INSELGRUPPE

"Knochengesundheit bei Erwachsenen, welche eine Krebstherapie v.a. im Kindes- und Jugendalter hatten"

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Leitender Arzt Rheumatologie RSE Burgdorf und Leiter Osteoimmunologie Inselspital

15. Februar 2023, 17.00–18.30 Uhr

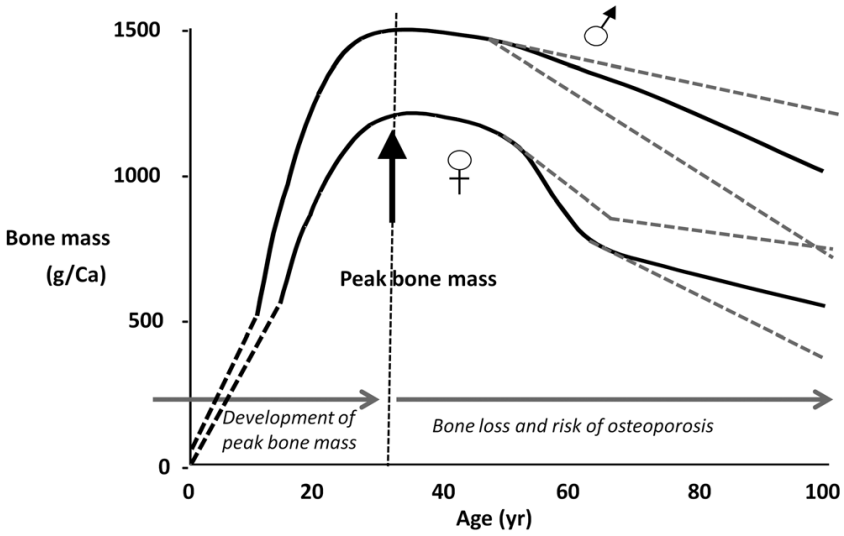
Übersicht Referat

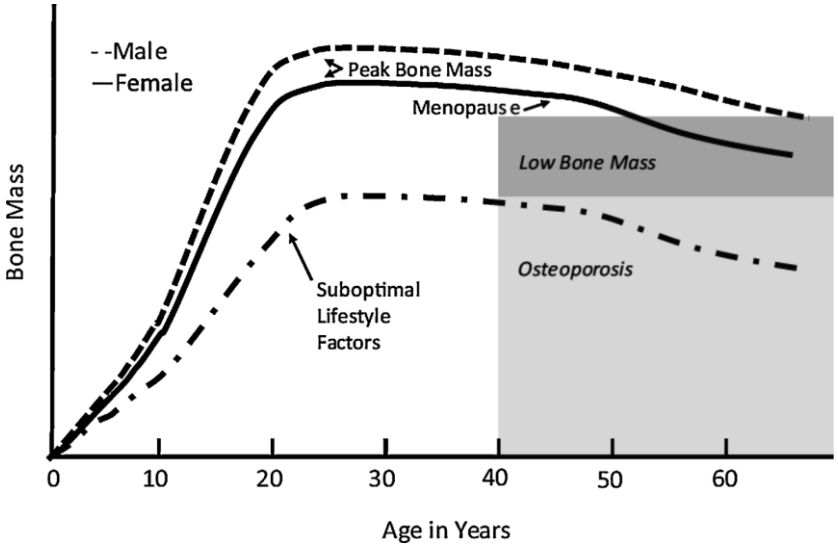
- Warum bestimmen wir die Knochengesundheit bei Erwachsenen, welche eine Krebstherapie v.a. im Kindes- und Jugendalter hatten
- Wie bestimmen wir die Knochengesundheit
- Einflussfaktoren auf die Knochengesundheit
- Bisherige Erfahrungen
- Empfehlungen (IGHG)
- Fragen und Diskussion

Warum und wie bestimmen wir die Knochengesundheit bei Erwachsenen, welche eine Krebstherapie v.a. im Kindes- und Jugendalter hatten

- Osteoporotische Frakturen sind häufig und bei älteren Menschen mit erhöhter Morbidität und Mortalität verbunden
- Frühes Erkennen von Knochenverlust und Osteoporose verhindert Frakturen
- Spezifische osteologische Therapien sind wirksam, insbesondere bei Patienten >50 Jahre
- Nicht spezifische osteologische Therapien sind zahlreich: Ernährung, Bewegung, Entzündungshemmung
- **Erhöhter Anteil von Erwachsenen welche eine Krebstherapie im Kindes-und Jugendalter hatten, zeigt im Vgl. zu Allgemeinpopulation eine zu tiefe Knochendichte (peak bone mass): Tumor- und Therapie assoziiert**

Peak Bone Mass





Harvey et al, Osteoporosis: A Lifecourse Approach JBMR 2014

Rozenberg et al, Maturitas 2020

Warum und wie bestimmen wir die Knochengesundheit bei Erwachsenen, welche eine Krebstherapie v.a. im Kindes- und Jugendalter hatten

International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG):

- **PatientInnen mit Krebs bis 25 jährig,**
  vor allem mit Schädel – und Ganzachsenbestrahlung
  Ganzkörperbestrahlung, Glucokorticoidbehandlung
- **frühestens 2 (2-5) Jahre nach Abschluss der Krebstherapie**
- **Verlaufsmessung nach 2 Jahre, spätestens im 25. Lebensjahr**
  (Peak bone mass erreicht)
- **Verlaufsmessungen nach dem 25.Lebensjahr abhängig von der Dichte**

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Bestimmung der Knochengesundheit

ISCD Definition 2019: T-Score

BMD reporting in postmenopausal women and in men age 50 and older

- T-scores are preferred.
- The WHO densitometric classification is applicable.

The 2019 ISCD Position Development Conference; J of Clinical Densitometry: 2019

Bestimmung der Knochengesundheit

Definitionen WHO:

In 1994 a World Health Organisation study group recommended bone mineral density criteria for osteopenia and osteoporosis:

- A **T-score** at the spine, hip, or forearm ≤ -2.5 defines **osteoporosis**,
- a score of lower -1 to -2.5 SD denotes **osteopenia**,
- while a score ≥ -1 is regarded as **normal**.

World Health Organisation. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva: WHO, 1994.

Bestimmung der Knochengesundheit

ISCD Definition 2019: Z-Score

BMD reporting in females prior to menopause and in males younger than age 50

- Z-scores, not T-scores, are preferred. This is particularly important in children.
- A Z-score of −2.0 or lower is defined as "below the expected range for age", and a Z-score above -2.0 is "within the expected range for age."
- Osteoporosis cannot be diagnosed in men under age 50 on the basis of BMD alone.
- The WHO diagnostic criteria may be applied to women in the menopausal transition.

Z-score reference database

- Z-scores should be population specific where adequate reference data exist. For the purpose of Z-score calculation, the patient's self-reported ethnicity should be used.

The 2019 ISCD Position Development Conference; J of Clinical Densitometry: 2019

Bestimmung der Knochengesundheit

Children Cancer Survivor (CCS):

Outcomes	
Low BMD	Low BMD was defined as a BMD Z-score below -1.
Very low BMD	Very low BMD was defined as a BMD Z-score below -2.
Lower BMD	Lower BMD was defined as lower mean or median BMD Z-scores in the group with the risk factor compared to the group without the risk factor.

