
HRVATSKO DRUŠTVO
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JESENSKA AKADEMIJA
SUPLEMENTACIJE
U MEDICINI
Mjesto vitamina D u dermatologiji
Andrija Stanimirović

NASLOV SEKCIJE/ POGLAVLJA

Sadržaj poglavlja

Petak, 23.listopada 16.45h -17-00 h

Mjesto vitamina D u dermatologiji

Andrija Stanimirović

SYSTEMIC VITAMIN D THERAPY IN PATIENTS WITH SKIN DISEASES

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Vitamin D



The oldest hormone on Earth



The major amount of vitamin D is produced in the skin under the influence of the UV-B rays (80-90%)



From the food and supplements we get forms of D2 i D3 (10-20%)



50% of population has low values of the vitamin D3



Guidelines for the administration and real need-in discordance

Vitamin D – Vitamin or Hormone?

Hormon of the Modern Age
Role in numerous physiological and pathophysiological processes

40% of Europe

Vitamin D deficiency

Correlation of vitamin D and various diseases

Immunomodulatory potential→ Autoimmune diseases

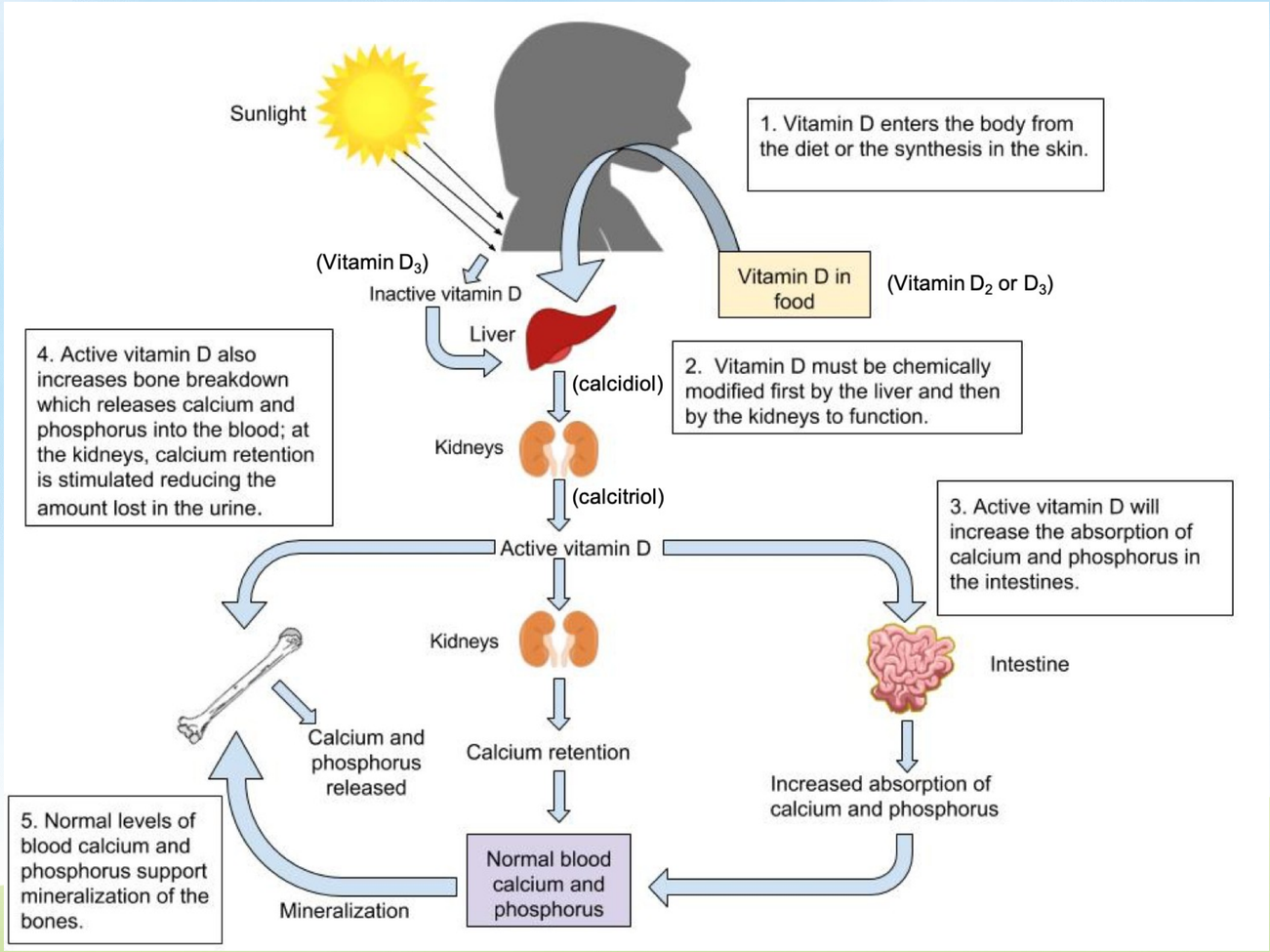


Eur J Clin Nutr. 2021; 74, 1498-1513.
Metabolites 2021; 11(4), 225
BMJ 2022; 376, e066452.

