Update Vitamin D bei älteren Menschen

ist die Nierenfunktion relevant?

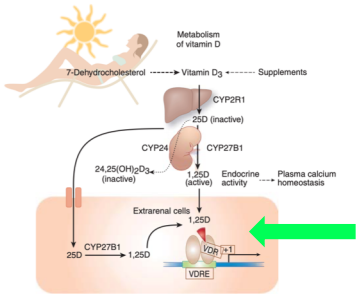
Prof. Dr. med. Heike A. Bischoff-Ferrari, DrPH
Klinikdirektorin Altersmedizin, USZ
Chefärztin, Universitäre Klinik für Altersmedizin, Stadtspital Zürich, Waid
Lehrstuhl Altersmedizin und Altersforschung, UZH
Direktorin, Zentrum Alter und Mobilität, USZ und UZH und Stadtspital Zürich
Chefärztin Universitärer Geriatrie-Verbund Zürich

Übersicht

- Vitamin D Stoffwechsel
- Vitamin D Nierenfunktion
- Update Vitamin D -- Frakturen / Stürze
- Update Vitamin D – Immunsystem
- Zusammenfassung

Update Vitamin D
Stoffwechsel

Update Vitamin D Stoffwechsel



Die meisten Zellen besitzen eine 25-Hydroxylase-Aktivität und können daher Cholecalciferol direkt verwerten.

99 % des 25(OH)D ist gebunden (oder in Fett abgelagert) und für die zelluläre Nutzung nicht verfügbar ist.

Außerdem wurde festgestellt, dass Cholecalciferol selbst größere zelluläre Wirkungen hat als 25(OH)D oder 1,25(OH)2D.

Vitamin D
Cholecalciferol

Morris HA. Kidney International (2015) 88, 936–938. doi:10.1038/ki.2015.257
Mazees R, Bischoff-Ferrari HA, Dawson-Hughes B, JBMR Plus 2021

Physiology of Vitamin D – Half-life *t*1/2

- Cholecalciferol is considered active intra-cellularly, short half-life
  *t*1/2: 20 hours
- 25(OH)D reflects vitamin D status for its relatively long half-life
  *t*1/2: 3–6 weeks
- 1,25-dihydroxyvitamin D, short half-life
  *t*1/2: 8–12 hours

Tägliche Zufuhr wichtig!

Mazees R, Bischoff-Ferrari HA, Dawson-Hughes B, JBMR Plus 2021

Melamed ML, Thadhani RI. Vitamin D Therapy in Chronic Kidney Disease and End Stage Renal Disease. *Clinical Journal of the American Society of Nephrology : CJASN*. 2012;7(2):358-365. doi:10.2215/CJN.04040411.
Hollis, B.W. and C.L. Wagner, *Clinical review: The role of the parent compound vitamin D with respect to metabolism and function: Why clinical dose intervals can affect clinical outcomes.* J Clin Endocrinol Metab, 2013. **98**(12): p. 4619-28.

Update Vitamin D
Nierenfunktion

Prävalenz CKD im Zurich Disability Prevention Trial

200 zu Hause lebende Menschen Alter 70+ mit einem Sturz im letzten Jahr

Stage	GFR	Description	ZDPT (70+) N = 200
1 to 2	> 60	"normal"	51%
3a	44-59	Mild to moderate loss of function	33%
3b	30-44	Moderate to severe loss of function	13%
4	15-29	Severe loss of function	3%
5	< 15	Kidney failure	0% (excluded)

* Cockcroft-Gault

Bischoff-Ferrari HA et al. ; JAMA Internal Medicine Jan-2016

PTH Suppression mit monatlichen Vitamin D Dosierungen

All Participants n = 200 (58% D-Deficient; 67% female, mean age 78 years)

	24'000 IU D3/month	60'000 IU D3/month	24'000 IU D3/month plus 300µg calcifediol/month	P-Value
Mean (95% CI) **PTH baseline**	53.0 (48.2-57.8)	50.8 (46.0-55.6)	52.5 (47.6-57.4)	0.79
Mean (95% CI) **PTH at 6 months**	41.1 (37.3-42.9)	39.6 (36.8-42.4)	40.7 (37.9-43.6)	0.84
Mean (95% CI) **PTH at 12 months**	42.7 (40.0-45.3)	40.3 (37.6-43.0)	40.8 (38.1-43.5)	0.41

