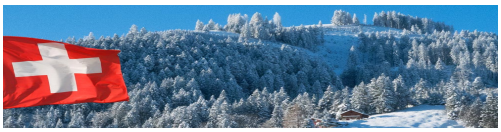

# „Meine Knie tun weh und meine Knochen werden immer brüchiger“

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## Übersicht

Epidemiologie Arthrose
Arthrose und Osteoporose,
Arthrose und Sturzrisiko
Arthrose und Knochenbruchrisiko
Arthrose und Schmerzen

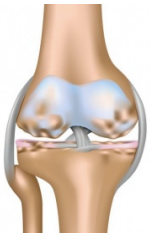
Umfassende Behandlung Arthrose + OP + Sturz

..... bei älteren Patienten



## Epidemiologie Arthrose

- **50%** aller Menschen 65+ haben radiologische Zeichen einer manifesten Arthrose
- **30%** aller Menschen 65+ haben eine symptomatische Arthrose mit Schmerzen im befallenen Gelenk



Felson DT: Epidemiology of osteoarthritis. Brandt KD, Doherty M, Lohmander LS eds. Osteoarthritis 2003; New York: Oxford Univ Press.



## Epidemiologie Sturz

- **30%** aller Menschen 65+ stürzen mindestens einmal pro Jahr
- **50%** aller Menschen 80+ stürzen mindestens einmal pro Jahr
- **6% aller Stürze führen zu** Knochenbrüchen
- 40% aller Pflegeheimeintritte sind aufgrund eines Sturzereignisses

Bischoff-Ferrari: Falls.
Primer of Metabolic Bone Disease 8th Edition 2015;



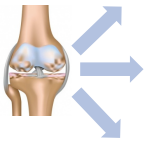
## Epidemiologie OP Frakturen

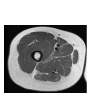
- **50%** aller Frauen 50+ erleiden eine OP-bedingte Fraktur
- **20%** aller Männer im Alter 50+ erleiden eine OP-bedingte Fraktur
- **Häufigeste Fraktur 75+ ist Hüftbruch**
  -- Hauptrisikofaktor Sturz, z.B. Arthrose-bedingt

Bischoff-Ferrari: Epidemiology of Fractures 70+. Duque G and Kiel D eds.; Osteoporosis in Older Persons, 2nd Edition 2016.



## Arthrose und wichtige Konsequenzen beim älteren Menschen





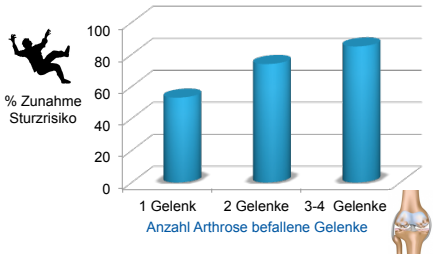
Hauptgrund für Disability 65+
Muskelschwäche
Sarkopenie

Gangstörung
1,6-fach erhöhtes Sturzrisiko

Abnahme Knochendichte
2-fach erhöhtes Hüftbruchrisiko

Arden NK et al.; Arthritis Rheum 2006
Bischoff-Ferrari HA et al.; Arthritis Rheum 2005
Doré AL et al.; Arthritis Care Res 2015

## Anzahl Arthrose-betroffene Gelenke untere Extremitäten und Sturz-Risiko

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*Doré AL et al.; Arthritis Care Res 2015*

## Warum ist Sturz-Risiko bei Arthrose der grossen Gelenke erhöht?

**Direkt:**

- Eingeschränkte Gelenkbeweglichkeit + Gangstörung
- Eingeschränkte Gelenkstabilität
- Schmerzen / Giving Way

**Indirekt:**

- Muskelschwäche / Sarkopenie durch eingeschränkte Mobilität um das betroffene Gelenk und generell

Bischoff-Ferrari: Falls. Primer of Metabolic Bone Disease 8th Edition 2015;

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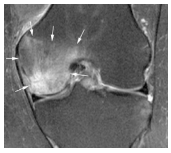
## Was macht Arthrose schmerzhaft?

