

Supplemental Table S1: Inclusion and exclusion criteria

Every patient has to fulfill the following inclusion criteria :
<ul style="list-style-type: none">• patients with a diagnosis of a chronic inflammatory rheumatic disease• patients who have/had already a glucocorticoid therapy, or patients in which the implementation of a new long-term GC therapy is expected• patients who, according to the DVO guidelines (see Supplemental Box 2), attend our osteoporosis and bone metabolism outpatient consultation hours or are referred by the hospital wards of the Charité for diagnosis, treatment or follow-up• capability to understand the patient information• consent to participation in the project and storage of data
If any of the following exclusion criteria is true, the patient must not be included in this study:
<ul style="list-style-type: none">• postmenopausal women without an inflammatory rheumatic disease• alcohol, medication and/or drug addiction• severe psychiatric diseases limiting the comprehension of the project plan and the study protocol (persons incapable of giving informed consent)• pregnant and lactating patients• patients incapable of giving informed consent for any reason• prisoners and all persons who are committed to an institution due to an official or judicial order

Supplemental Table S2: Medically pre-selected variables considered for the linear regression model on T-scores. Variables excluded from analysis due to >30% missing values are shown in italic font; exceptions were ALT (31.0% missings), alkaline phosphatase (32.1%), and deoxypyridinoline (34.0%). Disease specific scores were only included for subgroup analyses of RA patients.

Level of agreement		valid	
		n	%
known	Age at inclusion	1066	100.0
	Sex	1066	100.0
	BMI	1066	100.0
	Bisphosphonate	1066	100.0
	Teriparatide	1066	100.0
	Denosumab	1066	100.0
	Menopause	1058	99.2
highly expected	GC current	1066	100.0
	GC duration (years)	868	81.4
	GC, cumulative dose (g)	928	87.1
	disease duration (years)	1046	98.1
	<i>CDAI* (only RA)</i>	72	16.6
	<i>DAS28(ESR)* (only RA)</i>	245	56.5
	<i>DAS28(CRP)* (only RA)</i>	402	92.6
	<i>SDAI* (only RA)</i>	68	15.7
	NSAIDs	1066	100.0
	bDMARD	1066	100.0
	csDMARD	1066	100.0
	tsDMARDs	1066	100.0
	need for low level care support	933	87.5
	Family history of osteoporosis	776	72.8
	Family history of osteoporotic fractures	766	71.9
	Vitamin D supplementation	1066	100.0
	Daily calcium intake	1055	99.0
	Alcohol intake	1051	98.6
	Smoking	1058	99.2
	Smoking, pack-years	932	87.4
	Sun exposure	1052	98.7
	History of recurrent falls	1061	99.5
	Vertebral (low impact) fractures	1066	100.0
	Non-vertebral (low impact) fractures	1066	100.0
	25(OH)VitD (nmol/l)	943	88.5
	Vitamin D deficiency (<50 nmol/L)	943	88.5
	HAQ	1028	96.4

weakly expected	CRP (mg/l)	926	86.9
	PPI	1066	100.0
	Antidiabetics	1066	100.0
	Folic acid	1066	100.0
	Antidepressants	1066	100.0
	L-thyroxine	1066	100.0
	Renal insufficiency	1066	100.0
	Diabetes mellitus (type I or II)	1066	100.0
	Gout/ hyperuricaemia	1066	100.0
	Hyperthyroidism	1066	100.0
	Calcium supplementation	1066	100.0
	<i>Bone specific alkaline phosphatase (ug/l)</i>	734	68.9
	<i>Osteocalcin (ng/ml)</i>	527	49.4
	Parathyroid hormone (ng/l)	897	84.1
	Urinary deoxypyridinoline (nmol/l)	704	66.0
	<i>Chloride (mmol/l)</i>	236	22.1
	Alkaline phosphatase (U/l)	724	67.9
	ALT (U/l)	736	69.0
	AST (U/l)	696	65.3
	<i>Phosphate (mmol/l)</i>	336	31.5
	<i>ESR (mm/h)</i>	391	36.7
	Calcium (mmol/l)	989	92.8
	Gamma-GT (U/l)	791	74.2
	<i>Uric acid (mg/dl)</i>	458	43.0
	Creatinine (Jaffe) (mg/dl)	995	93.3
	Regular physical exercise	1041	97.7
	ACPA* (<i>only RA</i>)	306	70.5

* RA-specific activity scores/ biomarker were only considered for RA patients.