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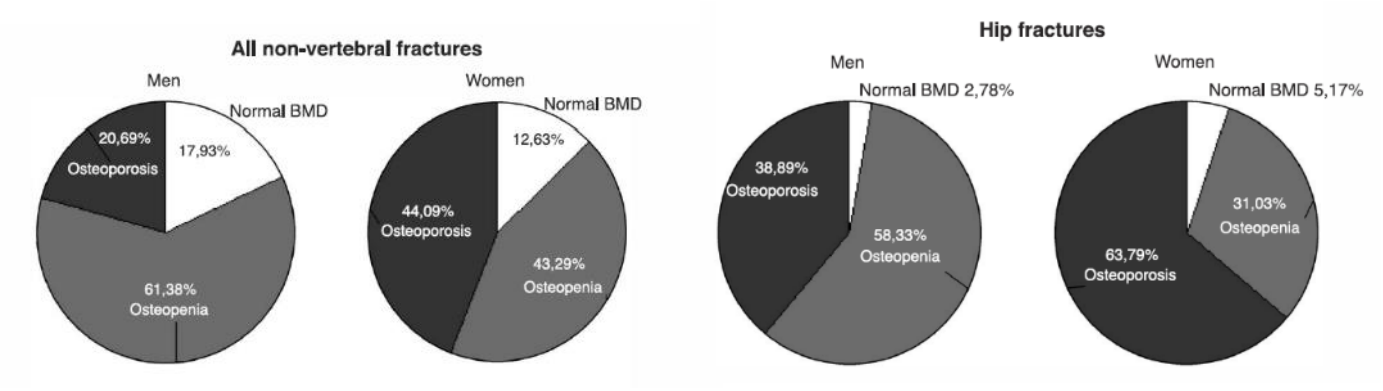
Knochendichte und Fraktur-Risiko

Postmenopausale Fraktur Rate



Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study
(Schuit SCE et al. Bone 2004)

Knochendichte und Fraktur-Risiko

"Only 44% of all non-vertebral fractures occurred in women with a T-score below -2.5SD; in men, this percentage was even lower (21%). Thus, there is a clear need for the development of more sensitive risk assessment tools, using not only BMD, but also other clinical predictors of fractures."

Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study
(Schuit SCE et al. Bone 2004

Knochendichte und Fraktur-Risiko

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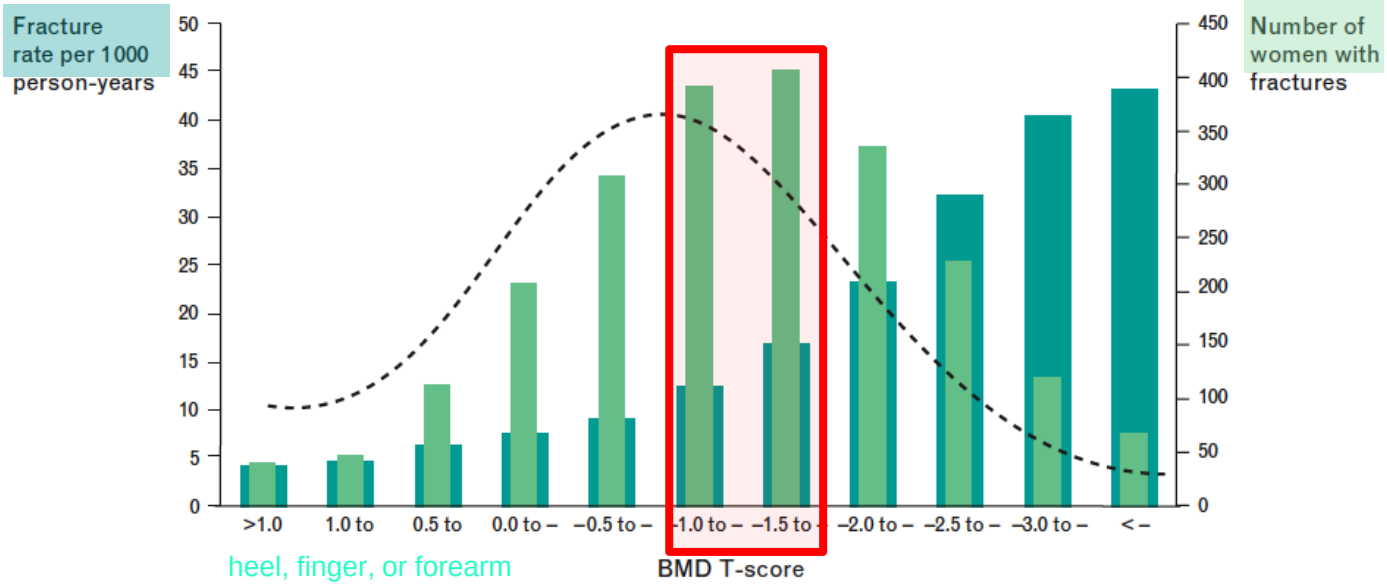


National Osteoporosis Risk Assessment (NORA) Inzidenz von postmenopausalen Frakturen bei einem Kollektiv von 149 524 Frauen.

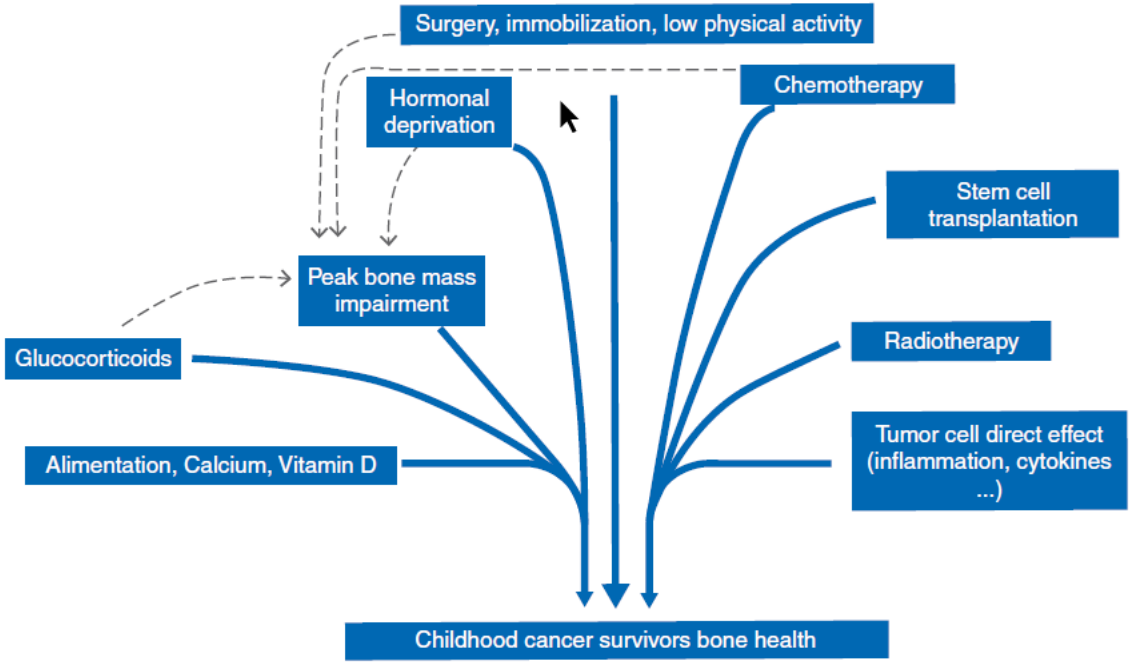
(Siris et al. Arch Int Med 2004)

Risikofaktoren DVO Leitlinie 2017

Allgemeine Risikofaktoren	Krankheiten	Risikofaktoren Medikamente
Singuläre WK FX 1° Deckplattenimpression (M)	B-II Resektion, Gastrektomie (S)	Antiepileptika (S)
Singuläre nicht-vertebr. Fraktur nach 50. Lebensjahr (M)	Cushing Syndrom (S)	Antiandrogene Therapie (M)
Zwei nichtvertebrale Frakturen nach dem 50. Lebensjahr (S)	Diabetes mellitus Typ I < 70 Jahre (S)	Aromatasehemmer (M)
Hyponatriämie (M)	Herzinsuffizienz (S)	Dopaminerge Medikamente (M)
hs CRP erhöht (M)	Subklinischer Hypercortisolismus (S)	Glitazone (S)
Immobilität (M)	Prim. Hyperparathyreodismus (S)	Glucocorticoide oral >7.5mg/d (M)
Multiple intrinsische Stürze (S)	Subkl oder manifeste Hyperthyreose (S)	Glucocortikoide inhalativ (M)
Proximale Femurfraktur bei Vater oder Mutter (M)	Rauchen und/oder COPD (M)	Protonenpumpenhemmer (M)
Untergewicht (M)	Rheumatoide Arthritis (M)	Schleifendiuretika (M)
	Spondylitis ankylosans (M)	Sturzbegünstigende Medi: Antidrepessiva, Sedativa, Neuroleptika, Orthostase-verursachende Medikamente (M)
	Wachstumshormonmangel (S)	
	Zöliakie (M)	
(M) Moderater Risikofaktor	(S) Starker Risikofaktor	