**Verlust an Knorpel (überholt):**
Knorpel hat keine Nervenversorgung

**Neue Daten:**

- **Synovitis**: 80% schmerzhafter Arthrose Gelenke haben eine Synovitis
- Wahrscheinlichkeit Schmerz 9.2-fach erhöht bei nachgewiesener Synovitis
- **Bone Marrow Edema**
- **Weichteile:** Muskeln und Sehnenansätze
- **Zentrale Komponente**



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*Baker K, et al. Ann Rheum Dis 2010*
*Sofat N, et al. Rheumatology 2011*

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## Wie behandeln?

Verschiedene Versuche von Disease Modifying Drugs blieben bisher erfolglos (DMOADS)!

Arthrose ist komplex und eine weiterhin eine therapeutische Herausforderung

Bezüglich nicht-pharmakologischen Massnahmen sind Training und Gewichtsreduktion belegte Massnahmen zur Schmerzreduktion

Im Vordergrund stehen weiterhin Schmerzbehandlung mit NSAIDS und im fortgeschrittenen Stadium Gelenkersatz

**Bei älteren Menschen**
NSAIDS sind keine Langzeit-Option
wegen alters-abhängig eingeschränkter Nierenfunktion
plus Gefahr Magentoxizität
**Gewichtsreduktion** bedeutet oft Muskelmassenverlust – unerwünscht!

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## Wie behandeln Alter 65+?

Umfassend!

Erhaltung Mobilität steht im Vordergrund

Nicht-pharmakologische Massnahmen stehen im Vordergrund

*Baker K, et al. Ann Rheum Dis 2010*
*Sofat N, et al. Rheumatology 2011*

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## Umfassende Risiko-Erfassung Sturz – Geriatrisches Assessment

**Exogene Faktoren**

- Stolperfallen
- Schlecht sitzendes Schuhwerk/ Kleidung
- Falsche Gehhilfen
- Brille / Hörgerät sitzt nicht richtig / insuffizient
- Unterkühlte Wohnung
- Schlechte Lichtverhältnisse / Ausleuchtung

**Intrinsische Faktoren**

- Immobilität / Sarkopenie
- Gangstörung
- **Arthrose**
- Sehstörung / Hörstörung
- Cognitive Einschränkung
- Medikamente
- Synkope
- Neurologische Erkrankungen
- Malnutrition
- Sturzangst
- Vitamin D Mangel / B12 Mangel

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Tinetti ME et al. New Engl. J. Med. 1994;331:821-827.
Tinetti ME et al. New Engl. J. Med. 1988;320:1055-1059.

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## Test und Diagnose-Zentrum USZ
## Umfassende Sturz-Abklärung

## Was wird erfasst?

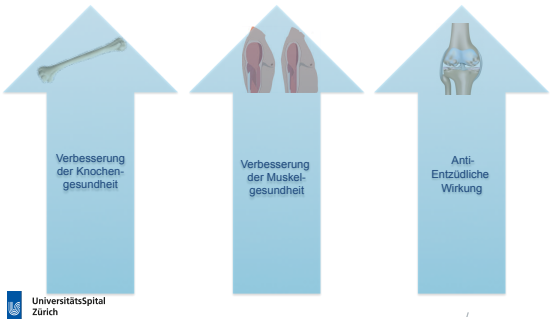
Erstellung eines umfänglichen Risikoprofils um gezielte Massnahmen zur Verbesserung und Erhaltung der Funktion einzuleiten und Stürze im Risiko zu vermindern

- Co-Morbidität, Medikamente
- Funktion Muskel, Gelenke, Knochen, Sinnesorgane, Cognition
- Frailty, ADL, IDAL
- Ernährung, Mangelzustände (z.B. Vitamin D, B12, Protein)
- Lebensumstände – Ressourcen Patient und Umfeld

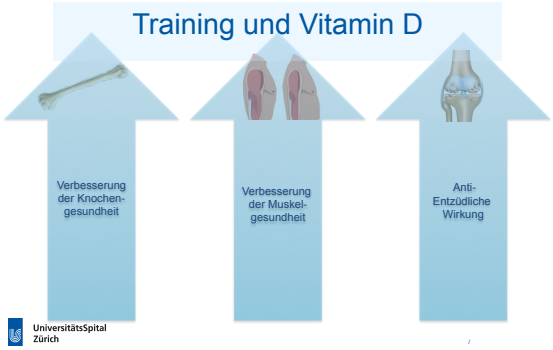
## Topische Behandlung Arthrose?