Introduction

Vitamin D synthesis

PTH-do not forget



Low vitamin D staus in adults

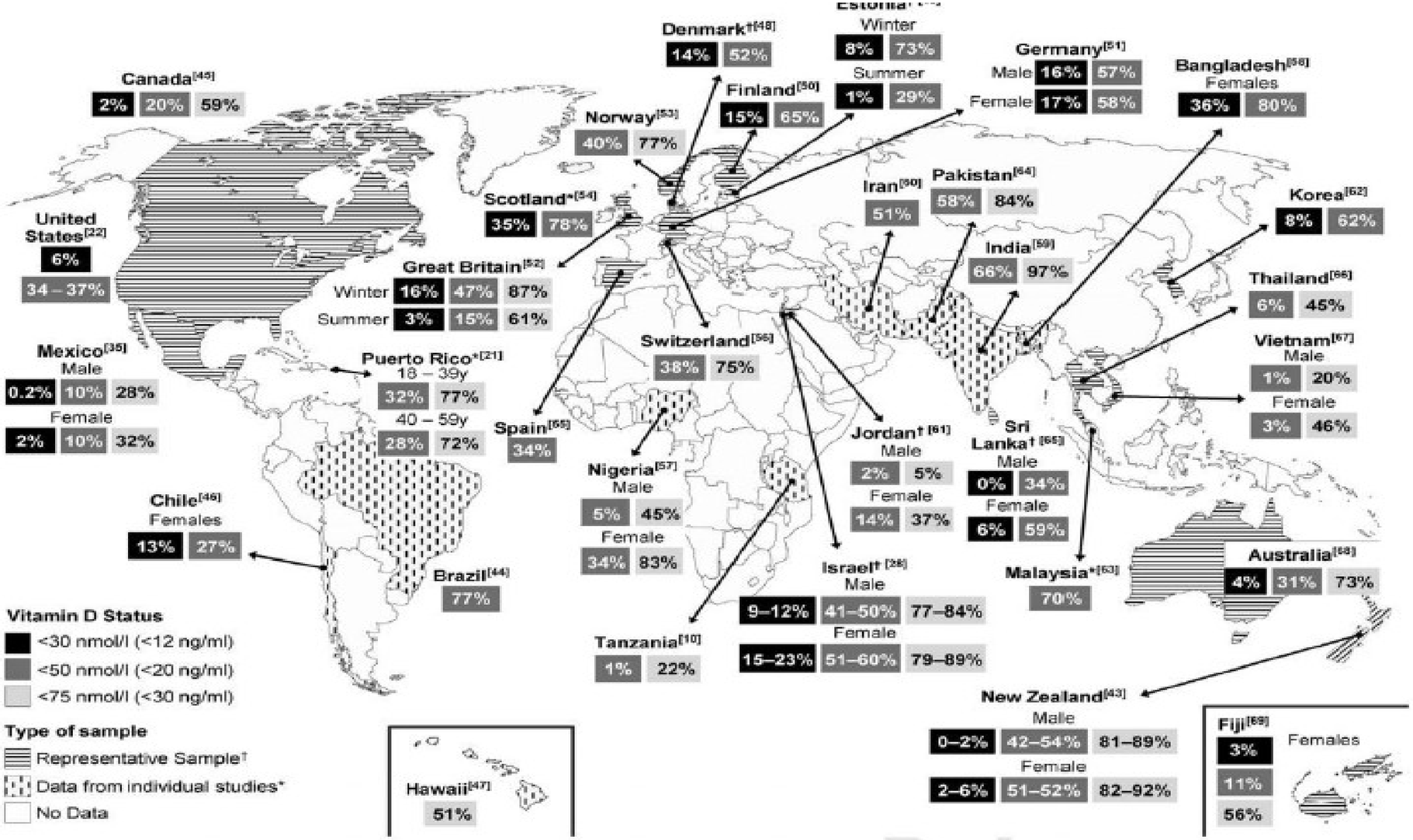


Fig. 4. Prevalence of low vitamin D status in adults worldwide.