Einflussfaktoren auf die Knochengesundheit bei Erwachsenen, welche eine Krebstherapie v.a. im Kindes- und Jugendalter hatten

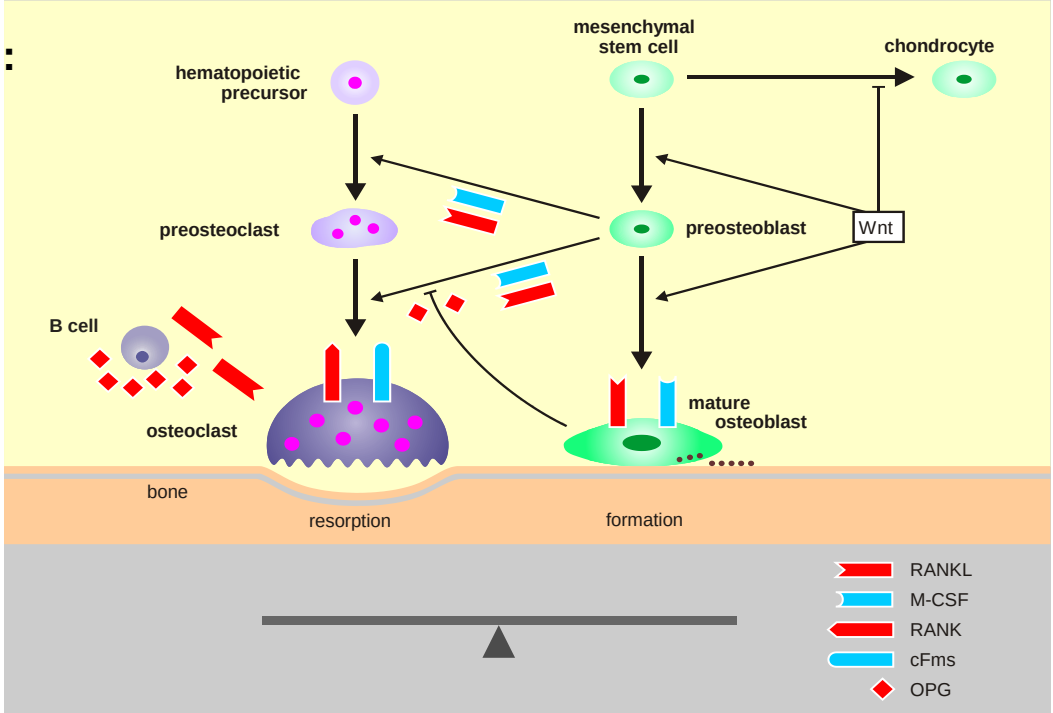
- Genetisch
- Inflammation
- Muskelkraft
- Ernährung
- Medizinische Comorbiditäten/ Medikamente/ Radiatio
- Tumorerkrankung



Marcucci et al A Oncology 2019

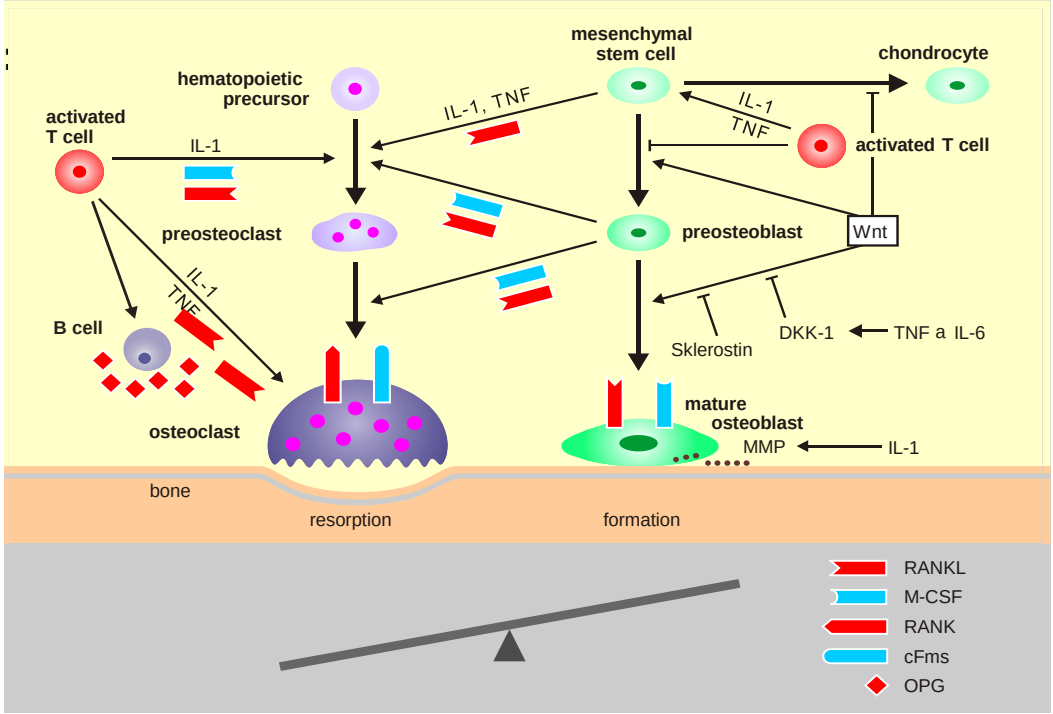
Einflussfaktoren auf die Knochengesundheit

Inflammation:



Einflussfaktoren auf die Knochengesundheit

Inflammation:



Einflussfaktoren auf die Knochengesundheit

Inflammation:

Anti-osteoclastogenic:	Pro-osteoclastogenic:
GM-CSF (20-23)	RANKL; via RANK (24, 25)
Type 2 interferons; via RANKL, cytokines, differentiation (26, 27)	M-CSF; via CFMS
IL-4 (28)	TNFα; (via TNFR) (29) and via RANKL (30)
IL-10; via RANKL (31, 32)	IL-1b; via IL-1RI (33, 34) and indirect via MCSF, RANKL (35)
IL-12; indirect via T-cells (36)	IL-11 (37)
IL-18; indirect via T-cells (36)	Oncostatin M (38)
IL-27; via IL-27R (39)	IL-6; direct via (IL-6R) (37, 40) and indirect via RANKL (41)
IL-33 (42, 43)	IL-15; direct via IL-15R (44)
IL-17; indirect via GM-CSF (17)	IL-17; direct and indirect via RANKL (18, 45)
IL-23; indirect via GM-CSF(19)	IL-23; indirect via RANKL (19)
	PGE2; indirect via RANKL (46)
	SOFAT (47)
IFNγ; indirect via NO synthesis (48)	IFNγ; direct and via RANKL and TNF(49)
MIF (50)	MIF (51, 52)

Einflussfaktoren auf die Knochengesundheit

Lebensgewohnheiten, endokrine Faktoren

	Very low bone mineral density (Z-score ≤–2)	Low bone mineral density (Z-score ≤–1 and ≤–2)	Lower bone mineral density Z-score (continuous)	Fractures (all types)
(Continued from previous page)				
Medical conditions affecting risk				
Growth hormone deficiency	↑ Low[10,54,82,83]	↑ Moderate[10,54,61,68,82,83]	= Low[67,75]	No studies
Hypogonadism	↑ Moderate[10,54]	↑ Low[10,38,51,54,61,68,82,84]	↑ Very low[38,67]	No studies
Vitamin D deficiency	No studies	No studies	No studies	No studies
Hyperthyroidism	No studies	No studies	No studies	No studies
Endocrine dysfunction†	No studies	↑ Very low[62]	No studies	No studies
Health behaviours affecting risk				
Inadequate vitamin D intake	No studies	= Moderate[51]	No studies	No studies
Vitamin D deficiency	No studies	↑ Low[65]	No studies	No studies
Inadequate calcium intake	No studies	= Moderate[51]	↑ Very low[23]	No studies
Inadequate vitamin B intake	No studies	No studies	No studies	No studies
Little exercise	No studies	↑ Moderate[11,40,51,56]	↑ Low[39,63]	= Low[11,80]
Current or previous smoking	= Moderate[6]	↑ Moderate[6,9,56,61]	= Low[9]	↑ Very low[80]
Alcohol consumption	No studies	↔ Very low[61]	No studies	No studies
Carbonated beverages	No studies	No studies	No studies	No studies

↑ indicates an increased risk. = indicates no significant effect. ↔ indicates conflicting evidence. *Higher versus lower doses. †Growth hormone deficiency, hypogonadism, or thyroid dysfunction.