- Kühlung / Wärme
- Einfaches Kühlelement sind getrocknete Linsen in einem Damenstrumpf
- Ruhig stellen für ein paar Stunden
- Gehhilfe zur Entlastung

## Umfassende Nicht-Pharmakologische Behandlung Arthrose 65+ hat 3 Langzeit-Handlungsfelder




## 2 einfache Massnahmen für die 3 Handlungsfelder




## Training

Iversen M; Ther Adv Musculoskelet Dis. 2010.
Effectiveness and safety of strengthening, aerobic, and coordination exercises for patients with osteoarthritis
Bischoff-Ferrari HA and Roos E; Current Opinion in Rheumatology 2003

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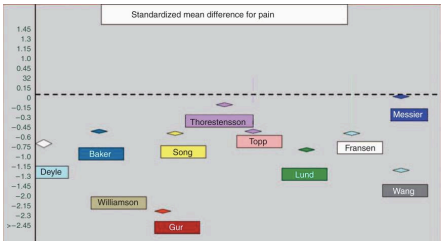
## RCTs Training und Schmerzreduktion bei Arthrose




Iversen M; Ther Adv Musculoskelet Dis. 2010.
Effectiveness and safety of strengthening, aerobic, and coordination exercises for patients with osteoarthritis
Bischoff-Ferrari HA and Roos E; Current Opinion in Rheumatology 2003

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## Training und Schmerzreduktion bei Arthrose

- Training wirkt anti-entzündlich
- Training verbessert die Funktion
- Training stabilisiert das Gelenk
- Training senkt das Sturzrisiko und erhält die Mobilität
- Training hemmt den Knochenabbau

Iversen M; Ther Adv Musculoskelet Dis. 2010.
Effectiveness and safety of strengthening, aerobic, and coordination exercises for patients with osteoarthritis
Bischoff-Ferrari HA and Roos E; Current Opinion in Rheumatology 2003

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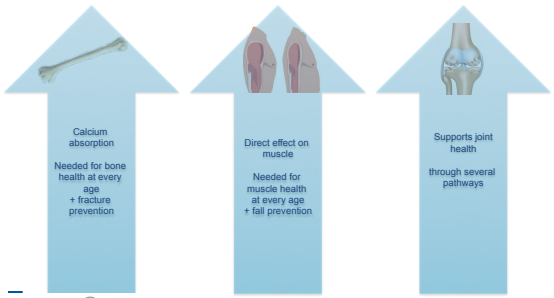
## Vitamin D
## and its 3 roles in musculoskeletal health

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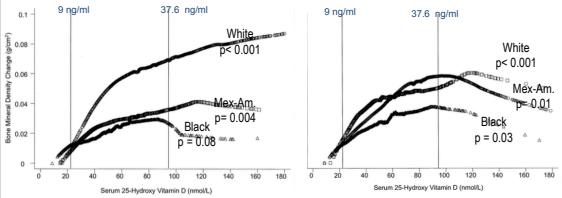
## Bone Health – 25(OH)D status associated with hip BMD in younger and older adults

Age 20 to 49 | Age 50+




N = 13,432 / NHANES III: Circles represent whites, squares represent Mexican Americans, and triangles represent blacks. LOWES plot is adjusted for sex, age, body mass index, smoking, poverty income ratio, daily calcium intake, and estrogen use among women.

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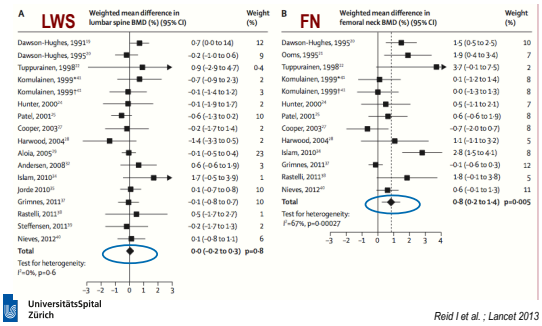
*Bischoff-Ferrari HA et. al. ; AJM 2004*

## Based on Clinical Trials
## *(double-blind and open designs)*
## effect of vitamin D on BMD is small – hip BMD significant