BMI *body mass index*; GC *glucocorticoids*; RA *rheumatoid arthritis*; CDAI *clinical disease activity index*; DAS28 *disease activity score-28*; ESR *erythrocyte sedimentation rate*; NSAIDs *non-steroidal anti-inflammatory drugs*; bDMARD *biological disease-modifying antirheumatic drugs*; csDMARD *conventional synthetic disease-modifying antirheumatic drugs*; tsDMARD *targeted synthetic disease-modifying antirheumatic drugs*; HAQ *health assessment questionnaire*; CRP *C-reactive protein*; PPI *proton-pump inhibitors*; ALT *alanine aminotransferase*; AST *aspartate aminotransferase*; Gamma-GT *gamma-glutamyltransferase*; ACPA *anti-citrullinated protein antibody*

Supplemental Table S3: The impact of seropositivity for anti-citrullinated protein antibody (ACPA)/rheumatoid factor (RF) on bone mineral density (BMD; given as lowest (minimum = min.) T-Score) in multivariable linear regression models for RA patients described as four combinations: i) positive ACPA status, ii) positive RF status, defined as either IgA or IgM positivity; iii) double positive, defined as both positive ACPA and RF status; and iv) double negative, defined as both negative ACPA and RF status. Shown are regression coefficients β and respective 95% confidence intervals.

All patients	Min. T-Score			Min. lumbar T-Score			Min. T-Score femoral neck		
	Reg. coefficient (95%CI)	<i>p</i> -value		Reg. coefficient (95%CI)	<i>p</i> -value		Reg. coefficient (95%CI)	<i>p</i> -value	
ACPA positive	0.064 (-0.259;0.386)	0.696		0.147 (-0.315;0.608)	0.531		0.096 (-0.186;0.378)	0.503	
RF positive	-0.026 (-0.353;0.301)	0.873		-0.057 (-0.580;0.465)	0.826		0.002 (-0.285;0.288)	0.992	
Double positive	-0.009 (-0.296;0.277)	0.948		0.083 (-0.389;0.554)	0.726		0.013 (-0.252;0.278)	0.922	
Double negative	-0.074 (-0.524;0.376)	0.741		0.030 (-0.559;0.618)	0.920		-0.121 (-0.476;0.233)	0.500	

Supplemental Table S4: Multivariable linear regression. Factors are sorted by descending number and then average strength of association. Variables with at least one significant impact in multivariable linear regression of the lowest (minimum = min.) T-Score at I) any site, II) lumbar spine (L1-L4) and III) right and left femoral neck in **a)** all patients and **b)** in patients with RA. **c)** lists results of a sensitivity analysis excluding patients on specific antiosteoporosis drugs (bisphosphonates and denosumab). Shown are regression coefficients β and respective 95% confidence intervals. Significant impact factors are highlighted in bold. For a complete set of considered variables see **Supplemental Table S2**.

a)