Low vitamin D in elders

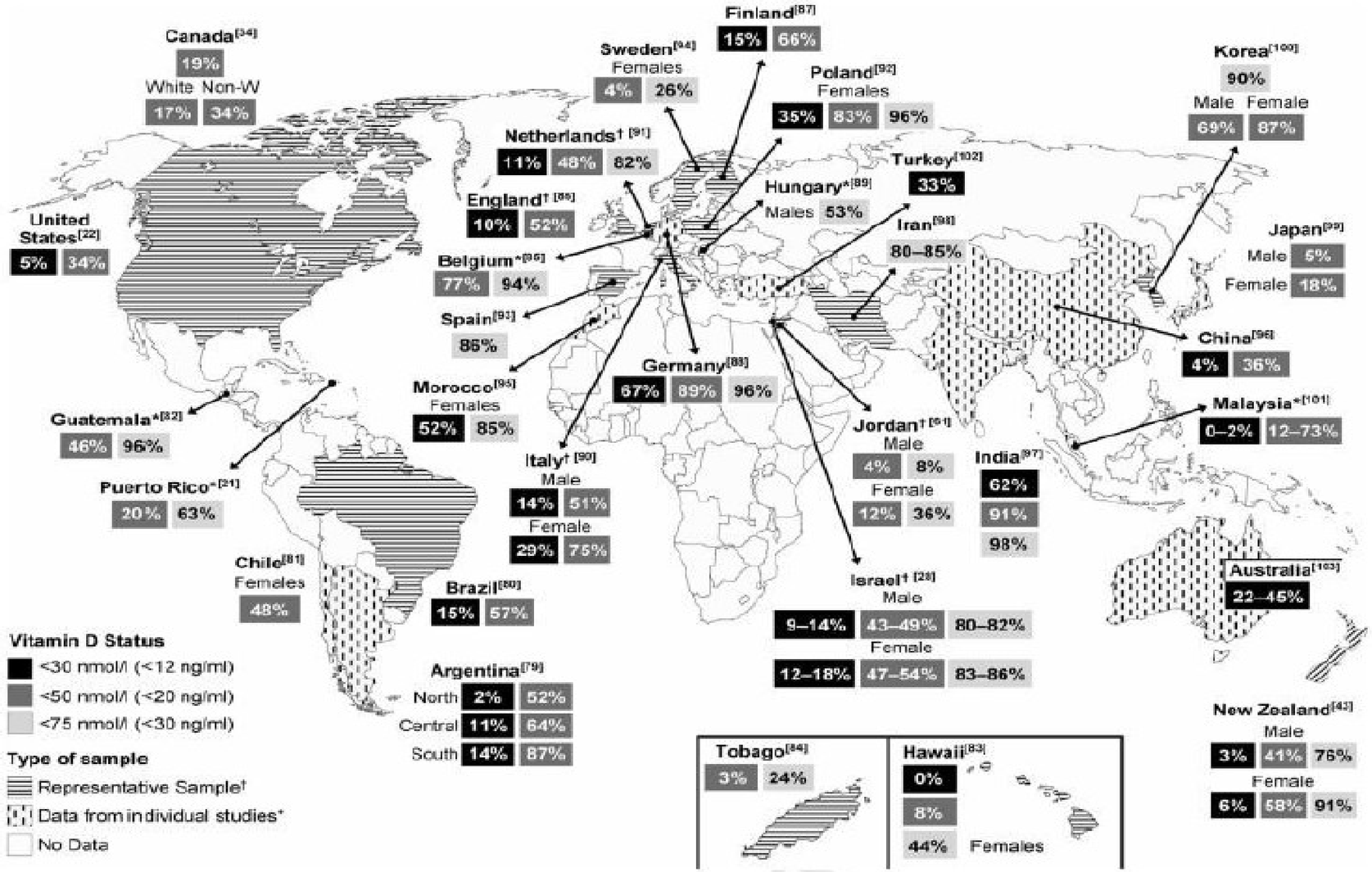


Fig. 6. Prevalence of low vitamin D status in elders worldwide.

Biological effects of $1,25(OH)_2D_3$ in the Skin

Inhibition of Proliferation of Keratinocytes

Induction of Differentiation of Keratinocytes

Immunomodulatory Effects

CD4+/CD8+ T cells, IL-12, IgE ↓

ACE2,CD25+/CD4+ T cells, IL-10 ↑

VDR (vitamin D receptor) ↑

VDRE

Regulation of apoptosis

Cytoprotective Effects

Mitochondrial citochrome c ↓

Antioxidative Effects

Metallothionein (MT) Mrna, NADH, Bcl 2 ↑

Lea Tremezaygues, Jörg Reicharth. Relevance of the Cutaneous Vitamin D Endocrine System for Skin Physiology and Treatment of Skin Diseases. A.Pappas (ed.), Nutrition and Skin, Springer Science + Business Media, LLC 2011, p. 27-31.

Skin Diseases Related to Alterations in Vitamin D levels

- **1. Psoriasis**
- **2. Vitiligo**
- **3. Scleroderma**
- **4. Alopecia areata**
- **5. Congenital ichthyosis**
- **6. Atopic Dermatitis**
- **7. Acne Vulgaris**
- **8. Hidradenitis suppurativa**
- **9. Lupus Erythematosus**
- **10. Skin tumors**



The aim of the study

Vitamin D status in patients?

Vitamin D status	25(OH)D serum concentration
Deficiency	< 20 ng/ml*
Insufficiency	20 – 29,9 ng/ml
Normal	30 – 100 ng/ml

Table 1.
Mesquita K de C, Igreja AC de SM, Costa IMC. Atopic dermatitis and vitamin D: facts and controversies. An Bras Dermatol. 2013 Dec;88(6):945–53.