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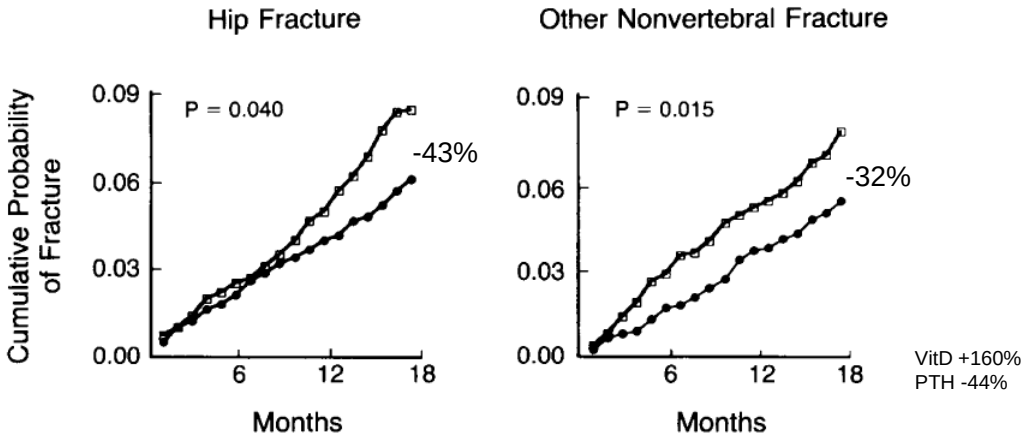
Einflussfaktoren auf die Knochengesundheit

Ernährung

- Calcium und Vitamin D Supplementation
- Eiweisszufuhr

Calcium und Vitamin D_3: Hüft- Frakturen



VitD +160%
PTH -44%

Figure 1. Cumulative Probability of Hip Fracture and Other Nonvertebral Fracture in the Placebo Group (□—□) and the Group Treated with Vitamin D_3 and Calcium (●—●), Estimated by the Life-Table Method and Based on the Length of Time to the First Fracture.

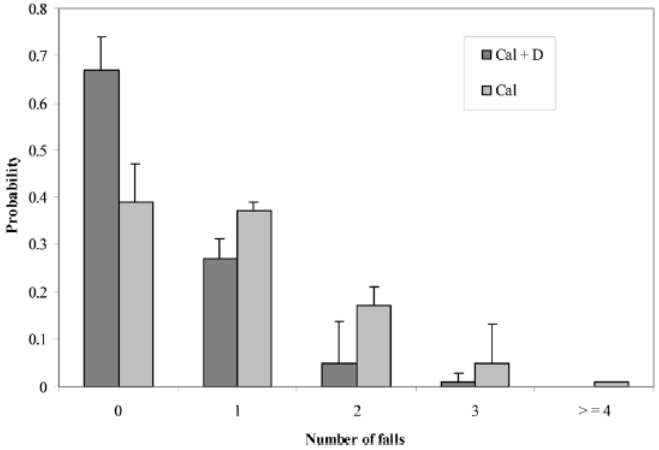
3270, (Alter 84J), Altersheim, 18 Monate: 1,2g Calcium (tricalcium Phosphat)/d & 20ug(800IE) Vitamin D3 oder Placebo

Vitamin D3 and calcium to prevent hip fractures in elderly women, Chapuy et al NEJM 1992

Calcium vs. Calcium und Vitamin D_3: Stürze

TABLE 3. ABSOLUTE DISTRIBUTION OF FALLS

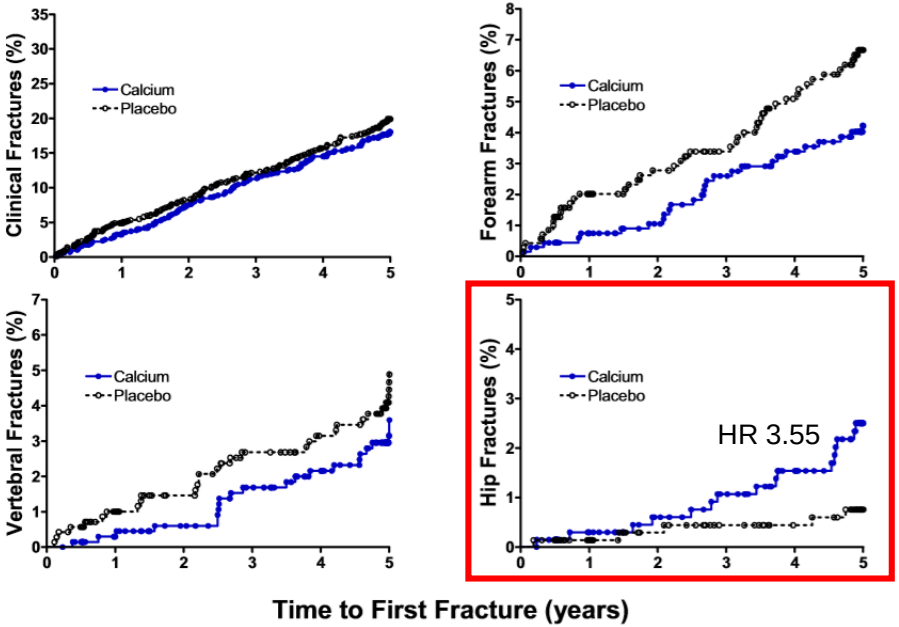
	Before therapy (6 weeks)		*With therapy (12 weeks)*	
Number of falls	*Subjects (Cal)*	*Subjects (Cal + D)*	*Subjects (Cal)*	*Subjects (Cal + D)*
0	46	47	42	48
1	11	11	8	10
2–5	3	4	7	3
6–7	0	0	2	1
>7	0	0	1	0
Total	20	22	55	25
Number of fallers	14	15	18	14



122, (Alter 85.3J), in Altersheim, 3 Monate: 1,2g Calcium & 800IE Vitamin D3/d oder 1,2g Calcium/d

Effects of Vitamin D and Calcium Supplementation on Falls: A Randomized Controlled Trial, Bischoff et al JBMR 2003