All patients	I) Min. T-Score			II) Min. lumbar T-Score			III) Min. T-Score femoral neck		
	Reg. coefficient (95%CI)	<i>p</i> -value		Reg. coefficient (95%CI)	<i>p</i> -value		Reg. coefficient (95%CI)	<i>p</i> -value	
BMI	0.070 (0.058;0.082)	<0.001		0.067 (0.049;0.085)	<0.001		0.069 (0.057;0.081)	<0.001	
Bisphosphonates	-0.451 (-0.644;-0.258)	<0.001		-0.490 (-0.774;-0.206)	0.001		-0.415 (-0.605;-0.224)	<0.001	
Alkaline phosphatase (Units/l)	-0.005 (-0.008;-0.002)	0.001		-0.008 (-0.012;-0.004)	<0.001		-0.004 (-0.007;-0.002)	0.002	
Menopause	-0.436 (-0.696;-0.177)	0.001		-0.555 (-0.925;-0.185)	0.003		-0.349 (-0.599;-0.100)	0.006	
Proton pump inhibitors	-0.179 (-0.304;-0.054)	0.005		-0.342 (-0.525;-0.159)	<0.001		-0.138 (-0.260;-0.016)	0.027	
Gamma-GT (Units/l)	0.002 (0.001;0.004)	0.007		0.003 (0.001;0.005)	0.015		0.002 (0.000;0.004)	0.033	
Age (years)	-0.012 (-0.018;-0.006)	<0.001		-0.007 (-0.016;0.001)	0.097		-0.015 (-0.021;-0.009)	<0.001	
Male sex	-0.447 (-0.726;-0.169)	0.002		-0.222 (-0.619;0.175)	0.273		-0.445 (-0.713;-0.176)	0.001	
Current GC dose (mg/day)	0.003 (0.001;0.005)	0.004		0.001 (-0.002;0.004)	0.382		0.003 (0.001;0.005)	0.006	
HAQ-Score	-0.126 (-0.226;-0.026)	0.014		-0.065 (-0.215;0.086)	0.399		-0.165 (-0.264;-0.066)	0.001	
NSAIDs	0.113 (-0.033;0.259)	0.130		0.175 (-0.038;0.387)	0.107		0.181 (0.038;0.324)	0.013	
Denosumab	-0.417 (-0.784;-0.051)	0.026		-0.421 (-0.960;0.118)	0.126		-0.219 (-0.574;0.137)	0.228	
Current GC dose \geq 5mg/day	-0.093 (-0.224;0.038)	0.162		-0.105 (-0.296;0.086)	0.281		-0.129 (-0.257;-0.001)	0.049	
Prior non-vertebral fracture	-0.427 (-0.903;0.050)	0.079		0.200 (-0.508;0.909)	0.580		-0.526 (-0.990;-0.063)	0.026	
Prior vertebral fracture	-0.393 (-0.773;-0.012)	0.043		0.008 (-0.534;0.549)	0.978		-0.340 (-0.709;0.029)	0.071	
Diabetes (Type I or II)	0.103 (-0.150;0.355)	0.426		0.411 (0.031;0.791)	0.034		-0.027 (-0.274;0.220)	0.830	
Calcium supplementation	-0.089 (-0.370;0.193)	0.537		-0.457 (-0.858;-0.056)	0.026		0.028 (-0.249;0.305)	0.843	
Sun exposure (>30 min/day)	0.034 (-0.090;0.159)	0.591		0.027 (-0.155;0.210)	0.768		0.122 (0.001;0.242)	0.048	

b)

RA patients	I) Min. T-Score			II) Min. lumbar T-Score			III) Min. T-Score femoral neck		
	Reg. coefficient (95%CI)		<i>p</i> -value	Reg. coefficient (95%CI)		<i>p</i> -value	Reg. coefficient (95%CI)		<i>p</i> -value
BMI	0.054	(0.035;0.073)	<0.001	0.044	(0.014;0.074)	0.004	0.057	(0.038;0.076)	<0.001
Alkaline phosphatase (U/l)	-0.004	(-0.008;0.000)	0.041	-0.007	(-0.013;0.000)	0.039	-0.005	(-0.009;-0.001)	0.022
Age (years)	-0.025	(-0.036;-0.014)	<0.001	-0.016	(-0.032;0.001)	0.065	-0.028	(-0.039;-0.018)	<0.001
Current GC dose > 5 mg/day	-0.487	(-0.850;-0.124)	0.009	-0.772	(-1.314;-0.230)	0.005	-0.332	(-0.677;0.014)	0.060
Male sex	-0.582	(-1.072;-0.093)	0.020	-0.709	(-1.446;0.029)	0.060	-0.526	(-0.990;-0.062)	0.026
Menopause	-0.546	(-1.000;-0.091)	0.019	-0.958	(-1.634;-0.283)	0.005	-0.302	(-0.731;0.126)	0.167
Bisphosphonates	-0.405	(-0.697;-0.113)	0.007	-0.298	(-0.758;0.162)	0.204	-0.414	(-0.698;-0.131)	0.004
Disease duration (years)	0.017	(0.002;0.032)	0.030	0.014	(-0.009;0.037)	0.223	0.014	(-0.001;0.029)	0.062
Sun exposure (>30 min/day)	0.166	(-0.031;0.364)	0.098	0.146	(-0.159;0.452)	0.348	0.219	(0.031;0.406)	0.022
Teriparatide	-1.242	(-2.729;0.244)	0.101	-1.028	(-3.246;1.191)	0.364	-1.514	(-2.931;-0.097)	0.036
CRP (mg/l)	-0.008	(-0.017;0.000)	0.051	-0.005	(-0.018;0.008)	0.474	-0.008	(-0.016;0.000)	0.050
Denosumab	-0.626	(-1.220;-0.032)	0.039	-0.466	(-1.401;0.468)	0.328	-0.324	(-0.892;0.244)	0.263