Oral vitamin D as a therapy?

- MEDLINE
- Cochrane
- Google Scholar

Methods

Search strategy

- **AD & Psoriasis:** PRISMA flowchart for each skin disease
- Randomised Controlled Trials
- Databases: PubMed, Cochrane & Google Scholar
- Keywords: psoriasis, atopic dermatitis, oral vitamin D & treatment

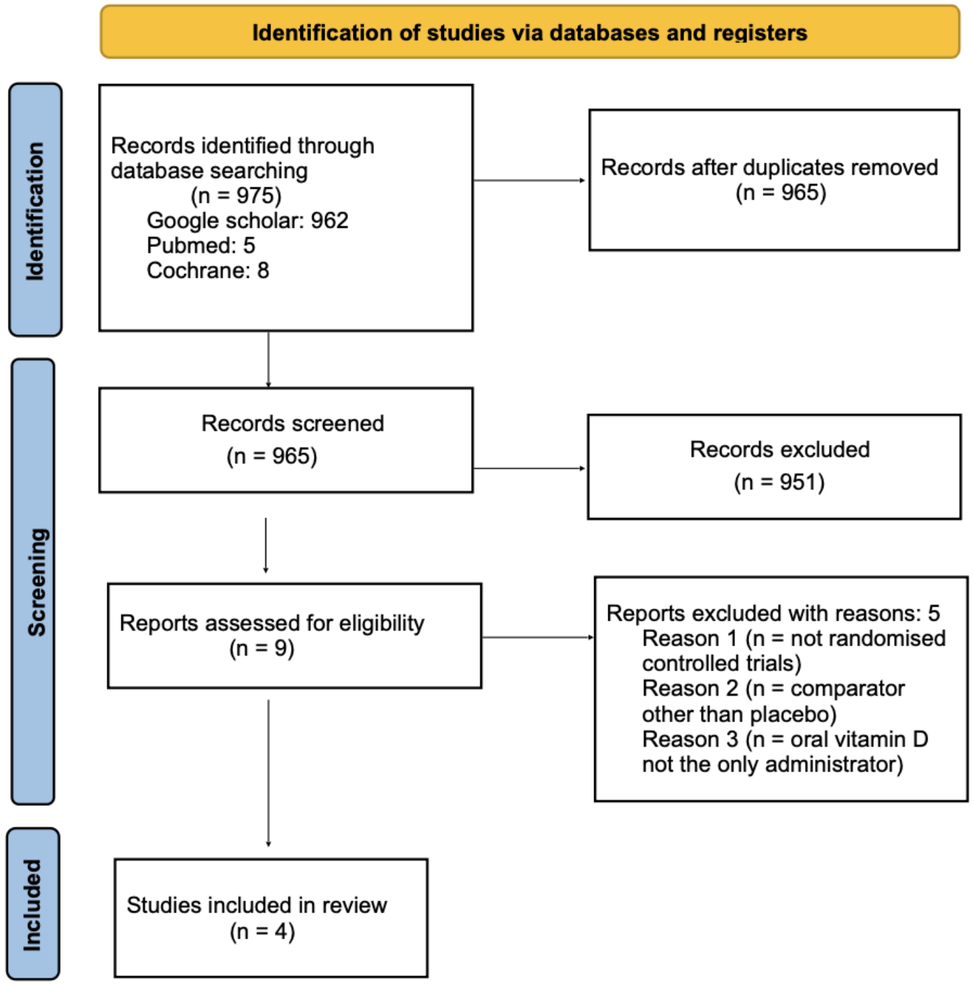


Figure 1. PRISMA flowchart of search in regards to AD and oral vitamin D treatment

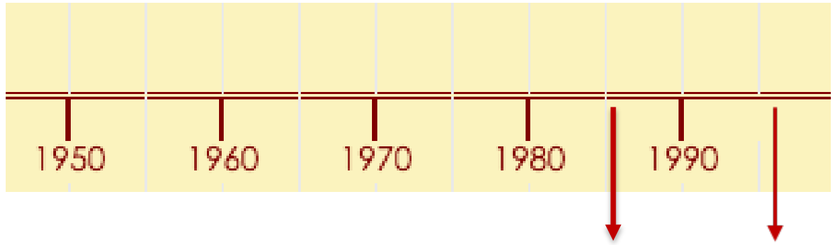
Methods- PICOS

Study selection

Table 1.	PICOS criteria	
Parameter	**Inclusion**	**Exclusion**
Population	Humans	Animals
Intervention	Oral vitamin D treatment	Any other treatment
Comparator	Placebo	Other than placebo
Outcomes	Symptom beneficial, unbeneficial or neutral	None
Study design	Qualitative synthesis of RCTs	Other than RCTs

Vitamin D and Psoriasis

- 1985.: Patient who was treated orally with 25(OH)D for osteoporosis had a drastic remission of psoriatic skin lesions
- 1986.: 80% of 17 patients with psoriasis who were treated orally with 25(OH)D at a dose 40 IU/day for up to 6 months showed clinically significant improvement
- 1996. 88,0% of patients with psoriasis who received oral calcitriol in a dose of 2-4mcg/night had some alleviation of their disease after 36 months



Morimoto S, Yoshikawa K, Kozuka T, Kitano Y, Imanaka S, Fukuo K, et al. An open study of vitamin D3 treatment in psoriasis vulgaris. Br J Dermatol. 1986 Oct;115(4):421–9.