Almost equal reductions in PTH between standard 24'000 IU/month and the higher monthly doses

Bischoff-Ferrari HA et al. ; JAMA Internal Medicine Jan-2016

PTH Suppression mit monatlichen Vitamin D Dosierungen

CKD Stage 3a,3b,4 Participants n = 98 (GFR 15 to 59)

	24'000 IU D3/month	60'000 IU D3/month	24'000 IU D3/month plus 300µg calcifediol/month	P-Value
Mean (95% CI) **PTH baseline**	51.4 (43.1-59.8)	55.0 (46.0-63.8)	55.8 (47.9-63.8)	0.71
Mean (95% CI) **PTH at 6 months**	41.1 (37.2-45.0)	40.0 (35.7-44.1)	40.3 (36.6-44.0)	0.89
Mean (95% CI) **PTH at 12 months**	45.0 (40.5-49.4)	42.0 (37.0-46.9)	40.0 (35.7-44.3)	0.25

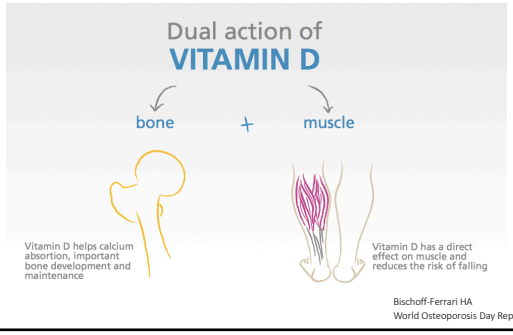
Almost equal reductions in PTH between standard 24'000 IU/month and the higher monthly doses – and compared with "all"

Bischoff-Ferrari HA et al. ; JAMA Internal Medicine Jan-2016

Update Vitamin D

Stürze & Knochenbrüche

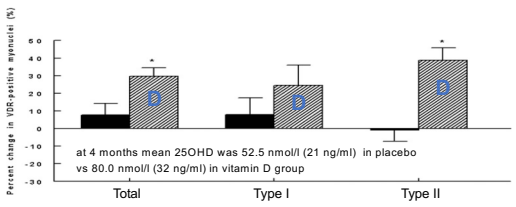
USZ Universitäts Spital Zürich · Universität Zürich · Stadtspital Zürich Waid · DO HEALTH



Bischoff-Ferrari HA
World Osteoporosis Day Report 2011

Muscle-VDR is upregulated by Vitamin D treatment

4-month RCT of 4000 IU vitamin D3 vs placebo
21 postmenopausal women

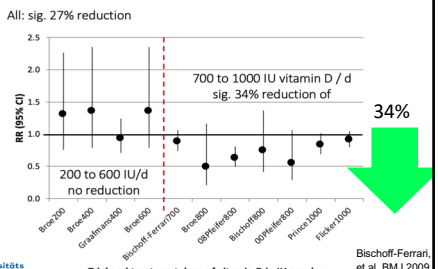


at 4 months mean 25OHD was 52.5 nmol/l (21 ng/ml) in placebo
vs 80.0 nmol/l (32 ng/ml) in vitamin D group

Ceglia L, Dawson-Hughes et al.; J Clin Endocrinology Metab. 2013

Meta-Analysis double-blind RCTs Daily Dosing of Vitamin D: in vitamin D deficient adults age 65+

Meta-Analysis 8 RCTs (n = 2426) sorted by dose

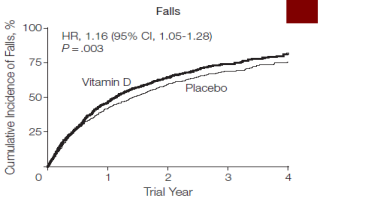


Bischoff-Ferrari, et al. BMJ 2009 and 2011

Großer jährlicher Bolus von Vitamin D 500'000 IU

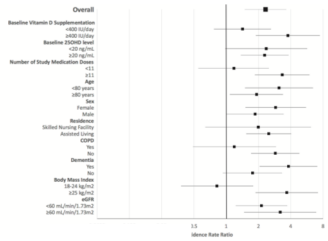
- 2 256 Frauen ab 70 Jahren mit Risiko für Hüftfrakturen
- 500'000 IU Vitamin D jährlich versus Placebo

16% erhöhtes Sturzrisiko
26% erhöhtes Frakturrisiko



Sanders KM. JAMA 2010;303:1815-1822.

