempo stesso, il legame $1,25(OH)_2D$-VDR a livello degli osteoblasti determina un incremento della neoformazione ossea.



Goltzman, *Histochemistry and Cell Biology*, 2018

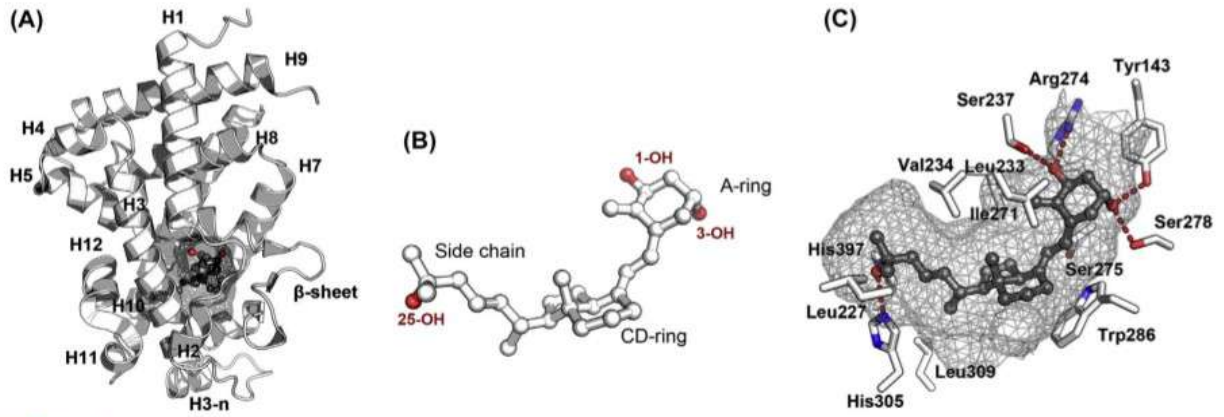
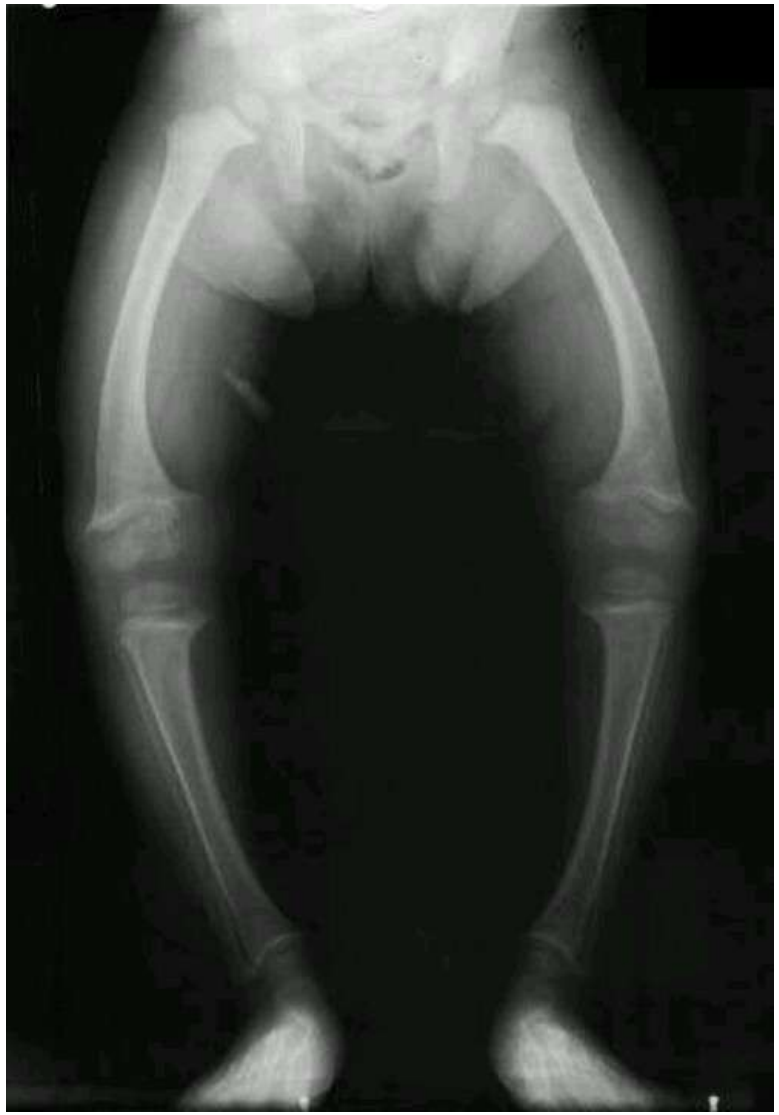


FIGURE 11.3 1α,25-dihydroxyvitamin D_3 recognition by vitamin D receptor (VDR). (A) Overall structure of the VDR ligand-binding domain (LBD). The VDR LBD bound to $1,25(OH)_2D_3$ is composed of 13 helices (H1,2, 2n,3–12) (protein data bank identifier: 1DB1). (B) Conformation of $1,25(OH)_2D_3$ in the ligand-binding pocket (LBP). (C) Binding mode of $1,25(OH)_2D_3$ in the VDR LBP. The volume of the LBP is shown as a grey surface. Specific H-bonds anchoring the three hydroxyl-groups of the $1,25(OH)_2D_3$ are shown as *dash lines*.

VDR contiene un dominio legante il DNA (DBD) ed uno legante il ligando (LBD)

Mutazioni «loss of function» di VDR o iper-espressione di proteine che impediscono il legame della vitamina D con VDR determinano patologie quali il **rachitismo ereditario vitamina D resistente** e il **rachitismo ereditario vitamina D dipendente**



Classificazione delle OM

- **Ridotto apporto**

vit D (ridotta esposizione alla luce solare, dieta, nutrizione parenterale totale)

Ca (dieta, nutrizione parenterale totale)

P (nutrizione parenterale totale)

- **Alterato assorbimento (Ca, P, Vit D)**

morbo celiaco

ittero ostruttivo cronico

gastrectomia

malattie pancreatiche

by-pass digiuno-ileale

S. dell'ansa cieca

antiacidi; fitati

- **Alterato metabolismo (vit D)**

cirrosi biliare

anticonvulsivanti

insufficienza renale cronica

rachitismo vit D dipendente I

rachitismo vit D dipendente II

- **Aumentata perdita (P, Ca)**
- (S. Ipofosfatemiche)

rachitismo ipofosfatemico vit D resistente (X Dom., Autos. Dom., Autos. Rec.)

osteomalacia oncogenica

idiopatica

S. di Fanconi (P, Ca, bicarbonati, aminoacidi, glicidi…)

acquisite (uropatia ostruttiva, gammopatie, S.Sjogren, amiloidosi, oro, mercurio, cadmio, idiopatica …)

ereditarie (cistinosi, tirosinemia, glicogenosi, M. di Wilson …)

- **Alterazione diretta della mineralizzazione**

acidosi metabolica (acidosi tubulare I e II tipo)

alluminio (dialisi, antiacidi, chelanti P nell' ins. renale cronica)

bisfosfonati (etidronato, pamidronato)

intossicazione fluoro

ipofosfatasia

Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis

Dr Benjamin MP Tang, MD • Guy D Eslick, PhD • Prof Caryl Nowson, PhD • Caroline Smith, PhD • Prof Alan Bensoussan, PhD

A FAVORE

Ampia metanalisi del 2007 che ha raccolto 29 RCT (n=63 897) aventi come outcomes il rischio di frattura complessivo e/o la BMD dopo integrazione con calcio e vitamina D.

I dati, specialmente nei pazienti con elevata compliance, erano favorevoli dopo 3-5 anni e mostravano una significativa riduzione del rischio fratturativo e della perdita di massa ossea. Gli autori suggerivano quindi un dosaggio minimo di 1200 mg di calcio e 800 UI di vitamina D al giorno.