Perez A, Raab R, Chen TC, Turner A, Holick MF. Safety and efficacy of oral calcitriol (1,25-dihydroxyvitamin D3) for the treatment of psoriasis. Br J Dermatol. 1996 Jun;134(6):1070–8.

High – dose treatment in psoriasis?

- Patients, who were receiving 35,000 IU of vitamin D3 once daily for 6 months, had significant improvement in psoriasis area severity index score (PASI) with an increase in their serum 25(OH)D level (Finamor et al., 2013.)
- Intakes of oral vitamin D up to 10,000 IU daily were not associated with harmful effects (Barrea et al., 2017.)
- In another study was shown that vitamin D3 dose higher than 40,000 IU was associated with hypercalcemia toxicity! (Stanescu et al., 2021.)



Finamor DC, Sinigaglia-Coimbra R, Neves LCM, Gutierrez M, Silva JJ, Torres LD, et al. A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of vitiligo and psoriasis. Dermatoendocrinol. 2013 Jan;5(1):222–34.
Barrea L, Savanelli MC, Di Somma C, Napolitano M, Megna M, Colao A, et al. Vitamin D and its role in psoriasis: An overview of the dermatologist and nutritionist. Rev Endocr Metab Disord. 2017 Jun;18(2):195–205.
Stanescu AMA, Simionescu AA, Diaconu CC. Oral Vitamin D Therapy in Patients with Psoriasis. Nutrients. 2021 Jan 6;13(1):163.

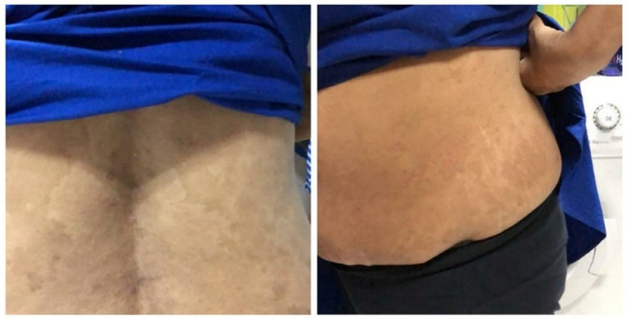
High – dose treatment in psoriasis?

- 2022.: 6 cases of psoriasis treated with daily oral Vitamin D3 in doses ranging from 30,000 IU to 60,000 IU over a period of 2 to 6 months
- All patients achieved a complete control of the disease with PASI and VAS scores

Baseline



After treatment



Baseline



After treatment



Baseline





After treatment



Mahtani R, Nair PMK. Daily oral vitamin D3 without concomitant therapy in the management of psoriasis: A case series. Clin Immunol Commun. 2022 Dec;2:17–22.

Vitamin D and Vitiligo

- Vitamin D serum levels in all patients with vitiligo were lower, independent of season, concomitant autoimmune disease, and clinical type of vitiligo (Akpolat et al., 2022.)
- Children with vitiligo treated with oral vitamin D and topical tacrolimus (Karagüzel et al.):

25(OH)D < **20ng/ml** → **1500** IU/day

25(OH)D < **10 ng/ml** → **3000** IU/day

- Lesion size decreased after six months of treatment in patients who received combination treatment ($p < 0.001$)

Akpolat ND, Metin A. Plasma vitamin D levels in patients with vitiligo. Bosphorus Med J. 2022;9(1):0–0.

Karagüzel G, Sakarya NP, Bahadır S, Yaman S, Ökten A. Vitamin D status and the effects of oral vitamin D treatment in children with vitiligo: A prospective study. Clin Nutr ESPEN. 2016 Oct 1;15:28–31.

High – dose treatment in vitiligo?

- 16 patients with vitiligo, who had low vitamin D status at baseline (≤ 30 ng/mL) received vitamin D3 35,000 IU once daily for six months in association with a low-calcium diet
- 14 of 16 patients with vitiligo had 25–75% repigmentation
- Serum urea, creatinine and calcium (total and ionized) did not change and urinary calcium excretion increased within the normal range

Psoriasis	Vitiligo
Grade B recommendation with a IIa level of evidence	Grade B recommendation with a IIa level of evidence

Finamor DC, Sinigaglia-Coimbra R, Neves LCM, Gutierrez M, Silva JJ, Torres LD, et al. A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of vitiligo and psoriasis. Dermatoendocrinol. 2013 Jan;5(1):222–34.