Monatlicher Vitamin-D-Bolus von 100'000 IE bei Langzeitpflegepatienten: doppelblinder RCT

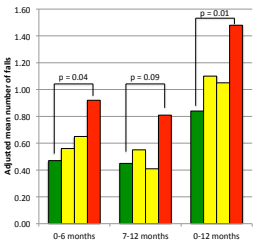


Long-term care residents aged 60 and older (n = 107)

Sturzrate:
2.3-fach erhöht mit Bolus D

Ginde AA, JAGS 2017

Adjusted mean number of falls by quartile of achieved 25(OH)D levels



Wird in 97% der Fälle sicher erreicht mit 800-1000 IE/Tag

Zielspiegel 25(OH)D 20 bis 30 ng/ml 50 bis 75 nmol/l

Bischoff-Ferrari HA et al. ; JAMA Internal Medicine 2016

DO HEALTH

Hüft-Frakturen: Pooled-Analyse von doppelblinden RCTs mit täglicher Dosierung: Bei Erwachsenen ab 65 Jahren mit Risiko Vitamin-D-Mangels

30% Reduktion Hüftbruchrisiko mit täglich 800 IU Vitamin D bei älteren Menschen mit Mangel

Table 3. Subgroup Benefits at the Highest Actual-Intake Level of Vitamin D (792–2000 IU per Day), as Compared with Control

Subgroup	Treatment Group	Control Group	Hip Fracture			
			Treatment Group	Control Group	Relative Risk (95% CI)	P Value
	no. of participants		no. of fractures			
Age						
All	3966	15,495	151	586	0.70 (0.58–0.86)	<0.001
65–74 yr	1018	7,521	13	128	0.72 (0.39–1.31)	0.27
75–84 yr	2603	5,989	130	332	0.72 (0.58–0.89)	0.003
≥85 yr	345	1,985	8	126	0.54 (0.25–1.20)	0.13
Type of dwelling						
All	3966	15,495	151	586	0.70 (0.58–0.86)	<0.001
Community dwelling	2103	10,735	42	253	0.68 (0.48–0.96)	0.03
Institution	1863	4,760	109	333	0.70 (0.55–0.89)	0.004
Baseline 25-hydroxyvitamin D						
All†	412	2,220	11	177	0.55 (0.29–1.05)	0.07
<30 nmol/liter	106	517	2	42	0.40 (0.08–1.91)	0.25
≥30 nmol/liter	306	1,703	9	135	0.60 (0.29–1.22)	0.17

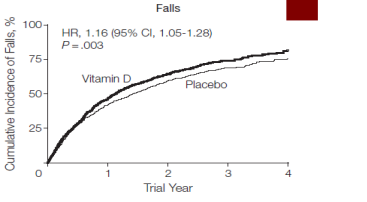
Median = 800 IU

Bischoff-Ferrari, et al. NEJM 2012

Großer jährlicher Bolus von Vitamin D 500'000 IU

- 2 256 Frauen ab 70 Jahren mit Risiko für Hüftfrakturen
- 500'000 IU Vitamin D jährlich versus Placebo

16% erhöhtes Sturzrisiko
26% erhöhtes Frakturrisiko



Sanders KM. JAMA 2010;303:1815-1822.