c) Sensitivity analysis: Exclusion of patients with denosumab, bisphosphonates or teriparatide.

All patients (after exclusion of patients with denosumab, bisphosphonates or teriparatide)	I) Min. T-Score			II) Min. lumbar T-Score			III) Min. T-Score femoral neck		
	Reg. coefficient (95%CI)	<i>p</i> -value		Reg. coefficient (95%CI)	<i>p</i> -value		Reg. coefficient (95%CI)	<i>p</i> -value	
BMI	0.073	(0.060;0.086)	<0.001	0.069	(0.051;0.088)	<0.001	0.070	(0.057;0.083)	<0.001
Age (years)	-0.012	(-0.019;-0.005)	<0.001	-0.007	(-0.017;0.002)	0.132	-0.015	(-0.021;-0.008)	<0.001
Menopause	-0.481	(-0.755;-0.208)	0.001	-0.620	(-1.000;-0.239)	0.001	-0.408	(-0.675;-0.142)	0.003
Prior vertebral fracture	-0.848	(-1.384;-0.312)	0.002	-0.848	(-1.586;-0.110)	0.024	-0.642	(-1.165;-0.119)	0.016
Male sex	-0.463	(-0.757;-0.170)	0.002	-0.279	(-0.690;0.132)	0.183	-0.467	(-0.754;-0.181)	0.001
Alkaline phosphatase (Units/l)	-0.005	(-0.008;-0.001)	0.005	-0.007	(-0.011;-0.003)	<0.001	-0.004	(-0.007;-0.001)	0.007
Current GC dose (mg/day)	0.003	(0.001;0.005)	0.007	0.001	(-0.002;0.004)	0.539	0.003	(0.001;0.005)	0.006
Proton pump inhibitors	-0.173	(-0.311;-0.036)	0.013	-0.338	(-0.536;-0.140)	0.001	-0.134	(-0.269;0.001)	0.051
Gamma-GT (Units/l)	0.002	(0.000;0.004)	0.027	0.002	(0.000;0.005)	0.066	0.002	(0.000;0.003)	0.055
Calcium supplementation	-0.560	(-1.091;-0.028)	0.039	-0.662	(-1.424;0.100)	0.089	-0.570	(-1.097;-0.044)	0.034
Current GC dose ≥ 5mg/day	-0.138	(-0.284;0.007)	0.063	-0.090	(-0.299;0.118)	0.394	-0.153	(-0.296;-0.010)	0.036
HAQ-Score	-0.102	(-0.216;0.011)	0.077	-0.095	(-0.259;0.070)	0.258	-0.147	(-0.260;-0.034)	0.011
NSAIDs	0.098	(-0.059;0.255)	0.223	0.167	(-0.056;0.391)	0.143	0.168	(0.014;0.323)	0.033
Sun exposure (>30 min/day)	0.079	(-0.057;0.214)	0.254	0.064	(-0.130;0.257)	0.518	0.146	(0.014;0.278)	0.030
Diabetes (Type I or II)	0.104	(-0.185;0.394)	0.480	0.478	(0.059;0.897)	0.025	-0.062	(-0.348;0.224)	0.669

Supplemental Table S5: Multivariable linear regression with backward selection on the variables which have emerged from the data mining regression for the three T-scores (compare **Supplemental Table S4a**). Coefficients of the variables which were selected into the respective model are highlighted in bold font; only diabetes and calcium supplementation were not confirmed for the lumbar T-score model.