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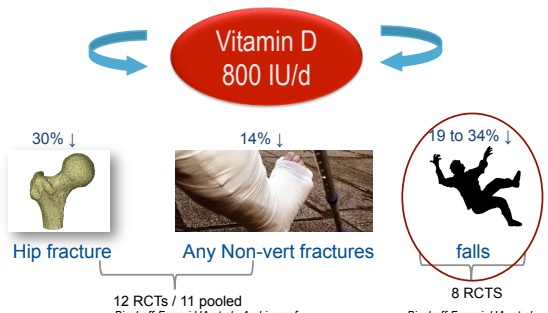
*Reid I et al. ; Lancet 2013*

## Evidence from Double-blind RCTs

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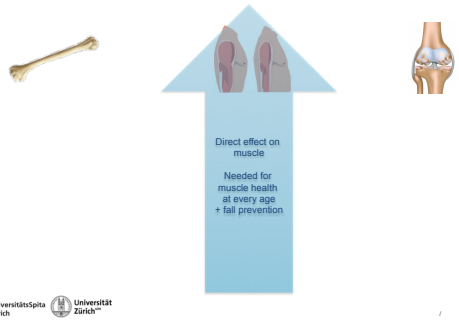
*Bischoff-Ferrari HA et al.; Archives of Internal Medicine 2009 ; Bischoff-Ferrari HA et al.; NEJM 2012*

*Bischoff-Ferrari HA, et al.; BMJ 2009 +2011*

## Vitamin D
## and its 3 roles in musculoskeletal health

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## Mechanistic Evidence

**Mechanistically, several lines of evidence link vitamin D to muscle strength:**

VDR (-I-) mice have small and variable muscle fibers

the vitamin D receptor (VDR) is expressed in human muscle tissue, as documented in all but one investigation

1-alpha hydroxylase is expressed in muscle tissue

Vitamin D supplementation has been shown to up-regulate VDR expression among postmenopausal women – preferentially Type II fast muscle fibers

Ceglia, L., et al., *A randomized study on the effect of vitamin D3 supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women.* J Clin Endocrinol Metab, 2013.
Bischoff-Ferrari, H.A., *Relevance of vitamin D in muscle health.* Rev Endocr Metab Disord, 2012.
Wang, Y. and H.F. DeLuca, *Is the vitamin d receptor found in muscle?* Endocrinology, 2011.
Ratchakrit Srikuea et al. Am J Physiol Cell Physiol. 2012

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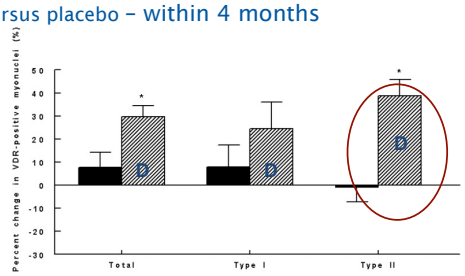
## Percent changes in VDR concentration in muscle by fiber type and group with 4000 IU Vitamin D versus placebo – within 4 months




- 21 mobility-limited women (aged ≥65 years) serum 25-hydroxyvitamin D (25OHD) levels of 22.5 to 60 nmol/L muscle biopsy at baseline and at 4 month follow-up
- 25OHD was 52.5 nmol/l in placebo vs 80.0 nmol/l in vitamin D group at 4 months

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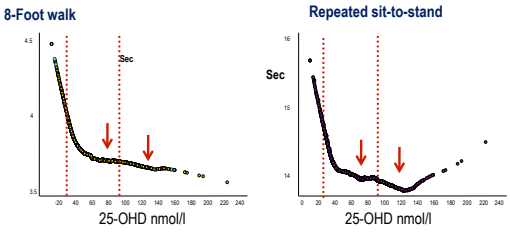
*Ceglia L, Dawson-Hughes et al.; J Clin Endocrinology Metab. 2013*

## Lower Extremity function and 25(OH)D statu




NHANES III: n = 4100 community –dwelling older individuals age 60+

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*Bischoff-Ferrari HA, Dawson-Hughes B et al. Am J Clin Nutr. 200*