Daily versus bolus D bei älteren Menschen mit Risiko Vitamin D Mangel und Stürze

Daily 800 IU | **Bolus dose**

34% reduction of falls	30% reduction of hip fractures	15% to 240% increase in falls	26% increase in any fractures
Bischoff-Ferrari, et al. BMJ 2009 and 2011	Bischoff-Ferrari, et al. NEJM 2021	Ginde AA, JAGS 2017 Bischoff-Ferrari JAMA Internal Med 2016	Sanders K JAMA 2010

Overview

Author	Target Population	Intervention tested	Result
Weaver et al. 2016 8 RCTs (n=30'970)	Mostly adults age 65+ at risk of vitamin D deficiency and at risk of OP	Combined effect of daily vitamin D with calcium compared with placebo	• 15% reduction of total fractures (RR = 0.85; 95% CI 0.73 to 0.98) • 30% reduction of hip fractures (RR = 0.70; 95% CI 0.56-0.87)
Zhao et al. 2017 33 RCTs (n = 51'145)	Adults age 50+ not at risk for osteoporosis or vitamin D deficiency	Calcium and vitamin D individually as well as their combination	No significant benefit on any intervention on the incidence of non-vertebral, vertebral, or total fractures.
US Preventive Task Force 2018 11 RCTs (n = 51' 419)	Adults age 50+ not at risk for osteoporosis or vitamin D deficiency	Calcium and vitamin D individually as well as their combination	For vitamin D doses greater than 400 IU, the panel concludes that there is insufficient evidence to assess a benefit.
Bolland et al. 2018 81 unblinded and blinded RCTS (n = 44790)	Adults age 50+	Vitamin D compared to untreated controls, placebo or another dose of vitamin D, excluding trials that combined vitamin D with Cal	No benefit on BMD, falls or fractures

Bolland et al. 2018

Author	Target Population	Intervention tested	Result
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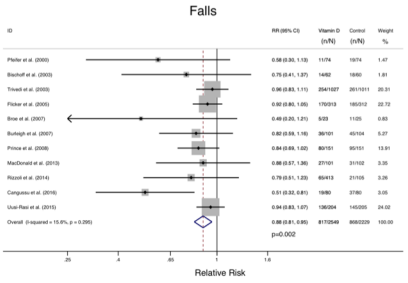
Kritik:
Bemerkenswerterweise war der Nutzen von Vitamin D in 3 von 5 BMD-Bereichen signifikant, nämlich 0,34 % für die Gesamt-BMD der Hüfte (p=0,002), 0,76 % für die BMD des Oberschenkelhalses (p<0,001) und 0,25 % für die Lendenwirbelsäule (p=0,05), was in der Tat darauf hindeutet, dass Vitamin D einen Nutzen für die BMD hat, insbesondere für die Hüfte.
Die Autoren schlossen 40 % der hochwertigen Daten zur Frakturreduktion aus, indem sie Studien ausschlossen, die Vitamin D mit Kalzium kombinierten, Studien mit offenem Design und mehrere Bolus-Vitamin-D-Studien einschlossen und keine Anpassung für die Adhärenz vornahmen.

Falls: Re-Analyses of trials 800-1000 IU included by Bolland et al. with > 50% adherence



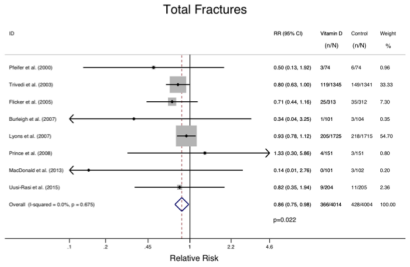
12 percent reduction in falls

(RR = 0.88; 95% CI 0.81-0.95)

Bischoff-Ferrari, H.A., et al., *Vitamin D supplementation and musculoskeletal health.* Lancet Diabetes Endocrinol, 2019. **7**(2): p. 85.

Universität Zürich

Fractures: Re-Analyses of trials 800-1000 IU included by Bolland et al. with > 50% adherence



14 percent reduction in total fractures

(RR = 0.86; 95% CI 0.75-0.98)

Bischoff-Ferrari, H.A., et al., *Vitamin D supplementation and musculoskeletal health.* Lancet Diabetes Endocrinol, 2019. **7**(2): p. 85.