All patients	I) Min. T-Score			II) Min. lumbar T-Score			III) Min. T-Score femoral neck		
	Reg. coefficient (95%CI)	<i>p</i> -value		Reg. coefficient (95%CI)	<i>p</i> -value		Reg. coefficient (95%CI)	<i>p</i> -value	
BMI	0.071 (0.060;0.082)	<0.001		0.066 (0.050;0.082)	<0.001		0.072 (0.061;0.083)	<0.001	
Bisphosphonates	-0.463 (-0.652;-0.275)	<0.001		-0.561 (-0.830;-0.292)	<0.001		-0.390 (-0.572;-0.207)	<0.001	
Alkaline phosphatase (Units/l)	-0.005 (-0.008;-0.002)	<0.001		-0.007 (-0.010;-0.003)	<0.001		-0.004 (-0.007;-0.002)	0.001	
Menopause	-0.440 (-0.688;-0.192)	0.001		-0.542 (-0.724;-0.359)	<0.001		-0.370 (-0.610;-0.131)	0.002	
Proton pump inhibitors	-0.221 (-0.341;-0.101)	<0.001		-0.375 (-0.546;-0.203)	<0.001		-0.148 (-0.267;-0.030)	0.014	
Gamma-GT (Units/l)	0.002 (0.001;0.004)	0.005		0.002 (0.000;0.005)	0.027		0.002 (0.000;0.004)	0.012	
Age (years)	-0.012 (-0.018;-0.007)	<0.001					-0.017 (-0.022;-0.012)	<0.001	
Male sex	-0.413 (-0.674;-0.152)	0.002					-0.435 (-0.687;-0.183)	0.001	
Current GC dose (mg/day)	0.002 (0.000;0.004)	0.005					0.003 (0.001;0.005)	0.002	
HAQ-Score	-0.137 (-0.217;-0.058)	0.001					-0.196 (-0.277;-0.115)	<0.001	
NSAIDs							0.190 (0.053;0.327)	0.007	
Denosumab	-0.537 (-0.895;-0.179)	0.003							
Current GC dose ≥ 5mg/day							-0.144 (-0.266;-0.023)	0.020	
Prior non-vertebral fracture							-0.232 (-0.360;-0.104)	<0.001	
Prior vertebral fracture	-0.322 (-0.573;-0.072)	0.012							
Diabetes (Type I or II)				0.215 (-0.054;0.484)	0.118				
Calcium supplementation				-0.006 (-0.177;0.165)	0.946				
Sun exposure (>30 min/day)							0.142 (0.027;0.256)	0.015	

Supplemental Box S1**Why are anti-inflammatory effects of low-dose glucocorticoids suggested to compensate – at least in part – for their detrimental effects on bone mineral density in patients with rheumatoid arthritis?**

1. There is no doubt that glucocorticoids applied in higher doses and for a longer time have deleterious effects on bone (Buttgereit, *Nat Rev Rheum* (2020); Rizzoli et al. *Nat Rev Rheum* (2015). They certainly can induce early and sometimes rapid bone loss which increases fracture risk.

2. Equally well known, however, is the fact that inflammation promotes bone resorption (Hardy and Cooper, *J. Endocrinol* 2009). Therefore, inflammation associated with iRMDs is an important determinant of bone fragility, as well (Briot et al., *Osteoporos. Int.* (2017); Ozen et al. *Ann. Rheum. Dis.* (2019).