Cochrane Library

Cochrane Database of Systematic Reviews

PARZIALMENTE A FAVORE

Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men (Review)

Avenell A, Mak JCS, O'Connell D

Cochrane del 2016 che analizza in 53 trial e 91791 pazienti l'efficacia di:

- Vitamina D o analoghi vs. placebo.
- Vitamina D + calcio vs. calcio.
- Vitamina D vs. calcio.
- Vitamina D + calcio vs. placebo.

Nella prevenzione delle fratture

VITAMINA D + CALCIO vs. PLACEBO

Comparison 4. Vitamin D [D2, D3 or 25(OH)D] plus calcium versus control or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new hip fracture	9	49853	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.96]
1.1 Not selected on the basis of previous osteoporotic fracture	5	43719	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.71, 0.94]
1.2 Selected on the basis of previous osteoporotic fracture	4	6134	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.71, 1.47]
2 Persons sustaining new hip fracture: subgroup analysis by residential status (institution vs community)	9	49853	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.96]
2.1 Resident in institution (nursing home, residential care etc)	2	3853	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.62, 0.92]
2.2 Community dwelling	7	46000	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.77, 1.09]
3 Persons sustaining new non-vertebral fracture	8	10380	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.78, 0.96]
3.1 Not selected on the basis of previous osteoporotic fracture	5	7560	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.95]
3.2 Selected on the basis of previous osteoporotic fracture	3	2820	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.13]
4 Persons sustaining new vertebral fracture	4	42185	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.74, 1.09]
4.1 Not selected on the basis of previous osteoporotic fracture	2	39477	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.10]
4.2 Selected on the basis of previous osteoporotic fracture	2	2708	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.04, 3.20]
5 Persons sustaining any new fracture	10	49976	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.90, 0.99]

Lieve efficacia di calcio + vit. D nel prevenire nuove fratture.

JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults

Evidence Report and Systematic Review for the US Preventive Services Task Force

Leila C. Kahwati, MD, MPH; Rachel Palmieri Weber, PhD; Huiling Pan, BA; Margaret Gourlay, MD, MPH; Erin LeBlanc, MD, MPH; Manny Coker-Schwimmer, MPH; Meera Viswanathan, PhD

CONTRARIO PER VIT. D+ CALCIO, INCONCLUDENTE PER IL SOLO CALCIO.

Undici RCT (51419 pazienti) per vedere l'efficacia della supplementazione con vitamina D, calcio o vitamina D + calcio nel ridurre il rischi fratturativo.

Key questions

1. Is there direct evidence for supplementation with vitamin D or calcium alone or vitamin D combined with calcium for prevention of fractures or reduction in fracture-related morbidity and mortality?

2. Is there direct evidence for the harms of supplementation with vitamin D or calcium alone or vitamin D combined with calcium?

The USPSTF found **adequate evidence** that daily supplementation with **400 IU or less** of vitamin D and **1000 mg or less** of calcium has no benefit for the primary prevention of fractures in community-dwelling, postmenopausal women.

The USPSTF found **inadequate evidence** to estimate the benefits of doses **greater than 400 IU** of vitamin D or **greater than 1000 mg** of calcium to prevent fractures in community-dwelling postmenopausal women.

These **recommendations do not apply** to persons with a history of **osteoporotic fractures, increased risk for falls, or a diagnosis of osteoporosis or vitamin D deficiency.**

Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults

A Systematic Review and Meta-analysis

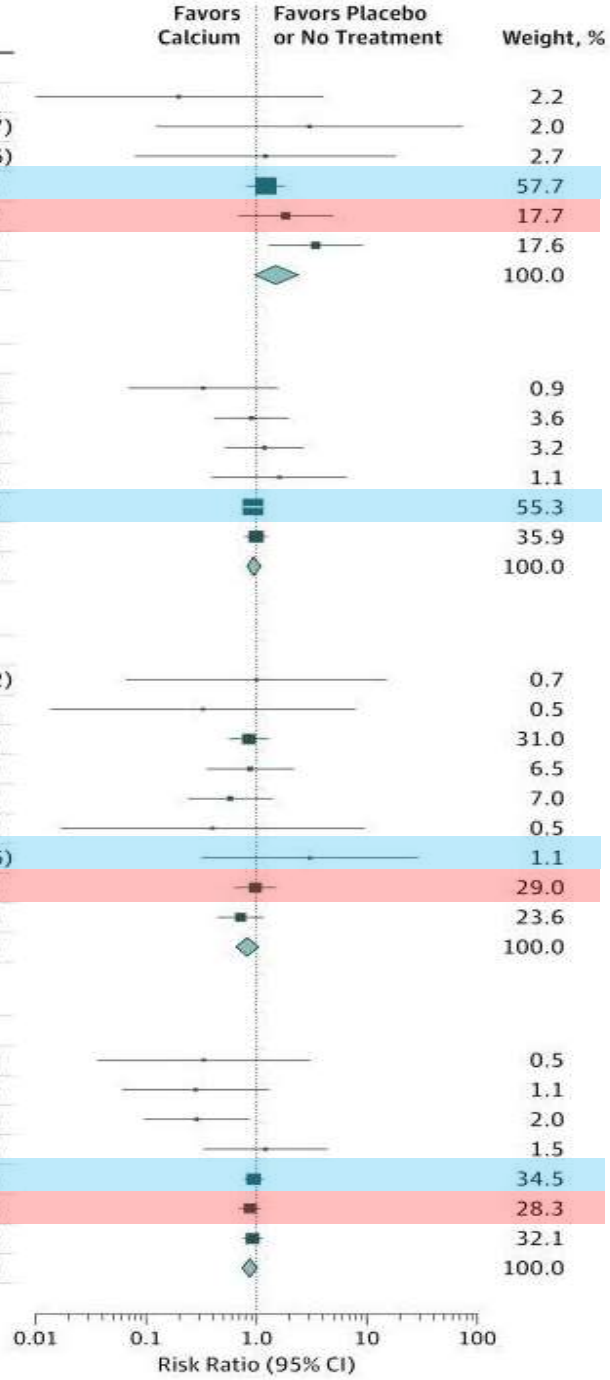
Jia-Guo Zhao, MD; Xian-Tie Zeng, MD; Jia Wang, MD; Lin Liu, MD

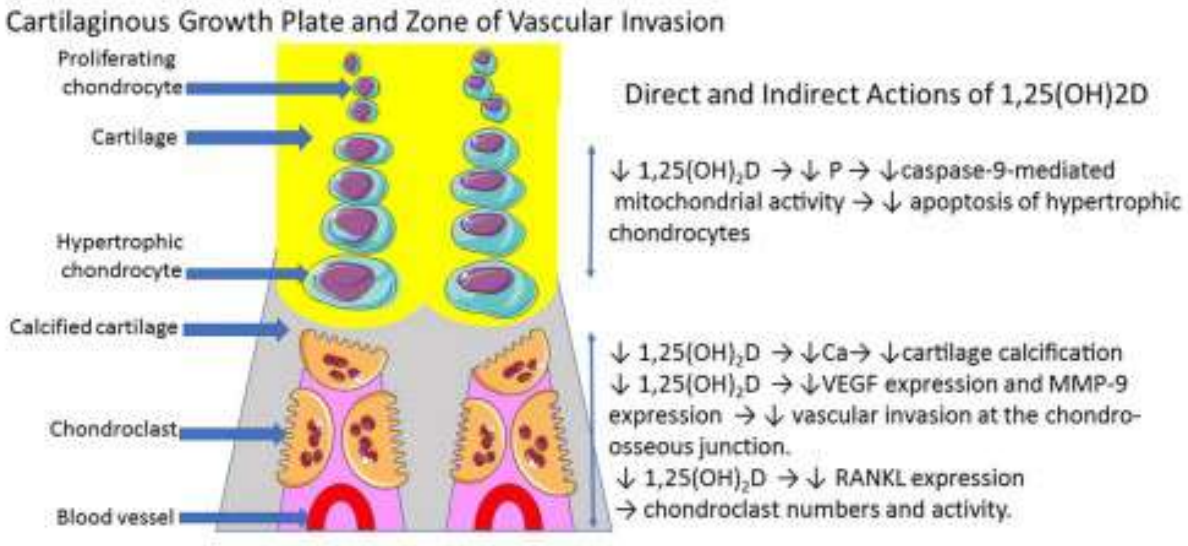
CONTRARIO

Metanalisi che raggruppa 33 RCT con un totale di 51145 pazienti cui erano stati somministrati calcio, vitamina D o entrambi nella prevenzione delle fratture.