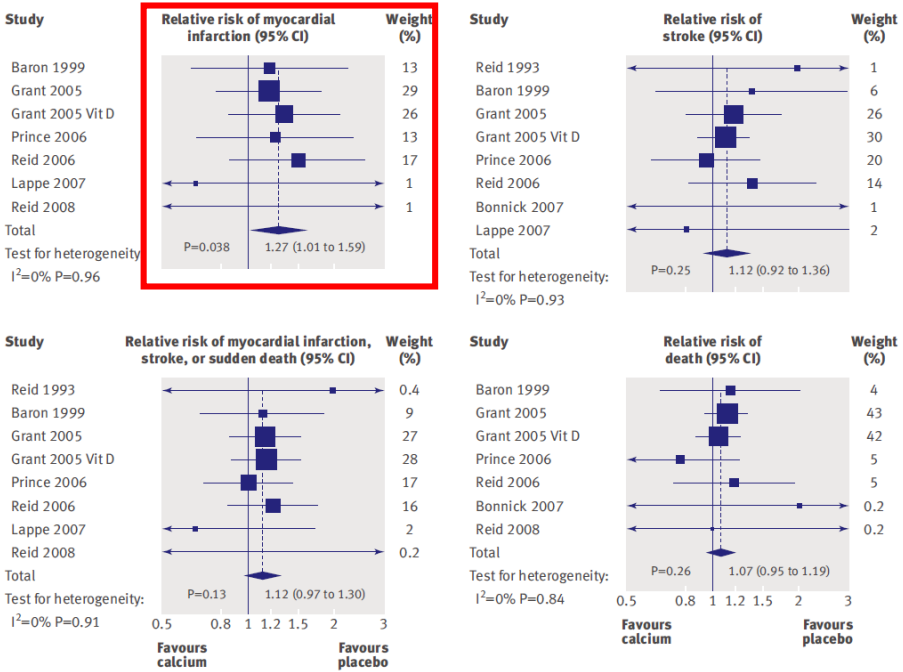
Calcium Supplementation:

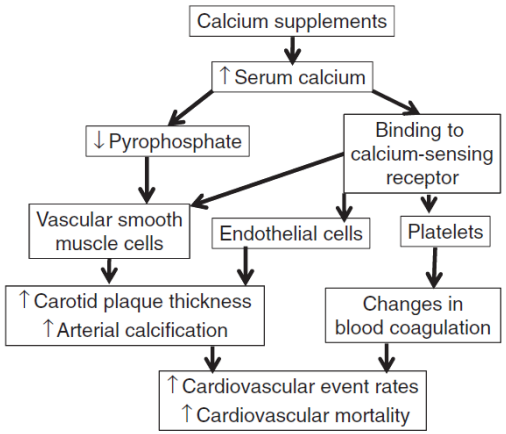


1471 Gesunde, (Alter 74 J):1g Calcium Citrat/d oder Placebo über 5 Jahre. 1) Effekt auf Density und Fraktur

The Auckland calcium study: Randomized Controlled Trial of Calcium in Healthy Older Women, Reid et al Am J Med 2006

Calcium Supplementation:





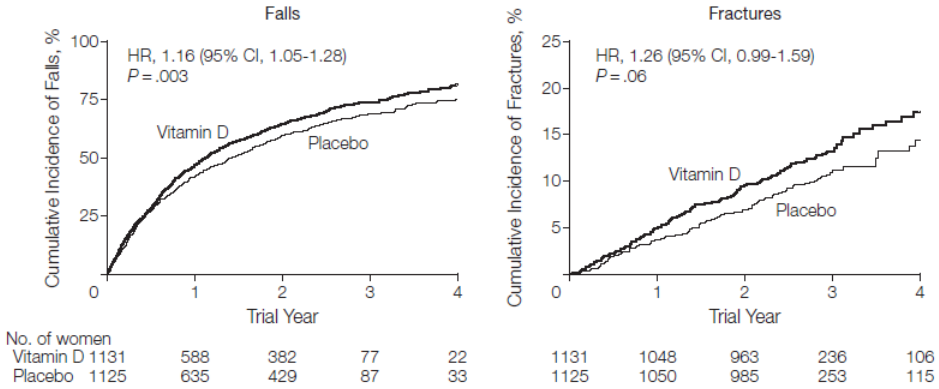
Reid I 2013

11921. (Alter >40 J):>400mg Calcium, Studiendauer >1 Jahre; Durschnitt 4 Jahre: Endpunkt Zeit bis erster MI, Stroke

Effect of calcium supplements on risk of myocardial infarction and cardiovascular events:metaanalysis, Bolland et al BMJ 2011

500 000 IU Vitamin D/ Jahr: Stürze

Kaplan-Meier Plots of Cumulative Incidence of Time to First Fracture and First Fall



Time after treatment, mo		
Falls		
Within 3	1.31 (1.12-1.54)	.001
After 3	1.13 (0.99-1.29)	.08

2256 (Alter >70 J) > 500’000 im Herbst für 3-5 Jahre

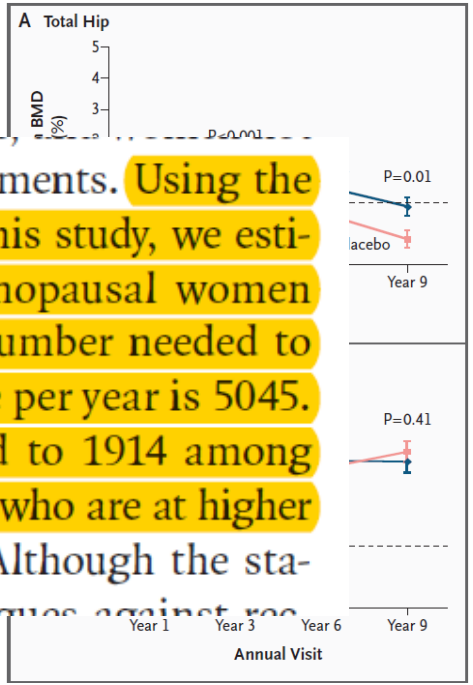
Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women: A RCT, Sanders et el JAMA 2010

Calcium und Vitamin D_3: Fraktur Risiko

Table 2. Effect of Calcium with Vitamin D Supplementation on Clinical Outcomes, According to Randomly Assigned Group.*

Analysis	Calcium + Vitamin D	Placebo	Hazard Ratio (95% CI)†
Intention-to-tre			
Follow-up time			
Rate of fracture (annual			
Hip			
Clinical ver			
Lower arm			
Total			
Analysis exclu time fo 6 mo af detecte			
Follow-up time			
Rate of fracture (annual			
Hip			
Clinical ver			
Lower arm or wrist	312 (0.45)	308 (0.43)	1.05 (0.90–1.23)
Total	1119 (1.63)	1222 (1.72)	0.94 (0.87–1.02)

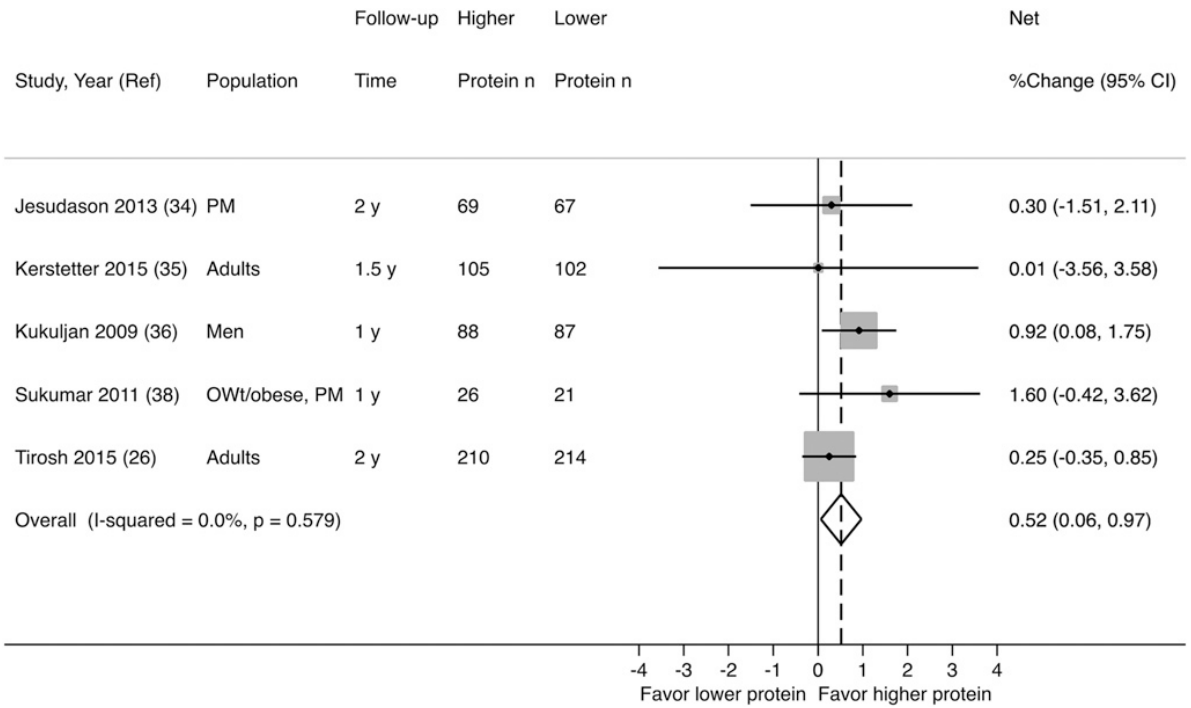
taking personal calcium supplements. Using the intention-to-treat results from this study, we estimate that for healthy postmenopausal women over the age of 50 years, the number needed to treat to prevent one hip fracture per year is 5045. This number would be reduced to 1914 among women over the age of 60 years, who are at higher absolute risk for hip fracture. Although the sta-