Vitamin D and Scleroderma

- Insufficient sun exposure due to skin fibrosis
- Insufficient intake because of malabsorption
- Modified Rodnan skin score (mRSS) – extent and severity of skin fibrosis
- Groseanu et al. (2016):
- 90.2% of patients in a study → mean 25(OH)D level of 17.06±9.3 ng/mL
- No correlation between vitamin D serum levels and mRSS

→ **Vitamin D deficiency**



Groseanu L, Bojinca V, Gudu T, Saulescu I, Predeteanu D, Balanescu A, et al. Low vitamin D status in systemic sclerosis and the impact on disease phenotype. Eur J Rheumatol. 2016 Oct 6;3(2):50–5.

Vitamin D treatment in Scleroderma?

- Oral administration of calcitriol 1.0-2.5mcg /day alleviates skin involvement
- Inhibition of fibroblast proliferation and dermal collagen deposition (Humbert et al., 1993.)
- A systematic literature review from 2021:
- No significant difference in mRSS after vitamin D supplementation

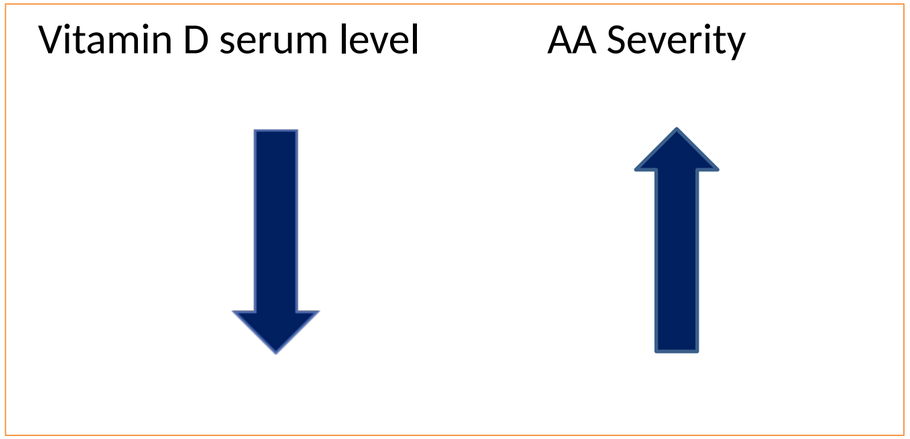
REMAINS CONTROVERSIAL

Humbert P, Dupond JL, Agache P, Laurent R, Rochefort A, Drobacheff C, et al. Treatment of scleroderma with oral 1,25-dihydroxyvitamin D3: evaluation of skin involvement using non-invasive techniques. Results of an open prospective trial. Acta Derm Venereol. 1993 Dec;73(6):449–51.

Diaconu AD, Ostafie I, Ceasovschih A, Șorodoc V, Lionte C, Ancuța C, et al. Role of Vitamin D in Systemic Sclerosis: A Systematic Literature Review. Padureanu V, editor. J Immunol Res. 2021 Nov 29;2021:1–15.

Vitamin D and Alopecia Areata (AA)

- Immunomodulatory effect of vitamin D
- Significantly higher prevalence of deficiency and lower levels of serum vitamin D
- Least values were significantly associated with alopecia totalis/universalis compared with patchy AA ($P < 0.001$) and ophiasis ($P = 0.04$)



Vitamin D supplementation in Alopecia Areata
Grade B recommendation with a IIb level of evidence

Tsai TY, Huang YC. Vitamin D deficiency in patients with alopecia areata: A systematic review and meta-analysis. J Am Acad Dermatol. 2018 Jan 1;78(1):207–9.
Bakry O, El Farargy S, El Shafiee M, Soliman A. Serum Vitamin D in patients with alopecia areata. Indian Dermatol Online J. 2016;7(5):371

Vitamin D and Congenital Ichthyosis (CI)

- European cohort of 53 patients with congenital ichthyosis:

1. More than 80% of total 53 didn’t have an optimal vitamin D status
2. The mean (+SD) serum level of 25(OH)D was **18.24 ± 10 ng/mL**
3. 15 of 53 patients had 25(OH)D status < **10 ng/ml**

- Low 25(OH)D levels were associated with high severity of scaling
- Mild ichthyosis phenotype - median 19.7ng/ml
- Keratinopathic ichthyosis - median 10.5 ng/ml

Frascari F, Dreyfus I, Rodriguez L, Gennero I, Ezzedine K, Salles JP, et al. Prevalence and risk factors of vitamin D deficiency in inherited ichthyosis: A French prospective observational study performed in a reference center. Orphanet J Rare Dis. 2014 Dec;9(1):127.
Kim M, Oji V, Valentin F, Traupe H, Nofer J, Hausser I, et al. Vitamin D Status in Distinct Types of Ichthyosis: Importance of Genetic Type and Severity of Scaling. Acta Derm Venereol. 2021;101(9):adv00546.