Nessuna differenza vs. placebo nella prevenzione dell'outcome, né nei pazienti trattati con calcio da solo, né in quelli con vitamina D da sola né con entrambi.

Study or Subgroup	Calcium		Placebo or No Treatment		Risk Ratio (95% CI)	Weight, %
	No. With Fracture	Total No.	No. With Fracture	Total No.		
Hip fracture						
Reid et al,[42] 1993	0	68	2	67	0.20 (0.01-4.03)	2.2
Baron et al,[47] 1999	1	464	0	466	3.01 (0.12-73.77)	2.0
Avenell et al,[51] 2004	1	29	1	35	1.21 (0.08-18.46)	2.7
RECORD,[54] 2005	49	1311	41	1332	1.21 (0.81-1.83)	57.7
Prince et al,[56] 2006	11	730	6	730	1.83 (0.68-4.93)	17.7
Reid et al,[57] 2006	17	732	5	739	3.43 (1.27-9.26)	17.6
Total	79	3334	55	3369	1.53 (0.97-2.42)	100.0
Heterogeneity: $\tau^2 = 0.05$; $\chi^2_5 = 5.74$ ($P = .33$); $I^2 = 13\%$ Test for overall effect: $z = 1.84$ ($P = .07$)						
Nonvertebral fracture						
Reid et al,[42] 1993	2	68	6	67	0.33 (0.07-1.57)	0.9
Riggs et al,[46] 1998	11	119	12	117	0.90 (0.41-1.96)	3.6
Peacock et al,[49] 2000	11	126	10	135	1.18 (0.52-2.68)	3.2
Avenell et al,[51] 2004	4	29	3	35	1.61 (0.39-6.62)	1.1
RECORD,[54] 2005	163	1311	178	1332	0.93 (0.76-1.13)	55.3
Reid et al,[57] 2006	107	732	109	739	0.99 (0.77-1.27)	35.9
Total	298	2385	318	2425	0.95 (0.82-1.11)	100.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_5 = 2.74$ ($P = .74$); $I^2 = 0\%$ Test for overall effect: $z = 0.62$ ($P = .54$)						
Vertebral fracture						
Hansson and Roos,[41] 1987	1	25	1	25	1.00 (0.07-15.12)	0.7
Reid et al,[42] 1993	0	68	1	67	0.33 (0.01-7.92)	0.5
Recker et al,[44] 1996	27	95	34	102	0.85 (0.56-1.30)	31.0
Riggs et al,[46] 1998	8	119	9	117	0.87 (0.35-2.19)	6.5
Peacock et al,[49] 2000	7	126	13	135	0.58 (0.24-1.40)	7.0
Avenell et al,[51] 2004	0	29	1	35	0.40 (0.02-9.46)	0.5
RECORD,[54] 2005	3	1311	1	1332	3.05 (0.32-29.26)	1.1
Prince et al,[56] 2006	38	730	39	730	0.97 (0.63-1.51)	29.0
Reid et al,[57] 2006	27	732	38	739	0.72 (0.44-1.16)	23.6
Total	111	3235	137	3282	0.83 (0.66-1.05)	100.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 3.37$ ($P = .91$); $I^2 = 0\%$ Test for overall effect: $z = 1.52$ ($P = .13$)						
Total fracture						
Inkovaara et al,[40] 1983	1	42	3	42	0.33 (0.04-3.08)	0.5
Reid et al,[42] 1993	2	68	7	67	0.28 (0.06-1.31)	1.1
Baron et al,[47] 1999	4	464	14	466	0.29 (0.10-0.87)	2.0
Avenell et al,[51] 2004	4	29	4	35	1.21 (0.33-4.41)	1.5
RECORD,[54] 2005	166	1311	179	1332	0.94 (0.77-1.15)	34.5
Prince et al,[56] 2006	110	730	126	730	0.87 (0.69-1.10)	28.3
Reid et al,[57] 2006	134	732	147	739	0.92 (0.75-1.14)	32.1
Total	421	3376	480	3411	0.88 (0.75-1.03)	100.0
Heterogeneity: $\tau^2 = 0.01$; $\chi^2_6 = 7.63$ ($P = .27$); $I^2 = 21\%$ Test for overall effect: $z = 1.56$ ($P = .12$)						





EFFETTI DELLA VITAMINA D SULLA CARTILAGINE

- Ridotti livelli sierici di vitamina D determinano ipofosfatemia.
- L'ipofosfatemia a sua volta riduce l'apoptosi dei condrociti ipertrofici.
- Si determina quindi un aberrante incremento dello spessore cartilagineo ed un alterato rimodellamento della crescita cartilaginea.
- A sua volta, l'ipovitaminosi D riduce la disponibilità di calcio e riduce la calcificazione della cartilagine.
- Si riducono anche VEGF e RANKL con minore attività di condroclasti ed osteoclasti.

VITAMIN D LEVELS AND OA

	Reference	Year	Country	Study design	Condition of samples	Samples	Age (years)†	Females (%)	Controls	Age (yrs)	% female	Vitamin D assay	Follow-up	Results
Development and progression	Lane et al. [11]	1999	USA	Case-cohort longitudinal	Participants of the Study of Osteoporotic Fractures (SOF)	237	>65	100	N/A	—	—	Radioimmunoassay	8 yrs	Low 25(OH)D = 3x as likely to develop hip OA (JSN) Low 25(OH)D ≠ osteophyte growth defined hip OA No association between $1,25(OH)_2D_3$ and hip OA
	McAlindon et al. [12]	1996	USA	Prospective observational study	Participants of the Framingham Study	556	70.3 ± 4.5	—	N/A	—	—	Competitive protein-binding assay	8 yrs	Low intake and serum Vit D ≠ ↑ risk for progression of knee OA Vit D positively correlated with BMD, Vit D intake, and physical activity Vit D inversely correlated with BMI Low Vit D = increased risk of knee OA Vit D levels predict osteophyte growth and cartilage loss (less so)
	Kinstari et al. [13]	2014	Finland	Longitudinal cohort	No hip or knee OA at baseline	5274	30–99	54.1	N/A	—	—		10 yrs	Low 25(OH)D ≠ development of hip or knee OA Baseline 25(OH)D was associated with known risk factors of OA except for traumatic injury
	Chaganti et al. [14]	2010	USA	Longitudinal cohort	Participants of the Osteoporotic Fractures in Men Study (MrOS)	1104	77.2 ± 5.3	0	N/A	—	—	MS	4.6 yrs	↑ 25(OH)D levels = ↓ prevalence of radiographic hip OA Vit D insufficient men (levels of 25[OH]D 15.1–30 ng/mL) = 2-fold ↑ likelihood of prevalent radiographic hip OA compared with Vit D sufficient men
	Abu El Maaty et al. [15]	2013	Egypt	Cross-sectional	Postmenopausal + clinically diagnosed knee OA	36	54.7 ± 3.2	100	10	25.8 ± 2	0	HPLC	N/A	↓ 25(OH)D levels are associated with newly diagnosed OA in postmenopausal Egyptian women
	Heidari et al. [16]	2011	Iran	Cross-sectional	Knee OA (ACR Criteria)	148	60.2 ± 12.9	—	150	60.1 ± 10.2	—	ELISA	N/A	↓ 25(OH)D in OA than control (NS) High prevalence rate of serum 25-OHD deficiency Significant positive association between serum 25(OH)D deficiency and knee OA in a subgroup of patients aged <60 years, greater association in younger patients
	Bergink et al. [17]	2009	Netherlands	Prospective population-based cohort study	Participants of the Rotterdam Study	1248	66.2 ± 6.7	58.3	N/A	—	—	Radioimmunoassay	6.5 yrs	↓ Dietary intake of vitamin D = ↑ knee ROA ↓ 25(OH)D = ↑ risk of progressive ROA, not in confounding factor adjusted results (including age, sex, BMD, smoking, JSN, fall tendency, health status, disability index, and caloric intake) ↓ Baseline BMD patients: ↓ 25(OH)D (serum and intake) = ↑ incidence of knee ROA
	Ding et al. [18]	2009	Australia	Cohort study, cross-sectional and longitudinal	Participants of the Tasmanian Older Adult Cohort Study (TASOAC); did not have RA	1002	51–79	50	N/A	—	—	Radioimmunoassay	2.9 yrs	of sex, ROA status, and knee pain Baseline Vit D levels predicted changes in medial and lateral tibial cartilage volume ↑ Serum 25(OH)D levels = ↑ knee tibial cartilage volume in older people, particularly in females, ROA patients, and those with knee pain Vit D insuff. = moderate-to-severe JSN in older adults
	Felson et al. [19]	2007	USA	2 longitudinal cohort studies	Participants of the Framingham Study	715 277	Framingham: 53.1 ± 8.7 BOKS: 66.2 ± 9.3	53.1 41.4	N/A N/A	— —	— —	Radioimmunoassay Radioimmunoassay	9.5 yrs 30 mo	Baseline Vit D ≠ radiographic worsening ↑ Vit D = slightly ↑ rates of worsening (NS after adjustment for risk factors) Vit D def. = slight ↑ in risk of JSN (NS after adjustment for risk factors) ↓ Vit D = slight ↓ risk of osteophyte growth Baseline Vit D ≠ radiographic worsening ↑ Vit D = ↑ risk of worsening No Vit D def. = slight ↑ risk of JSN (NS after adjustment for risk factors) ↓ Vit D ≠ osteophyte growth Vit D def. appears slightly protective against cartilage loss