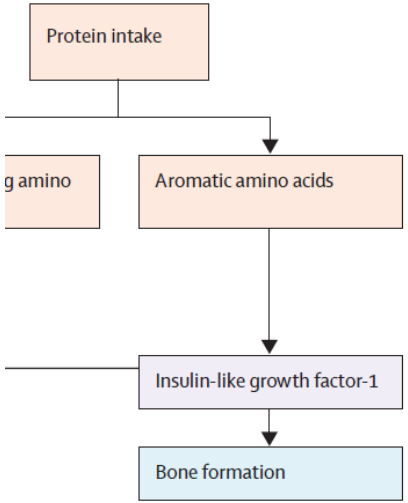


36’282 p.m. (Alter 50 -79 J):1g Calcium Carbonat und 400IE/d Vit D3/d oder Placebo über 5 Jahre. 1) Effekt auf Fraktur

Calcium plus Vitamin D Supplementation and the Risk of Fractures: WHI clinical trial, Jackson et al NEJM 2006

Eiweisszufuhr





Effect of protein intake on lumbar spine bone mineral density. Weights are from random-effects analysis, Shams-White et al, Am J Clin Nutr 2017

Rizzoli et al Lancet Diabet et Endo 2021

Einflussfaktoren auf die Knochengesundheit

Lebensgewohnheiten, endokrine Faktoren

	Very low bone mineral density (Z-score ≤–2)	Low bone mineral density (Z-score ≤–1 and ≤–2)	Lower bone mineral density Z-score (continuous)	Fractures (all types)
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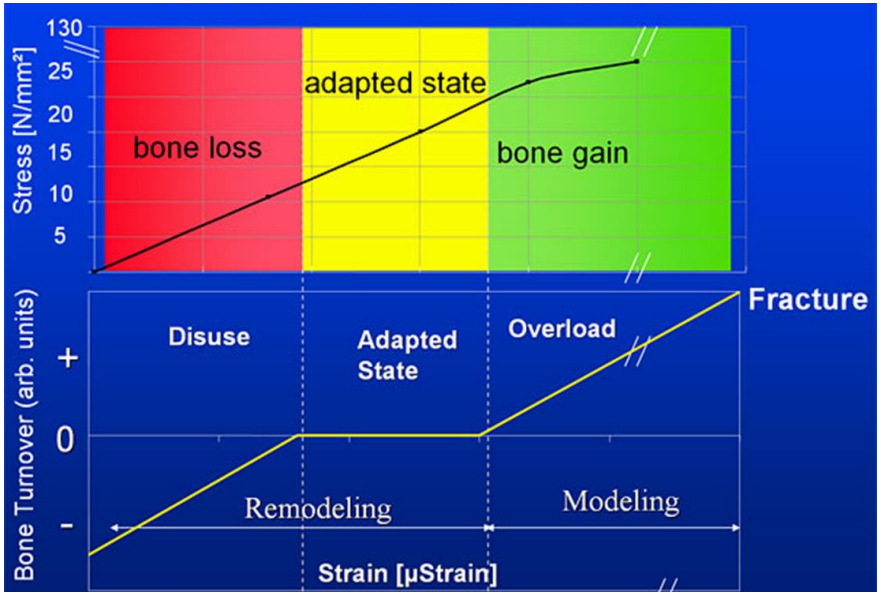
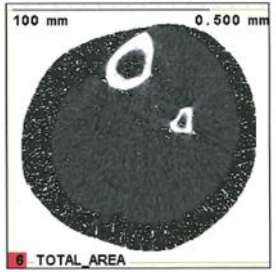
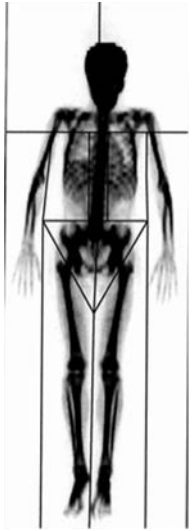
Einflussfaktoren auf die Knochengesundheit

Muskelkraft







Frost H. M Bone and Mineral 1992

Einflussfaktoren auf die Knochengesundheit

Muskelkraft

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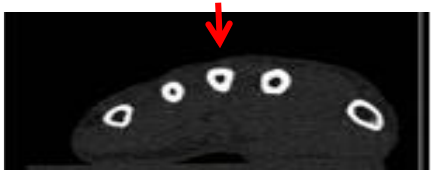

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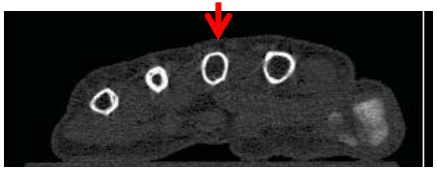
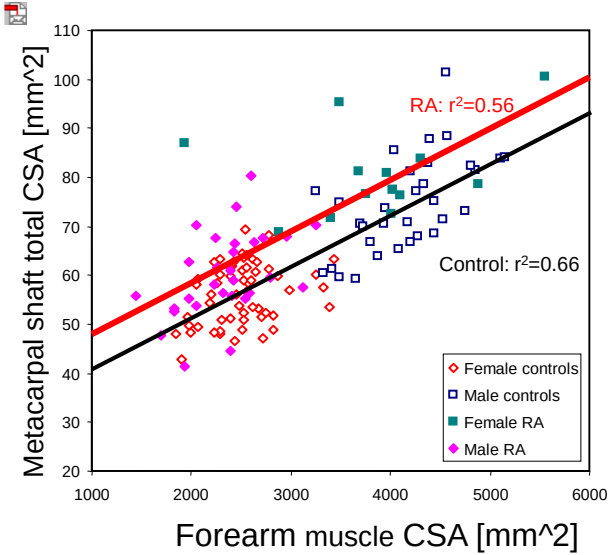
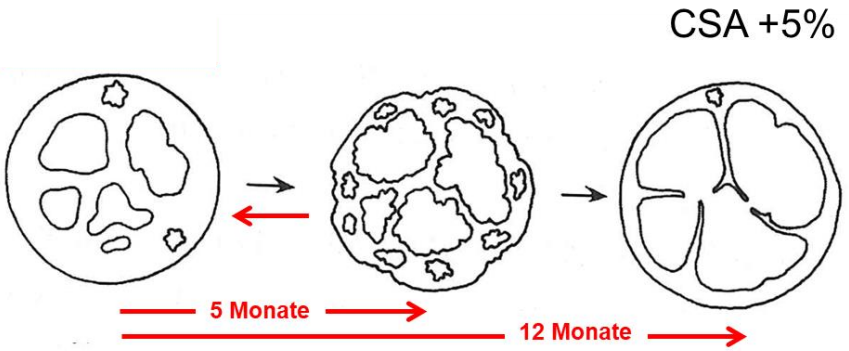