***Similar findings in LASA:*** *Wicherts, I.S, Lips, P.J Clin Endocrinol Metab 2007*

## Meta-Analyses of vitamin D trials on fall prevention

All but one* peer-reviewed meta-analyses of RCTs with vitamin D showed significant benefits on fall prevention

| | | |
|---|---|---|
| 2004 | Bischoff-Ferrari HA et al.; JAMA ***- double-blind RCTs -*** | **- 22%** |
| 2007 | Jackson C et al; QiM | - 12% |
| 2008 | O' Donnel S et al.; Bone Mineral Metab (Active D) | - 34% |
| 2008 | Richy F et al.; Calcif Tissue Int (Active D) | - 21% |
| 2009 | Bischoff-Ferrari HA et al.; BMJ ***- double-blind RCTs -*** | **- 34%** |
| 2010 | Kalyani RR et al.; J Am Ger Soc | - 14% |
| 2010 | Cameron ID et al.; Cochrane Database Syst Rev | - 28% |
| 2011 | Michael YL et al.; Ann Intern Med | - 17% |
| 2011 | Murad MH et al.; J Clin Endocrinol Metab | - 14% |
| 2014 | Bolland M et al.; Lancet Endocrinology | - 5%* |

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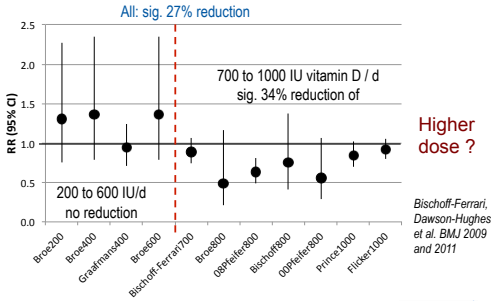
## Is dose of vitamin D relevant?

8 RCTs (n = 2426) sorted by dose




Higher dose ?

*Bischoff-Ferrari, Dawson-Hughes et al. BMJ 2009 and 2011*

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**Trial and treatment dose of vitamin D in IU per day**

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## Zurich Disability Prevention Trial

**Design, Participants:**
1-year double-blind randomized-controlled trial.
Participants were 200 community-dwelling men and women
age ≥ 70 with a prior fall in the preceding 12 months

**Interventions**:
Three randomly allocated study groups with monthly treatments

- ***referenceD*** (24'000 IU vitaminD3) -- control
- ***highD*** (60'000 IU vitaminD3)
- ***combinedD*** (24'000 IU vitamin D3 plus 300 µg calcifediol)

**Registration:** ClincalTrials.gov (NCT01017354)
Bischoff-Ferrari et al.; JAMA Internal Medicine 2016

## Disability Prevention Trial

**Follow-up:** Clinical visits at BL, 6 months, 12 month
+ 2 week safety visit
+ monthly phone calls for fall assessment

**Baseline characteristics**:

At least 1 fall in the year prior to enrollment
Mean age 78 years
67% women
58% vitamin D deficient (< 20 ng/ml)

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

## Results 1

HighD and combinedD were significantly more effective than referenceD in **reaching 25(OH)D levels of 30+ ng/ml** (p = 0.001) at 12 months

***referenceD:*** 15% BL --- to 55% M12
***highD***: 19% BL --- to 81% M12
***combinedD***: 12% BL --- to 83% M12

**lower extremity function did not differ** among treatment groups (p= 0.26) over time.

However, best within group improvement was in ***referenceD*** at 12 month
*change SPPB* +0.38; p = 0.01

**Analyses adjusted for age, gender and bmi*

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

## Results 2

**121 seniors fell during 12 month follow-up** reporting 275 falls
(141 in the first and 134 in the second 6 months of observation)

Both in highD and combinedD a higher **percentage of seniors fell** compared to referenceD (p = 0.048)

***referenceD*** *(24'000 IU):* 48%; 95% CI: 36-60%
***highD*** *(60'000 IU)*: 67%; 95% CI: 54-78%
***combinedD*** *(24'000 IU + calcifediol)*: 66%; 95% CI: 54-77%

A similar pattern was found for the **mean number of falls** (p = 0.09)
***referenceD****(24'000 IU):* 0.94
***highD*** *(60'000 IU)*: 1.47; p = 0.02 vs referenceD
***combinedD*** *(24'000 IU + calcifediol)*: 1.24; p = 0.22 vs referenceD

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

## Summary by treatment results

Seniors in the referenceD group (equivalent to 800 IU/day) experienced the most improved lower extremity function,
had the lowest percent of fallers,
and the fewest number of falls.