	Reference	Year	Country	Study design	Condition of samples	Samples	Age (years)†	Females (%)	Controls	Age (yrs)	% female	Vitamin D assay	Follow-up	Results
Pain and function	Muraki et al. [20]	2011	UK	Cross-sectional, cohort study	Participants of the Hertfordshire Cohort Study	787	65.6 ± 27	49.5	—	—	—	Chemiluminescent	—	25(OH)D ≠ knee ROA ↑ Vit D = ↑ knee pain FokI VDR polymorphism = knee ROA and pain
	Laslett et al. [21]	2014	Australia	Longitudinal population-based cohort study		769	62.1 ± 20	50.5	N/A	—	—	Radioimmunoassay	5 yrs	Vit D def. predicts knee pain over a 5-year period Vit D def. may predict hip pain over 2.4 yrs
	Yazmalar et al. [22]	2013	Turkey	Prospective cohort	Knee OA (ACR Criteria)	74	48.70 ± 7.14	67.6	70	41.39 ± 4.21	37	HPLC	~6 mo	No correlation between Vit D status and WOMAC or VAS
	Al-Jarallah et al. [23]	2011	Kuwait	Cross-sectional	Primary knee OA	99	56.49 ± 9.12	91	N/A	—	—	Radioimmunoassay	N/A	Most knee OA patients were Vit D def. 25(OH)D ≠ OA severity (radiographic) or functional assessment

	Reference	Year	Country	Study design	Condition of samples	Samples	Age (years)†	Females (%)	Controls	Age (yrs)	% female	Vitamin D assay	Follow-up	Results
BMD and body composition	Bischoff-Ferrari et al. [24]	2005	USA	Population-based cohort	Primary knee OA (Framingham Study)	228	74.4 ± 11.1	64	N/A	—	—	Radioimmunoassay and competitive protein-binding assay		↑ Vit D status = ↑ BMD (femoral neck) in primary knee ROA independent of sex, age, BMI, physical activity, knee pain, and disease severity
	Christensen et al. [25]	2012	Denmark	Prospective cohort study	Knee OA + obese (BMI >30 kg/m^2)	175	62.6 ± 6.3	81	N/A	—	—	Microparticle chemiluminescence immunoassay	16 we	Knee OA patients on a formula diet had ↑ Vit D levels and BMD
	Hunter et al. [26]	2003	UK	Cross-sectional twin study	Participants of St. Thomas' UK Adult Twin Registry	1644	24–79	100	N/A	—	—	Radioimmunoassay	N/A	Knee OA patients have ↓ Vit D levels Vit D levels ≠ osteophytes
	Barker et al. [27]	2014	USA	Cross-sectional	Knee OA	56	48 ± 1	55	N/A	—	—	Chemiluminescent immunoassay	N/A	Vit D def. = quadriceps dysfunction but ≠ inflammatory cytokines

† means at baseline in longitudinal studies. Vit D: vitamin D; ROA: radiographic osteoarthritis; ACR: American College of Rheumatology; NS: not statistically significant; BMI: body mass index; BMD: bone mineral density; HPLC: high performance liquid chromatography; ELISA: enzyme-linked immunosorbent assay; MS: mass spectrometry; Insuff.: insufficient; Def.: deficient; ↓: lower/decreased; ↑: higher/increased; ≠: no association; =: association; yrs: years; mo: months; we: weeks; JSN: joints space narrowing; N/A: not applicable.

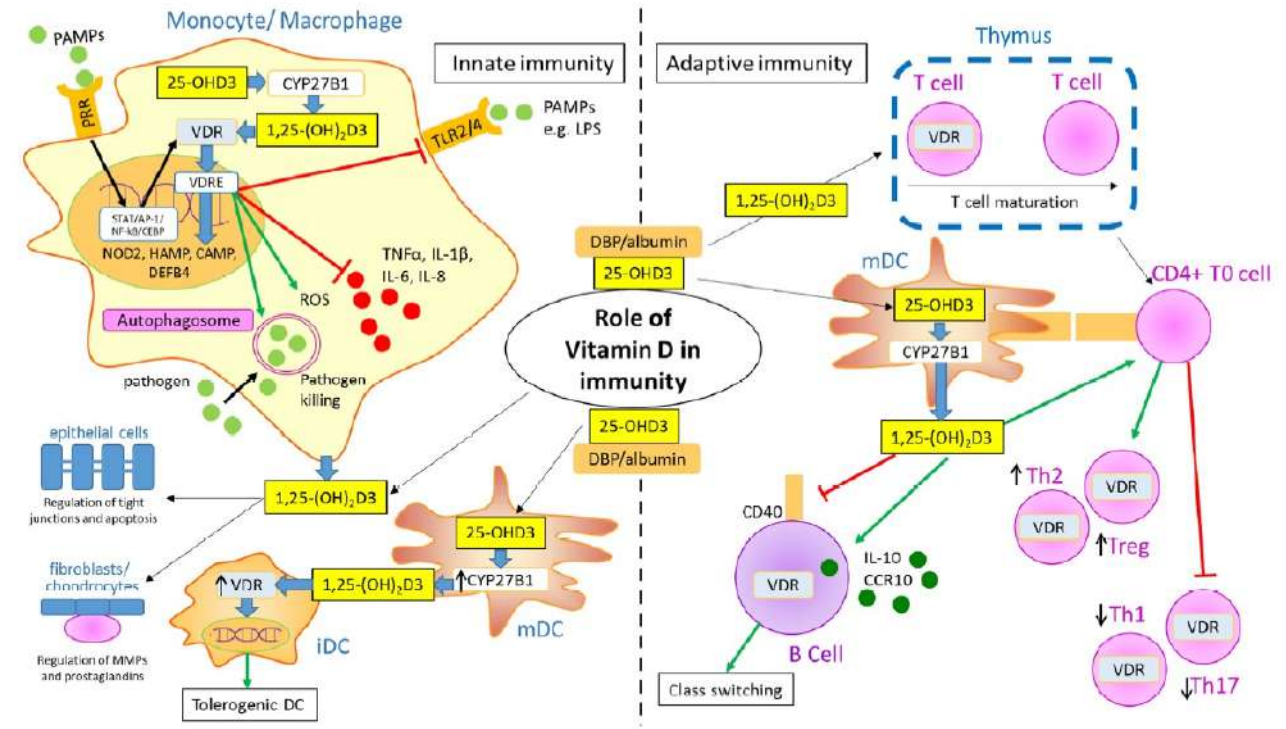
EFFICACY OF VITAMIN D SUPPLEMENTATION FOR THE TREATMENT OF KNEE OA

treatment of knee osteoarthritis.