Eser et al AC&R 2010

Einflussfaktoren auf die Knochengesundheit

Muskelkraft



Frost H.M.
Utah Paradima of Skeletal Physiology Vol I 2004
JBMR 1992

Einflussfaktoren auf die Knochengesundheit

Medikamente/ Bestrahlung

	Very low bone mineral density (Z-score ≤–2)	Low bone mineral density (Z-score ≤–1 and ≤–2)	Lower bone mineral density Z-score (continuous)	Fractures (all types)
Treatment factors affecting risk				
Corticosteroids	= Moderate[6,54]	↑ Moderate[6,9,51,54,68]	↑ Very low[9,38,44]	= Very low[80,127]
Higher corticosteroid dose	↑ Very low[69]	↑ Moderate[32,46,69]	↑ Moderate[41,67,70,72,74]	↑ Low[81]
Dexamethasone vs prednisone	No studies	No studies	= Very low[79]	No studies
Methotrexate	= Moderate[6,54]	= Moderate[6,9,54,68]	= Low[9,38]	↑ Very low[80,81]
Higher* methotrexate dose	No studies	= Low[32]	= Very low[79]	↑ Very low[127]
Ifosfamide	= Moderate[6]	= Moderate[6,9]	= Low[9]	= Very low[80]
Higher* ifosfamide dose	No studies	No studies	No studies	No studies
Cyclophosphamide	= Moderate[6]	= Moderate[6,9,68]	= Low[9]	= Very low[80]
Higher* cyclophosphamide dose	No studies	No studies	= Low[68,70]	No studies
Total body irradiation	No studies	↑ High[9,45,54,64,65]	↑ Low[9,44,67,75]	No studies
Higher* total body irradiation dose	No studies	No studies	No studies	No studies
Abdominal or pelvic irradiation	↑ Moderate[6]	↑ Low[6,9]	= Low[9]	= Very low[80]
Higher* abdominal or pelvic irradiation dose	No studies	No studies	No studies	No studies

(Table 1 continues on next page)

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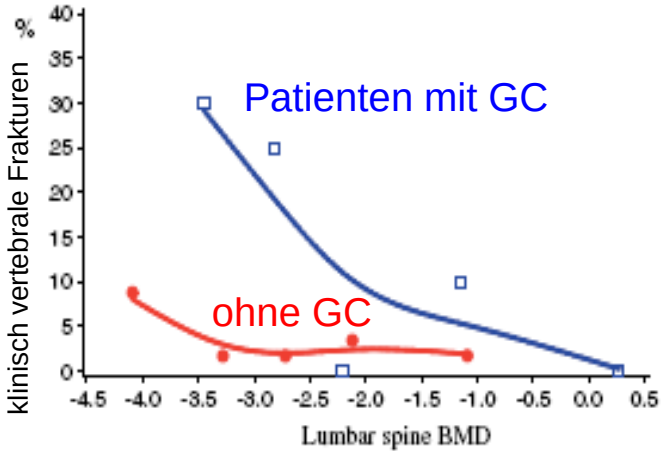
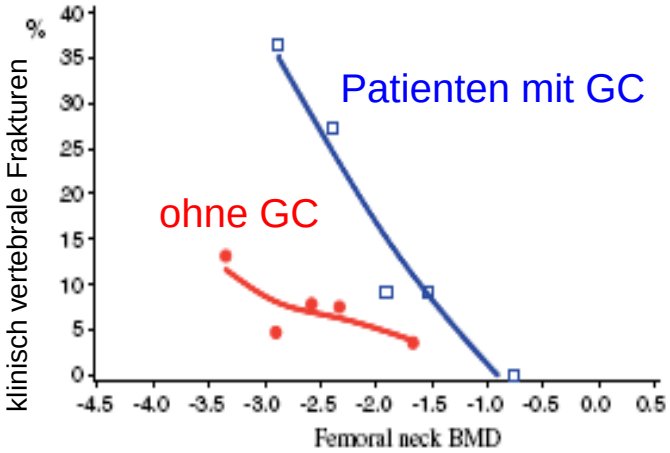
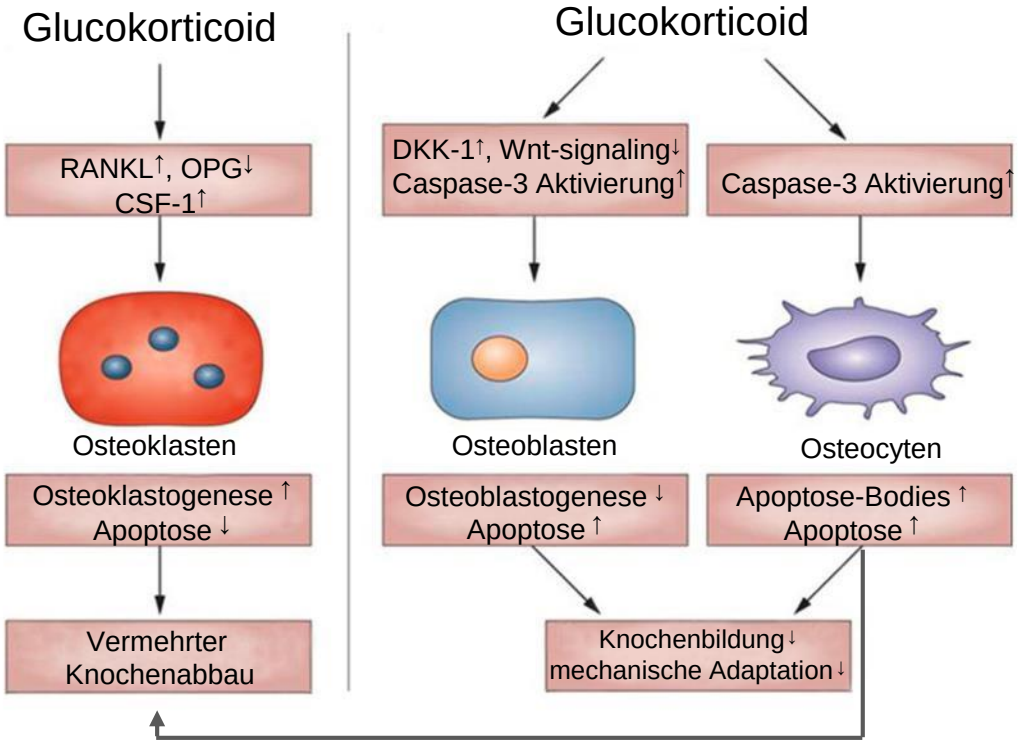
Glucokorticoid induzierte Osteoporose