Short-term high-dose treatment in CI

- 7 children with congenital ichthyosis and severe vitamin D deficiency (< 4 ng/mL)
- 60,000 IU of oral cholecalciferol daily for 10 days
- Followed by recommendend daily allowance of 400 to 600 IU of cholecalciferol
- Improvement in symptoms by the fifth day
- After a month the skin was almost normal in all 5 cases of autosomal recessive congenital ichthyosis

Vitamin D supplementation in Congenital Ichthyosis
Grade C recommendation with a IIIa level of evidence

Sethuraman G, Marwaha RK, Challa A, Yenamandra VK, Ramakrishnan L, Thulkar S, et al. Vitamin D: A New Promising Therapy for Congenital Ichthyosis. Pediatrics. 2016 Jan;137(1).

Vitamin D and Atopic Dermatitis (AD)

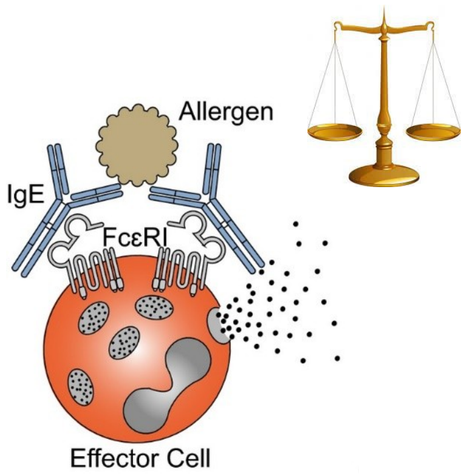
- The frequency of bacterial skin infections was higher in patients with AD who had lower 25(OH)D levels (Samochoki et al. 2013)
- Meta-analysis summarized the evidence by the year 2015:

1. Patients (pediatric population) with AD had lower levels of $25(OH_2)D_3$
2. Oral vitamin D supplements have been associated with reductions in SCORAD and Eczema Area and Severity Index scores in pediatric patients
3. Possible adjuvant treatment in patients with a deficiency (levels below 20 ng/mL)

Samochocki Z, Bogaczewicz J, Jeziorkowska R, Sysa-Jędrzejowska A, Glińska O, Karczmarewicz E, et al. Vitamin D effects in atopic dermatitis. J Am Acad Dermatol. 2013 Aug 1;69(2):238–44.
Kim M, Kim SN, Lee Y, Choe Y, Ahn K. Vitamin D Status and Efficacy of Vitamin D Supplementation in Atopic Dermatitis: A Systematic Review and Meta-Analysis. Nutrients. 2016 Dec 3;8(12):789.

Vitamin D and controversies in AD

- Higher intake of vitamin D during the first year of life was correlated with increased risk of eczema at age six
- Patients with low vitamin D (<10 ng/mL) or with very high vitamin D serum levels (>54 ng/mL) had significantly higher IgE levels than healthy individuals (40–50 ng/mL)



Vestita M, Filoni A, Congedo M, Foti C, Bonamonte D. Vitamin D and Atopic Dermatitis in Childhood. J Immunol Res. 2015;2015:1–7.

Vitamin D treatment in pediatric population with severe AD

- . Study from 2020.:

Atopic dermatitis patients	Peroral therapy	Topical therapy	Duration	EASI score	S.Aureus skin colonization
Group 1	D3 1600 IU/day	1% hydrocortisone cream	12 weeks	lower	reduced
Group 2	Placebo	1% hydrocortisone cream	12 weeks	higher	-

Vitamin D supplementation in Atopic Dermatitis
Grade B recommendation with a IIa level of evidence

Mansour NO, Mohamed AA, Hussein M, Eldemiry E, Daifalla A, Hassanin S, et al. The impact of vitamin D supplementation as an adjuvant therapy on clinical outcomes in patients with severe atopic dermatitis: A randomized controlled trial. Pharmacol Res Perspect [Internet]. 2020 Dec [cited 2022 Apr 16];8(6

Vitamin D and Acne Vulgaris

- 2021: serum 25(OH)D level in acne patients is lower than in healthy population (standardized mean difference = −7.66 ng/ml)
- Vitamin D decreases the expression of IL-6, IL-8 and matrix metalloproteinase-9 in sebocytes
- It regulates innate immunity by inducing the expression of antimicrobial peptides

- **Does Vitamin D supplementation improve inflammatory lesions in patients with acne?**

Wang M, Zhou Y, Yan Y. Vitamin D status and efficacy of vitamin D supplementation in acne patients: A systematic review and meta-analysis. J Cosmet Dermatol. 2021 Dec 1;20(12):3802–7.
Bhat Y, Latief I, Hassan I. Update on etiopathogenesis and treatment of Acne. Indian J Dermatol Venereol Leprol. 2017;83(3):298.

Peroral vitamin D therapy in Acne Vulgaris

Doktorsky and Platt 2015: 35 patients with acne was treated with 2,500 to 5,000 IU vitamin D daily for 1 month

Lim et al. 2016: Patients underwent 2-month oral administration of cholecalciferol (one drop of 1000 IU/day)

Ahmed Mohamed et al. 2021: Patients received 0.25ug alfacalcidol daily during 3 months

Results of peroral therapy

Doktorsky and Platt 2015: Improvement in 100% of 35 patients with acne after a month's treatment.