Reference	Country	Supplement	Dose	Condition of samples	Vitamin D status of participants	Samples/placebo	Vitamin D assay	Follow-up	Results
Sanghi et al. [28] 2013	India	Cholecalciferol granules or placebo	60,000 IU per day for 10days followed by 60,000 IU once a month for 12 months	>40 yrs old ACR Criteria WOMAC pain >4 for at least 6 months 6 months of conventional treatment BMI <30 No previous fracture or surgery to knee	Vitamin D insuffi-ciency (25(OH)D ≤ 50 nmol/L)	52/51	EIA	Multiple over a 12-month period	Vit D = ↓ VAS and WOMAC pain scores versus placebo Vit D = ↓ WOMAC physical + total versus placebo Vit D = ↑ serum calcium, 25(OH)D, and alkaline phosphatase versus placebo No difference in WOMAC stiffness
McAlindon et al. [29] 2013	USA	Cholecalciferol or placebo	2,000 IU daily with subsequent adjustment in 2000 IU increments at 4, 8, and 12 months for a target 25OHD level between 36 and 100 ng/mL	Age > 45 Symptomatic knee OA KL ≥ 2 (ACR Criteria) WOMAC = mild pain	Not selected for	73/73	LC/MS/MS	Multiple over a 24-month period	Vit D levels ↑ over the 2 years No significant difference in knee pain between groups No significant differences between cartilage loss, JSW, and BML size No significant difference in WOMAC pain or function scores

Vit D: vitamin D; BMI: body mass index; ↑: higher/increased; =: association; ACR: American College of Rheumatology; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; KL: Kellgren-Lawrence grading; VAS: visual analogue score; JSW: joint space width; BML: bone marrow lesion; EIA: enzyme immunoassay; LC/MS/MS: liquid chromatography-tandem mass spectrometry.

VITAMINA D E MALATTIE AUTOIMMUNI



- La vitamina D possiede proprietà immunoregolatorie e gioca un ruolo importante nell'infiammazione.
- VDR è espresso dai macrofagi, cellule dendritiche e cellule B e T attivate.
- Il calcitriolo è responsabile dell'equilibrio tra linfociti Th1 e Th2.
- Il calcitriolo può ridurre lo stimolo pro-infiammatorio di IL-17 e IL-4 tramite l'iperespressione di IL-13.
- Il calcitriolo può agire direttamente sulle cellule CD4+ nel promuovere Tregs che secernono IL-10

Mol Biol Rep (2011) 38:3643–3651
DOI 10.1007/s11033-010-0477-4

Associations between vitamin D receptor polymorphisms and susceptibility to rheumatoid arthritis and systemic lupus erythematosus: a meta-analysis

Young Ho Lee · Sang-Cheol Bae · Sung Jae Choi · Jong Dae Ji · Gwan Gyu Song

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity			
			OR	95% CI	*P*-value	Model	Q	*P*-value	I^2
FokI F vs. f	Overall	3	1.502	1.158–1.949	0.002	F	0.80	0.667	0
	Overall in HWE	0	NA	NA	NA	NA	NA	NA	NA
	European	3	1.502	1.158–1.949	0.002	F	0.80	0.667	0
	Asian	0	NA	NA	NA	NA	NA	NA	NA
FF vs. Ff + ff (Recessive)	Overall	3	1.820	1.266–2.117	0.001	F	0.54	0.760	0
	European	3	1.820	1.266–2.117	0.001	F	0.54	0.760	0
	Asian	0	NA	NA	NA	NA	NA	NA	NA
FF + Ff vs. ff (Dominant)	Overall	3	1.451	0.855–2.463	0.167	F	1.60	0.448	0
	European	3	1.451	0.855–2.463	0.167	F	1.60	0.448	0
	Asian	0	NA	NA	NA	NA	NA	NA	NA
FF vs. ff (Additive)	Overall	3	1.922	1.087–3.401	0.025	F	1.28	0.525	0
	European	3	1.922	1.087–3.401	0.025	F	1.28	0.525	0
	Asian	0	NA	NA	NA	NA	NA	NA	NA

RA rheumatoid arthritis, *HWE* Hardy-Weinberg equilibrium, *NA* not available

Meta-analisi che mostra un incrementato rischio di sviluppare artrite reumatoide nei pazienti con un determinato polimorfismo di VDR.

Contestualmente, il deficit di vitamina D è stato posto in correlazione a numerose altre patologie autoimmuni (lupus eritematoso sistemico, sclerosi multipla, diabete mellito tipo I, tiroiditi etc.) con risultati spesso contraddittori.

VITAMIN D AND DISEASE ACTIVITY IN RA

Author, Year	No. of Patients	Prevalence of Vitamin D Deficiency	Markers of Disease Activity	Findings
Bird *et al*., 1982	RA 30 OA 30	Not defined	ESR, Articular index	No correlation between serum $1,25(OH)_2D$ levels and disease activity
Kroger *et al*., 1993	RA 143	Not defined	ESR	Serum $1,25(OH)_2D$ levels lower in patients with ESR >30 mm/hr
Oelzner *et al*., 1998	RA 96	Serum 25(OH) D levels below normal in 32% of patients. $1,25(OH)_2D$ below normal in 12% of patients	CRP	Negative correlation between serum $1,25(OH)_2D$ and disease activity
Cutolo *et al*., 2006	RA Estonia 64 Italy 54 Controls Estonia 30 Italy 35	Not defined	DAS28	Negative correlation between serum 25(OH)D and disease activity
Patel *et al*., 2007	206 patients with inflammatory polyarthritis	Mean 25(OH)D levels 20 ng/ml	Tender joint count, DAS28, HAQ	Inverse association of serum 25(OH)D with disease activity Inverse association of serum $1,25(OH)_2D$ with HAQ
Turhanoglu *et al*., 2009	RA 65 Controls 40	Mean levels in RA patients 104.87 +/- 60.08 nmol/l (Conversion is 42.01 +/- 24 ng/ml)	DAS28, ESR, CRP, HAQ	Inverse association of serum 25(OH)D levels with disease activity
Rossini *et al*., 2010	RA 1191 Controls 1019	25(OH)D <20 ng/ml in 52% of patients.	HAQ, DAS28, Mobility activities of daily living score	Inverse association between serum 25(OH)D levels and disease activity
Craig *et al*., 2010	RA 266	25(OH)D <15 ng/ml in 50% of patients	ESR, CRP, HAQ-Disability, DAS28	Inverse association between serum 25(OH)D levels and disease activity (by univariate analysis only)
Haque *et al*., 2010	RA 62	25(OH) D <30 ng/ml in 61% of patients	Tender and swollen joint counts, ESR, CRP, Physician global assessment of disease activity, Patient global assessment of disease activity, DAS28, HAQ	Inverse association of serum 25(OH)D levels with DAS28, pain, and HAQ scores in active disease, but not in remission
Welsh *et al*., 2011	RA 170	25(OH)D <25 ng/ml in 75% of patients	DAS28, ESR	No association between serum 25(OH)D levels and disease activity
Kerr *et al*., 2011	RA 850	25(OH)D <30 ng/ml in 84% and 25(OH)D <20 ng/ml in 43% of patients	Tender joint count, Swollen joint count Modified-HAQ, DAS28, ESR, CRP	Inverse association between serum 25(OH)D and disease activity
Braun- Moscovici *et al*., 2011	RA 85 PsA 22 AS 14	25(OH)D <12 ng/ml in 42% of patients	DAS28 in RA patients	No correlation between serum 25(OH)D levels and disease activity
Baker *et al*., 2012	RA 499	25(OH)D levels <20 ng/ml in 48% of patients	van der Heijde Sharp scores (radiographic scores), DAS28, CRP	No association between serum 25(OH)D levels and disease activity or radiographic scores

Abbreviations: OA, osteoarthritis; RA, rheumatoid arthritis; C, controls; PsA, psoriatic arthritis; AS, ankylosing spondylitis; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; DAS28, disease activity score 28; HAQ, health assessment questionnaire.