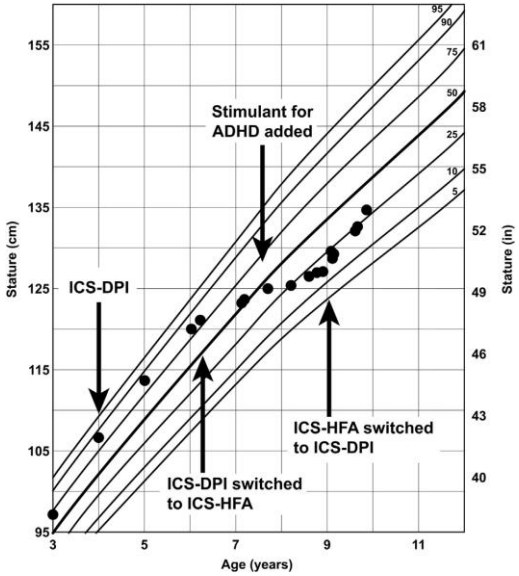
Van Staa. Calcif tissue Int 2006

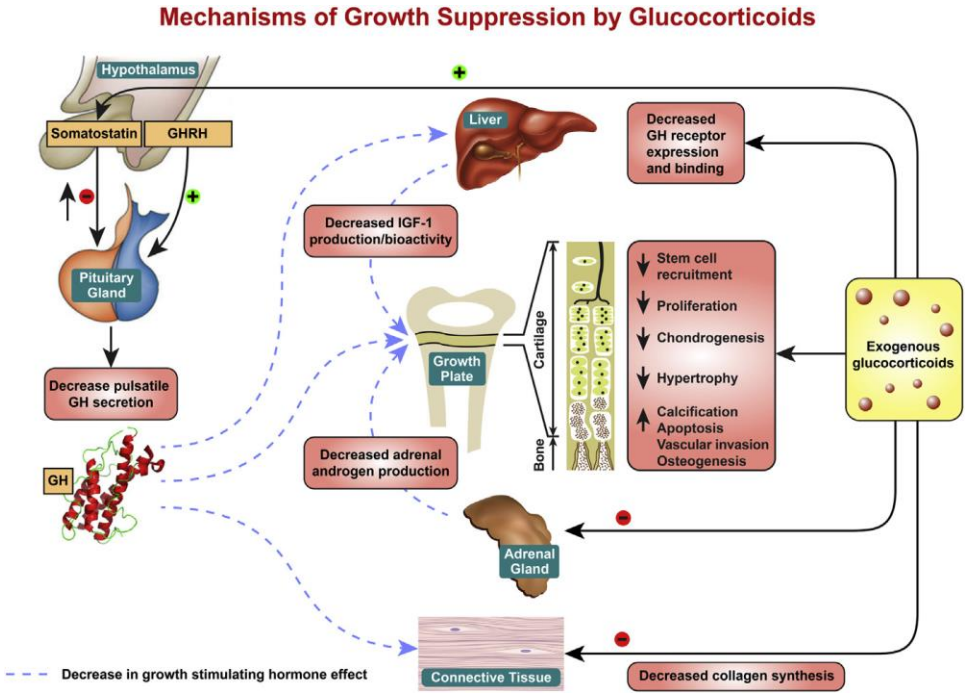
Glucokorticoid induzierte Osteoporose



nach Compston J Nat.Rev. Rheumatol 2010

Glucokorticoid induzierte Wachstumshemmung





Allen D, J of Pediatrics 2015

Einflussfaktoren auf die Knochengesundheit

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(Table 1 continues on next page)

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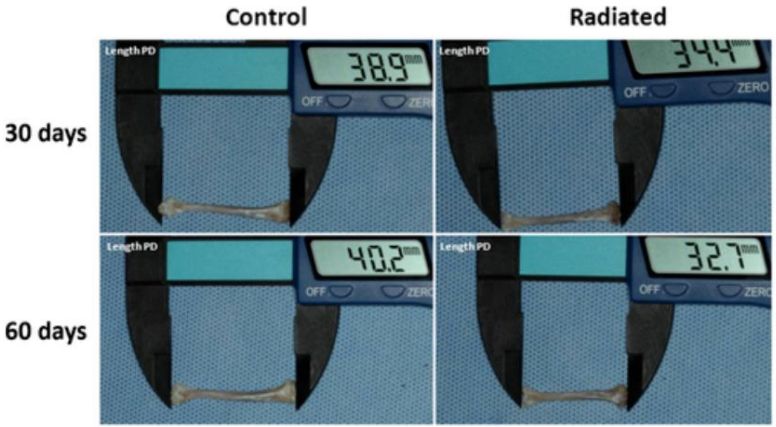
Einflussfaktoren auf die Knochengesundheit

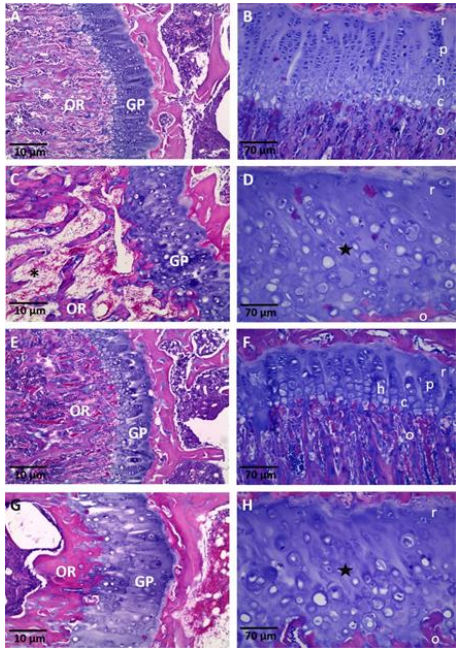
Bestrahlung

Golwein et al in Clinical Orthopaedics and related Research 1990

Einflussfaktoren auf die Knochengesundheit

Bestrahlung





Control

30 days

Control

60 days

Rocha et al, Microscopy Res & Technique, 2016

Einflussfaktoren auf die Knochengesundheit

Tumorerkrankungen:

• ALL;	low BMD, low bone formation marker, erhöhtes Fraktur Risiko
• Hodgkin und non-Hodgkin Lymphome	normale BMD
• Osteosarkome	low BMD, verminderte Muskelmasse, erhöhtes Fraktur Risiko
• Ewing’s Sarkome	low BMD, erhöhtes Fraktur Risiko
• Chondrosarkome	keine Evidenz
• Hirntumore und Neuroblastome	1/3 mit verminderter BMD, endokrin

Marcucci et al A Oncology 2019

Bisherige Erfahrungen

Messungen 2021-1/2023

Initials	Alter	DOB	Diagnose	Therapie	T-/Z-Score LWS	T-/Z-Score TH	T-/Z-Score FN
BT	55	18.08.1967	Morbus Hodgkin, 1991	Adjuvante supradiaphragmale Radiotherapie	0.1	**-1.3**	**-1.5**
PT	44	11.04.1978	Malignes T-Zell-Non-Hodgkin-Lymphom pleomorph, 1989	Chemotherapie nach Protokoll POG 8719	1.1	-0.1	-0.7
FS	37	23.03.1985	Osteosarkom der proximalen rechten Tibiametaphyse, 1991	Chirurgie, Chemotherapie gemäss Protokoll COSS 86	0.6	**-1.4**	**-1.2**
AM	29	02.12.1993	Grosszelliges diffuses B-Zell-Lymphom, 2010	Chemotherapie gemäss ANHL01P1	-1	0.5	1.5
BL	23	12.05.1999	Abdominelles Neuroblastom, 2000	Therapie mit 13-Cis-Retinoinsäure, Radiotherapie	-0.9	**-1.3**	**-1.5**
RJ	41	24.12.1981	Akute Prä-B-Lymphoblastische Leukämie, 1983	Chemotherapie, Radiotherapie	1.3	-0.4	-0.6
ZJ	45	09.09.1977	Wilmstumor Stadium II, 1980	Chemotherapie, Konventionelle Bestrahlung	-0.5	**-2**	**-1.4**
SB	38	03.04.1984	Akute myeloische Leukämie, 1997	Chemotherapie gemäss Protokoll AML-BFM 93, Schädelbestrahlung	-0.3	-0.9	-0.2
MA	42	17.07.1980	Morbus Hodgkin, 1996	Chemotherapie, Radiotherapie	1.6	0.1	0.2
SS	31	11.04.1991	Osteosarkom proximale Tibia rechts, 1998	Chemotherapie	**-1.1**	-0.6	**-1.3**
KA	21	25.08.2001	Prä-B-ALL ohne ZNS-Befall, 2006	Chemotherapie	2.1	1	0.3

Empfehlungen (IGHG):

International Late Effects of Childhood Cancer Guideline Harmonization Group:

- **Z-Score ≤ -2 SD:**
  vertiefte Analyse der DXA Messung, DXA Verlauf in 2 Jahren, endokrinologische Abklärung, spezifisch osteologische, Lifestyle Beratung
- **Z-Score ≤ -1 und >-2 SD:**
  Endokrinologische Abklärung: GH und Hypogonadismus
  DXA Verlauf in 2 Jahren, im Verlauf je nach Dichte Abnahme, Lifestyle
- **Z-Score > -1 SD:**
  Lifestyle Beratung (Bewegung: Axiale Belastung, Nikotinkarenz, Alkoholreduktion, Vitamin D und Calcium Zufuhr, Normgewicht)

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Fragen und Diskussion:

INSELGRUPPE

Vielen Dank für die Aufmerksamkeit.

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