This was contrary to our expectations

## Observational Analysis - Falls

| Variables | Quartile 1 *N = 48 25(OH)D at 12 months range: 21.3-30.3 ng/ml* | Quartile 2 *N = 48 25(OH)D at 12 months range: 30.4-37.4 ng/ml* | Quartile 3 *N = 48 25(OH)D at 12 months range: 37.6-44.5 ng/ml* | Quartile 4 *N = 48 25(OH)D at 12 months (--ref--) range: 44.7-98.9 ng/ml* |
|---|---|---|---|---|
| | **Secondary endpoint: prevention of falls** | | | |
| | | *Odds of being a faller* | | |
| Number of fallers at 0-12 months (95% CI) | --ref-- | 3.59 (1.47, 8.78) **p = 0.005** | 1.73 (0.74,4.02) p = 0.21 | 5.52 (2.10,14.50) **p = 0.0005** |
| | | *Mean Number of falls over time* | | |
| Mean at 0-12 months (95% CI) | -- ref-- 0.84 (0.46,1.22) | 1.10 (0.71,1.48) p = 0.36 | 1.06 (0.68,1.44) p = 0.42 | 1.59 (1.19,2.00) **p = 0.01** |

adjusted for age, gender and BMI as covariates.

## Summary observational results

- Fewest fallers + falls were observed at the lower replete 25(OH)D range of **21.3 to 30.3 ng/ml** with some extended benefits at moderately high levels up to 44.5 ng/ml

- no functional benefit plus the most frequent falls were observed between **44.7-98.9 ng/ml**

for the dosages examined in our study, referenceD (24'000 IU vitamin D3/months) was most likely to achieve the desirable lower replete range

## Implications

**High monthly doses** of vitamin D or a combination with calcifediol may not be warranted in seniors with a prior fall event due to an increased risk of falls

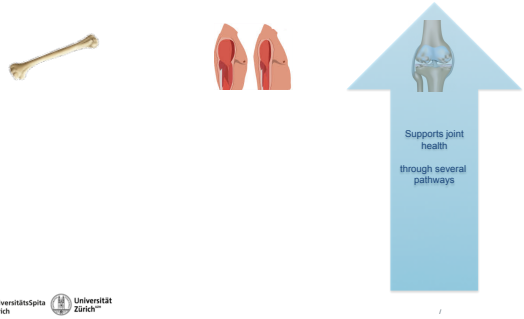
Are we seeing a **therapeutic range for fall prevention**?

Not too low (< 20 ng/ml / < 50 nmol/l)

Not too high (> 45 ng/ml / 112 nmol/l)

*Daily 800 IU or monthly 24'000 IU vitamin D is safe and effective*

## Vitamin D and its 3 roles in musculoskeletal health




## Mechanistic Pathways vitamin D benefits in OA

**Bone**: direct effect of vitamin D on bone – subchondral bone

+ less fractures

**Cartilage:** direct effect of vitamin D on cartilage cells (VDR present on cartilage cells)

**Muscle:** direct effect of vitamin D on muscle – less falls on the affected joints- less fractures

**Less Synovitis:** anti-inflammatory effects of vitamin D

*Arden NK, Nevitt MC, Lane NE, et al. Osteoarthritis and risk of falls, rates of bone loss, and osteoporotic fractures. Study of Osteoporotic Fractures Research Group. Arthritis Rheum 1999;42:1378-*
*Bhalla AK, Wojno WC, Goldring MB. Human articular chondrocytes acquire 1,25-(OH)2 vitamin D-3 receptors in culture. Biochim Biophys Acta 1987;931:26-32.*
*Boyan BD, Sylvia VL, Dean DD, Schwartz Z. 24,25-(OH)(2)D(3) regulates cartilage and bone via autocrine and endocrine mechanisms. Steroids 2001;66:363-74.*
*Yagami K, Suh JY, Enomoto-Iwamoto M, et al. Matrix GLA protein is a developmental regulator of chondrocyte mineralization and, when constitutively expressed, blocks endochondral and intramembranous ossification in the limb. J Cell Biol 1999;147:1097-108.*

## Epidemiology vitamin D – knee and hip OA progression

**In the Framingham cohort study** risk of radiographic **knee OA** progression increased 3- to 4-fold lower for participants in the highest tertile of both vitamin D intake and serum

**In the Study of Osteoporotic Fractures**, women in the highest tertile of 25-hydroxyvitamin D levels had a 2.5-fold lower risk of incident **hip OA** and a lower risk of radiographic progression

**In the Rotterdam Study**, men and women in the highest tertile of vitamin D intake had a 7.7-fold lower odds of radiographic **knee OA** progression