VITAMIN D AND CARDIOVASCULAR RISK IN RA

Author, Year	No. of Patients	Parameters Evaluated	Findings
Goshayeshi *et al.*, 2012	RA 120	Presence of metabolic syndrome as defined by ATP III criteria	Serum 25(OH)D levels predictive of metabolic syndrome and inversely related to BMI
Baker *et al.*, 2012	RA 499	Serum lipoprotein levels	Serum 25(OH)D levels inversely associated with LDL, triglyceride levels, and metabolic syndrome, not associated with HDL levels
Haque *et al.*, 2012	RA 179	Insulin resistance measured by Homeostatic Model Assessment 2 (HOMA) Serum lipoprotein levels CRP Fibrinogen E selectin s-ICAM Adiponectin Leptin	Serum 25(OH)D levels positively associated with HDL and inversely associated with Fibrinogen, E selectin, and s-ICAM
Ranganathan *et al.*, submitted	RA 87	Arterial pulse wave velocity Microvascular endothelial function Insulin resistance by HOMA ICAM-1 VCAM-1 MCP-1 IL-17 CRP	Serum 25(OH)D levels inversely associated with IL-17 and positively associated with microvascular endothelial function

Abbreviations: ATP III, adult treatment panel III; CRP, C reactive protein; ICAM, intercellular adhesion molecule; LDL, low density lipoprotein; HDL, high density lipoprotein; VCAM, vascular cell adhesion molecule; MCP, monocyte chemoattractant protein; IL-17, interleukin 17.

linical Nutrition 40 (2021) 2946–2957

Narrative Review

Vitamin D and cardiovascular health

Fernando de la Guía-Galipienso [a, b, c, 1], María Martínez-Ferran [d, 1], Néstor Vallecillo [e], Carl J. Lavie [f], Fabian Sanchis-Gomar [g, **], Helios Pareja-Galeano [a, *]

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[f] John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, LA, USA
[g] Dept. of Physiology, Faculty of Medicine, University of Valencia and INCLIVA Biomedical Research Institute, Valencia, Spain

Sono stati proposti diversi meccanismi che mettono in relazione la carenza di vitamina D con fattori di rischio CV:

- attivazione del sistema renina-angiotensina-aldosterone (mancata attivazione del VDR con aumento della reninemia)
- regolazione anormale dell'ossido nitrico
- stress ossidativo
- vie infiammatorie alterate

La vitamina D regola la **pressione sanguigna** agendo sulle **cellule endoteliali** e sulle **cellule muscolari lisce**. La sua **carenza** è stata associata a vari fattori di rischio CV e sembra essere collegata a una **maggiore mortalità** e incidenza di **malattie cardiovascolari**

Maggiore prevalenza dell' ipertensione arteriosa, di disfunzione endoteliale, di infarti del miocardio, di scompenso cardiaco e diabete mellito di tipo 2 in pazienti affetti da deficit di VIT D

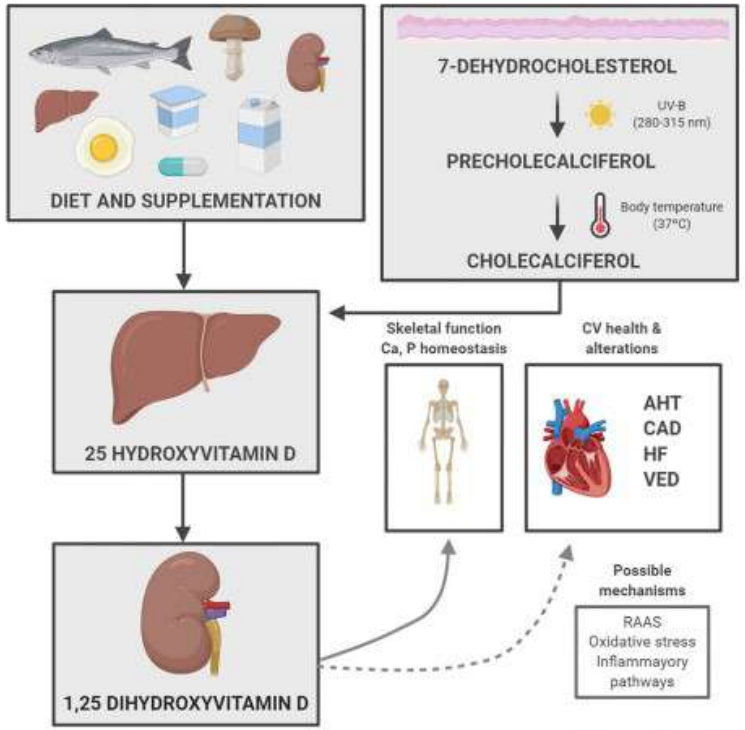

Fig. 3. Diagram showing how vitamin D from the diet and sun exposure can improve skeletal function and prevent several cardiovascular problems. AHT (arterial hypertension), CAD (coronary artery disease), CV (cardiovascular), HF (heart failure), RAAS (renin–angiotensin–aldosterone system), UV (ultraviolet), VED (vascular endothelial dysfunction).

JAMA Cardiology | Original Investigation

Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in the Vitamin D Assessment Study
A Randomized Clinical Trial

Robert Scragg, MBBS, PhD; Alistair W. Stewart, BSc; Debbie Waayer, MEd; Carlene M. M. Lawes, MBChB, PhD; Les Toop, MBChB, MD; John Sluyter, PhD; Judy Murphy, RN; Kay-Tee Khaw, MBBChir, MSc; Carlos A. Camargo Jr, MD, DrPH

INTERVENTIONS Oral vitamin D_3 in an initial dose of 200 000 IU, followed a month later by monthly doses of 100 000 IU, or placebo for a median of 3.3 years (range, 2.5-4.2 years).

CONCLUSIONS AND RELEVANCE Monthly high-dose vitamin D supplementation does not prevent CVD. This result does not support the use of monthly vitamin D supplementation for this purpose. The effects of daily or weekly dosing require further study.

NESSUN RCT HA FINORA EVIDENZIATO LA RIDUZIONE DEL RISCHIO CV CON LA SOLA SUPPLEMENTAZIONE DI VITAMINA D.

Calcif Tissue Int (2017) 100:122–132
DOI 10.1007/s00223-016-0226-3

REVIEW

Pathophysiology of Bone Fragility in Patients with Diabetes

Andrea Palermo[1] · Luca D'Onofrio[2] · Raffaella Buzzetti[2] · Silvia Manfrini[1] · Nicola Napoli[1,3]

- **Squilibrio insulinico**: osteoblasti ed osteoclasti esprimono recettore insulinico e la somministrazione di insulina stimola la formazione ossea, attraverso i pathways di Insulin Receptors 1 e 2 (IRS1 e IRS2).
- **IGF-1**: i suoi bassi livelli sono associati a ridotta BMD nei pazienti con DM1 e a fratture post-menopausali in pazienti con DM2
- **Glucotossicità:** ridotta vitalità e capacità riproduttiva della cellula staminale mesenchimale da cui derivano anche gli osteoblasti; AGE (advanced glycation end-products) sopprimono il reticolo endoplasmatico degli osteoblasti

- **Incretine (GIP e GLP-1):** GIP ha effetto osteoprotettivo stimolando la proliferazione degli osteoblasti e riducendo l'attività osteoclastica via cAMP.
- **Infiammazione sistemica:** ruolo di TNFα ed IL-1nell'aumentare il riassorbimento osseo. Disregolazione delle adipochine.
- **Sarcopenia:** rischio di cadute.
- **Metabolismo del calcio:** aumentata escrezione urinaria a causa della poliuria nel DM1 (si associa fosfaturia), con conseguente riduzione dei livelli sierici di PTH (Yamamoto et al.) ed ipoparatiroidismo funzionale (Thakassinos et al.)