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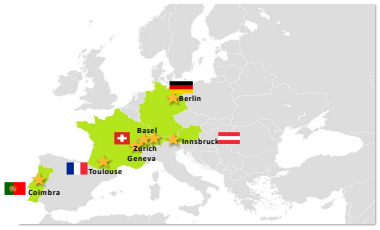
DO-HEALTH

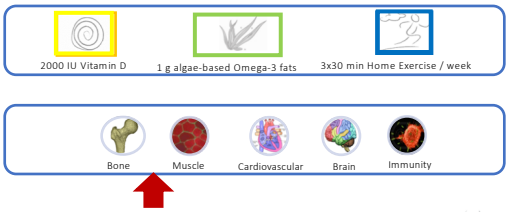
European Commission | DO HEALTH

DO HEALTH: Recruitment

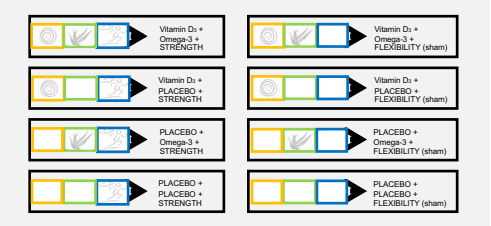


DO-HEALTH - Background

3 promising public health interventions to impact on 5 health domains



DO-HEALTH – 3 Interventions - 8 treatment arms – 2x2x2 double-blind RCT



Vitamin D Deficiency & Physical Activity at Baseline DO-HEALTH

Vitamin D deficiency

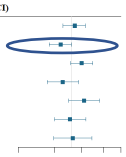
(VitD levels <20 ng/ml)

Physical activity

NHS – questionnaire:
83% engagend in moderate to high physical activity

DO-HEALTH: Results total falls

Treatments	No. of participants	No. of total falls	Incidence Rate Ratio (95%CI)
Vit D vs No Vit D	1076	1660	1.03 (0.92-1.14), p=0.64
Omega-3 vs No Omega-3	1073	1529	0.90 (0.81-1.00), p=0.04
SHEP vs No SHEP	1081	1755	1.10 (0.99-1.22), p=0.08
Vit D+ Omega-3 vs No VitD + Omega-3	529	750	0.92 (0.79-1.07), p=0.27
Vit D + SHEP vs No VitD + SHEP	539	902	1.13 (0.97-1.31), p=0.11
Omega-3 + SHEP vs No Omega-3 + SHEP	539	807	0.98 (0.85-1.14), p=0.84
Vit D + Omega-3 + SHEP vs Placebo	264	395	1.01 (0.84-1.21), p=0.92



No benefits of vitamin D or SHEP (simple home exercise program)
Reduction in the incidence rate of total falls by 10% in the Omega-3 group vs No Omega-3
No additive benefits

Estimates from negative binomial regression model with an offset of the log of person years in the study controlling for study site, sex, age, previous fall, baseline body mass index, and baseline use of walking aids

Bischoff-Ferrari HA, et al. *Am J Clin Nutr.* 2022:nqac022. doi: 10.1093/ajcn/nqac022

Zusammenfassung der 4 neusten meta-analyses zu Vitamin D & Stürze und Knochenbrüche

- Vitamin D in der täglichen Dosierung und heutigen Empfehlung (800 - 1000 IU) ist effektiv bei älteren Menschen mit erhöhtem Risiko für Vitamin D Mangel und Sturz/Knochenbruchrisiko.

– DO-HEALTH stellt dieses Empfehlung nicht in Frage!

- Vitamin D Supplementation ist nicht effektiv bei Menschen 50+ ohne Vitamin D Mangel ohne Risiko für Stürze/OP

Regarding Bolus Dosing

Falls
Fractures
Any Cancer
Cancer Mortality
Acute Respiratory Infections
Covid-19

Vitamin D: Bolus Is Bogus—A Narrative Review

Richard B. Mazess,[1] Heike A. Bischoff-Ferrari,[2,3] and Bess Dawson-Hughes[4]

[1]Department of Medical Physics, University of Wisconsin, Madison, WI, USA
[2]Department of Aging Medicine and Aging Research, University of Zurich, Zurich, Switzerland
[3]City Hospital Zurich, University Clinic for Aging Medicine, Zurich, Switzerland
[4]Jean Mayer US Department of Agriculture (USDA) Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA

ABSTRACT

In this review we summarize the impact of bolus versus daily dosing of vitamin D on 25(OH)D and 1,25$(OH)_2$D levels, as well as on key countervailing factors that block vitamin D functions at the cellular level. Further, we discuss the role of bolus versus daily dosing of vitamin D for several health outcomes, including respiratory infections and coronavirus disease 2019 (COVID-19), rickets, falls and fractures, any cancer, and cancer-related mortality. This discussion appears timely because bolus doses continue to be tested for various disease outcomes despite a growing amount of evidence suggesting lack of efficacy or even detrimental effects of bolus dosing of vitamin D for outcomes where daily dosing at modest levels was effective in the vitamin D deficient. As a result, these discordant results may bias health recommendations for vitamin D if the recommendations are based on meta-analyses combining both daily and bolus dosing trials. © 2021 The Authors. *JBMR Plus* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research.

KEY WORDS: PTH/VIT D/FGF23; CELL/TISSUE SIGNALING; ENDOCRINE PATHWAYS; CLINICAL TRIALS; NUTRITION; AGING

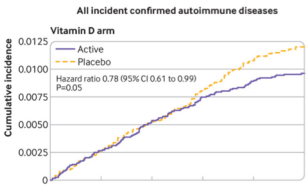
Mazess RB, Bischoff-Ferrari HA, Dawson-Hughes B; JBMRplus 2021

Update Vitamin D

Immunsystem

VITAL RCT – Vitamin D Effekt Autoimmun-Erkrankungen

- Daily 2000 IU D versus Placebo
- 25871 participants, consisting of 12786 men ≥50 years and 13085 women ≥55 years at enrollment.
- mean age 76; FU 5.3 Jahre
- Results: **22% reduction in incident autoimmune diseases** (rheumatoid arthritis, polymyalgia rheumatica, autoimmune thyroid disease, psoriasis, and all others); BMJ open 2022



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

BMJ 2022 ; 376 doi:https://doi.org/10.1136/bmj-2021-066452 (Published 26 January 2022)
Cite this as: *BMJ* 2022;376:e066452

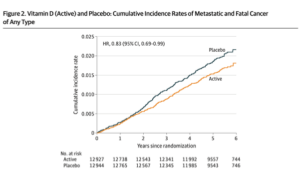
VITAL RCT – Vitamin D Effekt Cancer - Mortality

- Vitamin D reduzierte den primären Endpunkt der gesamten invasiven Cancerinzidenz nicht signifikant (HR = 0,96 [95% 0,88-1,06])
- Signal für eine Verringerung der Gesamtkrebsmortalität (HR = 0,83 [0,67-1,02])
  - Ohne Latenzzeit erstes Jahr (HR = 0,79 [0,63-0,99])
  - oder die ersten 2 Jahre (HR = 0,75 [0,59-0,96])

VITAL RCT – Vitamin D Effekt Advanced Cancer

17%

- Daily 2000 IU D versus Plazebo reduziert **fortgeschrittene Carzinom-Erkrankungen** (metastatic or fatal)
- HR, 0.83 [95% CI, 0.69-0.99]; *P* = .04). JAMA open 2020
  - BMI<25: HR, 0.62 [95% CI, 0.45-0.86]
  - BMI 25-<30: HR, 0.89 [95% CI, 0.68-1.17]
  - BMI≥30: HR, 1.05 [95% CI, 0.74-1.49])



JAMA network Open 2020

Effect of Vitamin D_3 Supplements on Development of Advanced Cancer
A Secondary Analysis of the VITAL Randomized Clinical Trial

Meta-Analyse 46 RCTs Vitamin D und Akute respiratorische Infekte

46 RCTs (75 541 participants) -- Alter 0–95 Jahre

- Any dose Vitamin D versus Placebo: OR 0·92 (95% CI 0·86–0·99)
- Daily vitamin D versus Placebo: OR 0·78 (95% CI 0·65–0·94)
- Daily 400 to 1000 IU: OR 0·70 (95% CI 0·55–0·89)

Kein Benefit mit Bolus-Dosierung Vitamin D!

Vielen Dank!