Lim et al. 2016: Inflammatory lesions decreased by 34.6% after 8 weeks of treatment.

Ahmed Mohamed et al. 2021: Significant higher level of 25(OH) D levels. Median serum level of IL6 and TNFα significantly decreased.

Lim SK, Ha JM, Lee YH, Lee Y, Seo YJ, Kim CD, et al. Comparison of Vitamin D Levels in Patients with and without Acne: A Case-Control Study Combined with a Randomized Controlled Trial. PLOS ONE. 2016 kol;11(8):e0161162.
Ahmed Mohamed A, Salah Ahmed EM, Abdel-Aziz RTA, Eldeeb Abdallah HH, El-Hanafi H, Hussein G, et al. The impact of active vitamin D administration on the clinical outcomes of acne vulgaris. J Dermatol Treat. 2021 Oct 3;32(7):756–61.
3SIMPSON CA, ELLIS FA, KIRBY-SMITH H. VITAMIN D IN THE TREATMENT OF ACNE. Arch Dermatol Syphilol. 1940 May 1;41(5):835–7.

Vitamin D and Hidradenitis Suppurativa

- 75% of patients had vitamin levels of less than 50 nmol/mL compared to 40% of general population (Kelly et al. 2014)
- One of the last studies in 2021:
- Patients with vitamin D deficiency showed significantly higher IHS4 values and CRP serum levels than those possessing vitamin D insufficiency
- 12.59 ± 0.64 vs. 3.06 ± 0.29, $p < 0.0001$, and 6.75 ± 0.34 vs. 1.39 ± 0.43 mg/L $p < 0.0001$
- Immunomodulatory effect of peroral vitamin D therapy?
- Further studies are needed

Kelly G, Sweeney CM, Fitzgerald R, O'Keane MP, Kilbane M, Lally A, et al. Vitamin D status in hidradenitis suppurativa. Br J Dermatol. 2014 Jun 1;170(6):1379–80.
Moltrasio C, Tricarico PM, Genovese G, Gratton R, Marzano AV, Crovella S. 25-Hydroxyvitamin D serum levels inversely correlate to disease severity and serum C-reactive protein levels in patients with hidradenitis suppurativa. J Dermatol. 2021 May 1;48(5):715–7.

Vitamin D and Lupus Erythematosus

- Plasma 1,25(OH)D was significantly inversely correlated with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), anti-dsDNA, plasma IFNα and levels of IFNα gene expression
  - Study by Magro et al.:

Vitamin D status	Patients (N)	Dosage	Duration of treatment	SLEDAI
Deficiency	13	8000 IU/day	8 weeks	↓
Insuficienty	18	8000 IU/day	4 weeks	↓

  - CLE?
    - High-dose vitamin D supplementation is required to restore vitamin D sufficiency
- Limited data about the efficacy of vitamin D administration in the cutaneous form of disease

Magro R, Saliba C, Camilleri L, Scerri C, Borg AA. Vitamin D supplementation in systemic lupus erythematosus: relationship to disease activity, fatigue and the interferon signature gene expression. BMC Rheumatol. 2021 Dec;5(1):53.

Vitamin D and Skin Tumors

- **Melanoma**

In a large melanoma cohort, Field et al. have observed that lower serum 25(OH)D levels at diagnosis were associated with thicker tumors and poorer prognosis

Recent review (2020): lower vitamin D level was related to greater progression of melanoma (Breslow thickness, Clark level, the American Joint Committee on Cancer stage)

- **Nonmelanoma skin cancer**

In a prospective study with more than 60,000 participants, vitamin D supplementation was not associated with squamous cell carcinoma risk other incidence of basal cell carcinoma

Vitamin D supplementation in Skin Tumors
Grade B recommendation with a IIb level of evidence

Field S, Davies J, Bishop DT, Newton-Bishop JA. Vitamin D and melanoma. Dermatoendocrinol. 2013 Jan;5(1):121–9.
Brożyna AA, Hoffman RM, Slominski AT. Relevance of Vitamin D in Melanoma Development, Progression and Therapy. Anticancer Res. 2020 Jan;40(1):473–89.
Park SM, Li T, Wu S, Li WQ, Qureshi AA, Cho E. Vitamin D Intake and Risk of Skin Cancer in US Women and Men. PloS One. 2016;11(8):e0160308.

Take - Home Messages

- An increasing number of studies demonstrate positive effects of vitamin D or its analogues in a variety of skin diseases.
- Up to now limited evidence has been reported about the efficacy of the highest doses of systemic vitamin D in skin diseases. Most studies did not observe any side effects.
- Further clinical studies are needed to determine the efficacy, optimal dosing, and adverse effects of vitamin D administration in patients with skin diseases.
-