Drabkin et al. Journal of Eating Disorders (2017) 5:42
DOI 10.1186/s40337-017-0172-0

Assessment and clinical management of bone disease in adults with eating disorders: a review

Anne Drabkin[1*], Micol S. Rothman[2], Elizabeth Wassenaar[3], Margherita Mascolo[1] and Philip S. Mehler[1,3]

- Una riduzione del BMD è estremamente comune in pazienti con disturbi dell'alimentazione
- Ruolo dell'ipoestrogenismo, mediante interazione con le citochine infiammatorie e RANKL
- Ipercortisolimo ed anomalie nel metabolismo gluco/lipidico
- Fondamentale integrare la dieta con dosaggi elevati di vitamina D e calcio (citrato se paziente assume IPP).
- Dubbia efficacia dei soli vitamina D e calcio nel favorire l'aumento di massa ossea nella paziente anoressica

Review > Atherosclerosis. 2018 Nov;278:49-59. doi: 10.1016/j.atherosclerosis.2018.08.046. Epub 2018 Aug 30.

Review article

CKD, arterial calcification, atherosclerosis and bone health: Inter-relationships and controversies

Allison B. Reiss, Nobuyuki Miyawaki, Jane Moon, Lora J. Kasselman, Iryna Voloshyna, Robert D'Avino Jr., Joshua De Leon*

Research Institute and Department of Medicine, NYU Winthrop Hospital, NY, USA

Osteodistrofia renale (Mineral bone disease: MBD) come complicanza dell'insufficienza renale cronica:

- Iperfosfatemia (ridotta escrezione urinaria)
- Ipocalcemia
- iperparatiroidismo secondario (ed infine terziario)
- ipovitaminosi D (ridotta attivazione renale)
- calcificazioni vascolari
- Osteoporosi ed alto rischio fratturativo (K.L. Naylor, *Kidney Int*. 2014)
- Rischio cardiovascolare collegato all'iperfosforemia
- Efficacia di calcimimetici e vitamina D anche per la cardioprotezione

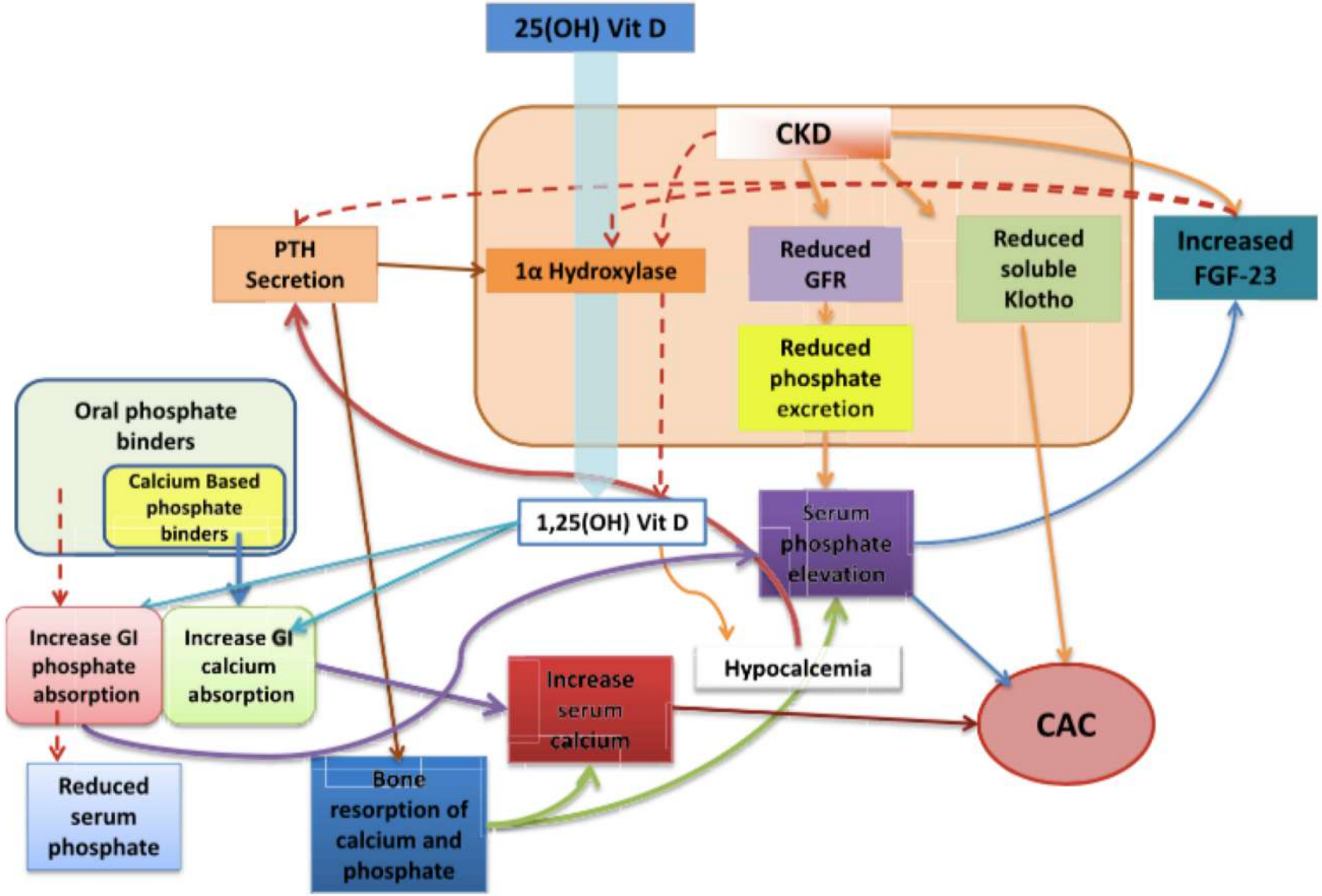

Fig. 3. Overview of mineral bone disease pathways leading to vascular calcification in CKD.
Reduced 1,25(OH) vitamin D impairs intestinal calcium absorption leading to hypocalcemia and secondary hyperparathyroidism. PTH elevation reduces urinary calcium excretion, increases urinary phosphate excretion, increases both calcium and phosphate bone resorption, increases 1-alpha-hydroxylase and gut absorption of calcium and phosphate. Phosphate excretion is progressively limited with advancing CKD, leading to hyperphosphatemia. This, along with exogenous 1,25(OH) vitamin D stimulate fibroblast growth factor 23 (FGF-23) release. FGF-23 suppresses PTH release, 1-alpha-hydroxylase, and increase renal phosphorus excretion. Oral phosphate binders reduce phosphate absorption but calcium-based binders may also lead to hypercalcemia. In late stage CKD positive calcium balance promotes VC.

TABLE 3 | Pooled Odds Ratios of death or ICU admission due to COVID-19 in specific subgroups, in relation to 25OHD thresholds for vitamin D insufficiency, deficiency, or severe deficiency.