**In the Finish National Health Examination**: no association

*McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. Ann Intern Med 1996;125:353-9.*
*Lane NE, Gore LR, Cummings SR, et al. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: a longitudinal study. Study of Osteoporotic Fractures Research Group. Arthritis Rheum 1999;42:854-60.*
*Konstari S et al. Scan J Rheum 2012. Bergink AP et al. J Clin Rheum 2009.*

## RCTs on Vitamin D and OA outcomes

**Boston**: n = 146 with symptomatic knee OA **age 45+**, mean age 62, randomized to 2000 IU vitamin D/d or placebo for 2 years;

**Results**: no difference in MRI cartilage properties and pain, possible benefit on WOMAC function (p difference = 0.07) *McAlindon T et al.; JAMA 2013*

**Australia:** n = 413 with symptomatic knee OA + low 25(OH)D (< 60 nmol/l), mean age 63, randomized to monthly 50'000 IU D3 or placebo

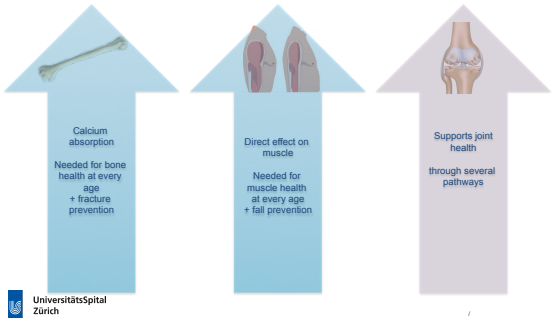
**Results**: no difference in MRI cartilage properties and pain, possible benefit on incident bone marrow lesions (p difference = 0.06)

*Xinghong J et al.; JAMA 2016*

**Zurich:** rapid disease progression model, n = 273 patients undergoing unilateral knee replacement, **age 60+**, 2000 IU versus 800 IU/D for 2 years (in data analysis stage; PI Bischoff-Ferrari) – OA symptoms + radiology

**DO-HEALTH:** seniors **age 70+**, n = 2158, 50% pre-frail, 3yr FU; 2000 IU versus placebo (ongoing to 2017; PI Bischoff-Ferrari; CO-PI DO-HEALTH OA endpoint D. Felson) – OA symptoms hand, knee, hip OA

## Vitamin D
2 roles in musculoskeletal health with evidence – 1 to confirm

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## Goal of recent recommendations on vitamin D 2010 to 2012 is to prevent vitamin D deficiency and improve bone health at all ages

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- 400 IU/d in the first year of life
- 600 IU/d age 2 to 64
- 800 IU/d age 65+

Will shift over 97% of the population out of vitamin D deficiency to at least 50 nmol/l (20 ng/ml)

safe recommendation at a public health level

Alternative: 24'000 IU monthly

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## Weitere verträgliche Massnahmen mit Evidenz?

### Chondroitine Sulfate

**Cochrane Review 2015**

*Supplement – soll Knorpelabbauhemmen und AA Bausteine liefern*

- Leichte Sz Verminderung in den ersten 6 Monaten, danach unklar
- 20% Verminderung Knieschmerz WOMAC
- Mögliche Verbessertung Lebensqualität
- Mögliche Verzögerung Gelenkspaltverminderung

### Glucosamine

**Cochrane Review 2005**

*Supplement – Knorpelbaustein*

- Hochqualitative Studien zeigen keine Schmerzreduktion
- Mögliche aber nicht konsistentente Funktionsverbesserung

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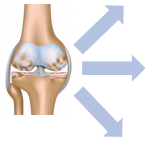
## Arthrose und wichtige Konsequenzen beim älteren Menschen



Hauptgrund für Disability 65+
Muskelschwäche
Sarkopenie

Gangstörung
1,6-fach erhöhtes Sturzrisiko

Abnahme Knochendichte
2-fach erhöhtes Hüftbruchrisiko

Arden NK et al.; Arthritis Rheum 2006
Bischoff-Ferrari HA et al.; Arthritis Rheum 2005
Doré AL et al.; Arthritis Care Res 2015

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## Umfassende Nicht-Pharmakologische Behandlung Arthrose 65+ hat 3 Langzeit-Handlungsfelder

### Training und Vitamin D


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## Vielen Dank

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