	Overall analysis		High Quality articles		Articles with high quality and Caucasian subjects		Articles with high quality and adjusted data	
	n	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
Death in patients with 25OHD <10 ng/mL	21	2.60 (1.93–3.49)	13	2.61 (1.73–3.94)	8	2.95 (1.56–5.57)	8	2.27 (1.37–3.76)
Death in patients with 25OHD <20 ng/mL	24	1.84 (1.26–2.69)	13	2.54 (1.56–4.12)	8	3.57 (1.87–6.82)	4	3.37 (1.96–5.82)
Death in patients with 25OHD <30 ng/mL	12	4.15 (1.76–9.77)	7	7.06 (2.08–23.94)	3	9.57 (1.82–50.26)	2	2.18 (1.36–3.51)
ICU in patients with 25OHD <10 ng/mL	11	2.63 (1.45–4.77)	6	2.14 (1.33–3.46)	4	2.30 (0.98–5.39)	3	2.27 (0.98–5.26)
ICU in patients with 25OHD <20 ng/mL	18	2.16 (1.43–3.26)	7	2.02 (1.32–3.08)	6	2.37 (1.68–3.34)	3	2.34 (1.51–3.62)
ICU in patients with 25OHD <30 ng/mL	11	2.83 (1.74–4.61)	5	1.90 (1.27–2.84)	6	2.73 (1.19–6.27)	3	2.11 (0.72–4.85)

ICU, intensive care unit; n, number of studies included in the analysis; OR, odds ratio.

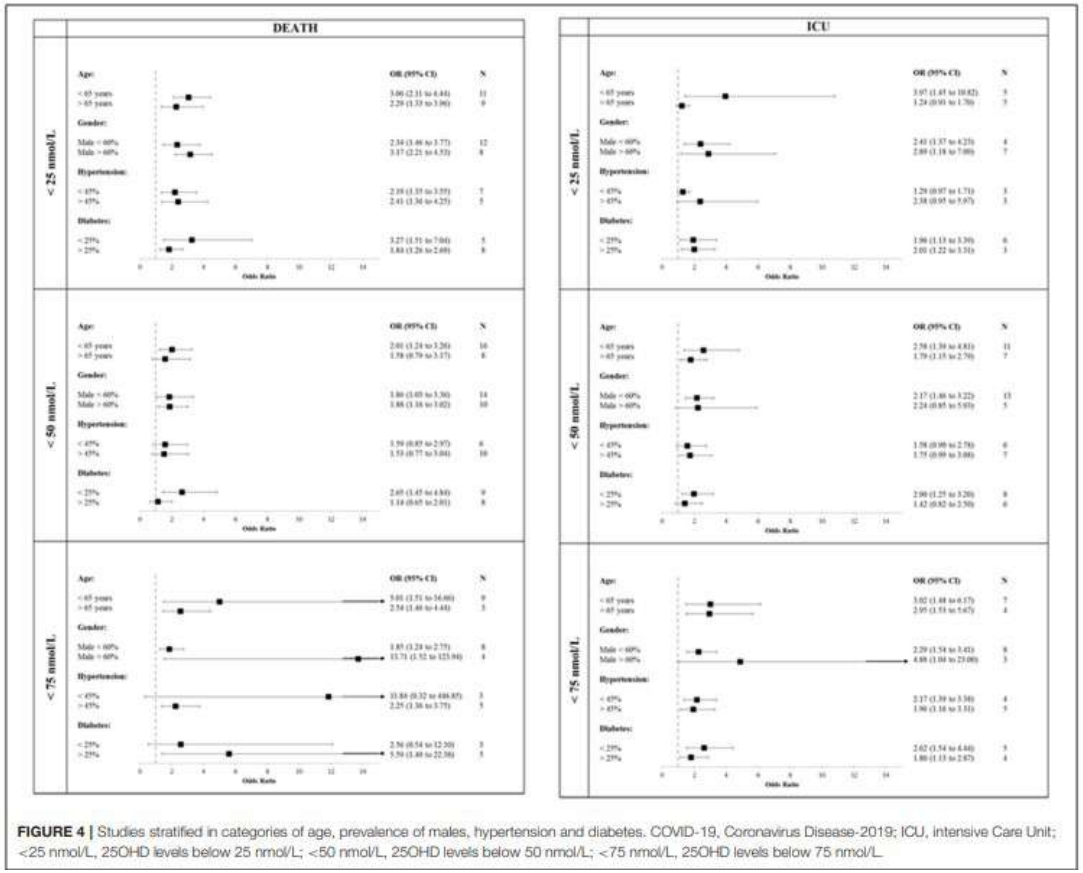

FIGURE 4 | Studies stratified in categories of age, prevalence of males, hypertension and diabetes. COVID-19, Coronavirus Disease-2019; ICU, intensive Care Unit; <25 nmol/L, 25OHD levels below 25 nmol/L; <50 nmol/L, 25OHD levels below 50 nmol/L; <75 nmol/L, 25OHD levels below 75 nmol/L.

frontiers in Public Health

SYSTEMATIC REVIEW
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Vitamin D Status and SARS-CoV-2 Infection and COVID-19 Clinical Outcomes

Iacopo Chiodini[1,2†], Davide Gatti[3†], Davide Soranna[4], Daniela Merlotti[5], Christian Mingiano[5], Angelo Fassio[3], Giovanni Adami[3], Alberto Falchetti[6], Cristina Eller-Vainicher[7], Maurizio Rossini[3], Luca Persani[1,2], Antonella Zambon[4,8] and Luigi Gennari[5]*

Meta-analisi che include 54 studi per un totale di 1 milione e mezzo di pazienti.

La severa deficienza, la deficienza e l'insufficienza di vitamina D sono tutte associate all'accesso in TI, alla mortalità, al rischio di contrarre l'infezione e all'ospedalizzazione.

Nessuna differenza statisticamente significativa quando i pazienti sono stati stratificati in base all'origine etnica e allo status socio-economico.

SUPPLEMENTAZIONE DI VITAMINA D: A CHI, COME E QUANTO?

nutrients

MDPI

Review

Role of Vitamin D in Preventing and Treating Selected Extraskeletal Diseases—An Umbrella Review

Friederike Maretzke [1], Angela Bechthold [1], Sarah Egert [2], Jana B. Ernst [1], Debora Melo van Lent [3], Stefan Pilz [4], Jörg Reichrath [5], Gabriele I. Stangl [6], Peter Stehle [7], Dorothee Volkert [8], Michael Wagner [9], Julia Waizenegger [1,*], Armin Zittermann [10] and Jakob Linseisen [1,11] on behalf of the German Nutrition Society (DGE)

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	SRs of	Effects of Vitamin D in Primary Prevention	Effects of Vitamin D in Patients
Asthma	Observational studies	-	no data
	RCTs	-	+[1,2]
COPD	Observational studies	no data	-
	RCTs	no data	+[1]
ARI	Observational studies	+[3]	no data
	RCTs	+[1]	o
Dementia and cognitive decline	Observational studies	+[1,4]	no data
	RCTs	-	no data
Depression	Observational studies	+[1,4]	no data
	RCTs	o (general)– (postpartum)	(major depression)
MS	Observational studies	-	no data
	RCTs	no data	o
T1DM	Observational studies	-	no data
	RCTs	no data	-

+ Beneficial effect suggested—final conclusion is not possible due to heterogeneity of data or limited data. - No clear statement possible due to inconclusive/insufficient data. o No beneficial effect suggested. [1] Especially or only in patients with circulating 25(OH)D concentrations <25 nmol/l (10 ng/mL). [2] Most results are based on SRs in children. [3] Results are based on SRs in adults. [4] Effects mainly seen in older persons.

Dati osservazionali mostrano una correlazione inversa tra i livelli sierici di vitamina D ed il rischio di infezioni delle vie respiratorie, demenza, declino cognitivo e depressione.

Scarse evidenze in merito ad asma, sclerosi multipla e diabete mellito tipo 1.

Non esistono RCT sul ruolo della vitamina D nella prevenzione di BPCO, sclerosi multipla e diabete mellito tipo 1.

La supplementazione di vitamina D sembra efficace nei pazienti con asma e BPCO, mentre i dati sulle patologie psichiatriche sono contraddittori.

CONCLUSIONI

- Le implicazioni ormonali, genomiche e immunologiche della VIT D sono molteplici
- La sua int
- I livelli di VIT D se
trattamento nell' artrite reumatoide
- Le soglie di Vit D da raggiungere nel sangue per esercitare i suoi effetti a livello di diversi organi, probabilmente non sono le stesse.
- Occorrono ulteriori RCTs per ottenere evidenze scientifiche di rilievo sugli effetti extrascheletrici.

Grazie dell'Attenzione!