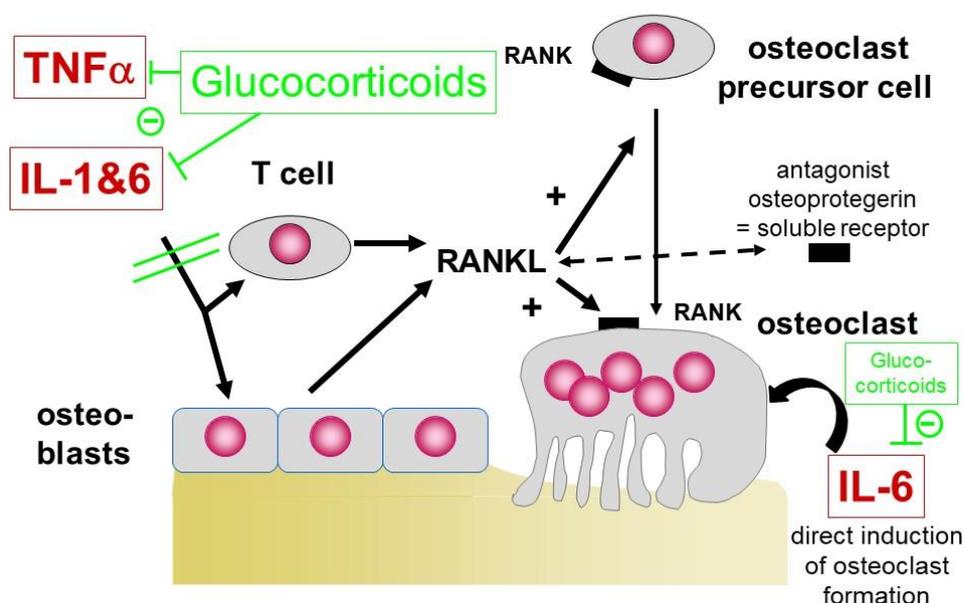
3. Excellent publications have recently reviewed the body of evidence how inflammation mechanistically skews the process of bone remodeling toward resorption. (Briot et al. *Osteoporosis Int.* 2017; Epsley et al. *Front Physiol*, 2021). The main message is that inflammatory mediators (including TNF α , interleukins 1 and 6) and their related peptides interact with osteoblasts, osteoclasts, and other immune cells to alter the expression of RANK and RANKL.

4. In rheumatoid arthritis, synovial macrophages produce inflammatory cytokines such as TNF- α , IL-1, and IL-6 which induce bone resorption, partly via increasing RANKL. Furthermore, RANKL is expressed in RA synovial fibroblasts, thereby promoting differentiation of synovial macrophages into osteoclasts (Epsley et al. *Front Physiol*, 2021; Bruno et al. *Front Med*, 2021; Llorente et al. *Front Med*, 2021).

5. Glucocorticoids – used in synergy with DMARDs - are capable of inducing strong immunosuppressive and anti-inflammatory on immune cells, tissues and organs (Strehl, Buttgereit et al. *Front Immunology*, 2019). An important underlying mechanism for these effects is that glucocorticoids influence cytokine production. In this context, it is well known that they reduce inflammation by downregulating the synthesis of proinflammatory mediators such as TNF- α , IL-1, and IL-6. (Stahn & Buttgereit *Nat Clin Pract Rheumatol.* 2008; Hardy et al, *Nat Rev Rheum.* 2020)

6. The following figure illustrates the above information. It highlights important mechanisms by which glucocorticoids lead to attenuation of inflammation-induced bone resorption and thereby may compensate - at least in part - for its detrimental effects on bone mineral density in patients with rheumatoid arthritis.

Key mechanisms of glucocorticoid-mediated inhibition of inflammation-induced bone resorption



7. This overall assessment is considered the current and state-of-the-art view as is evidenced by the following examples (selection of review articles, each citing respective original articles):

- a. "Prior and current exposure to glucocorticoids increases the risk of fracture and bone loss. A key point is that the underlying inflammation for which glucocorticoids are used also plays a role in bone fragility, as there is a strong relationship between inflammatory cells and bone cells. Rheumatoid arthritis doubles the risk of hip and vertebral fractures regardless of the use of glucocorticoids." (Dougados, *Curr Opin Rheumatol* 2016)
- b. "However, also the underlying inflammatory rheumatic disease is associated with the increased bone loss and fracture risk due to the chronic inflammation itself, and due to disability/immobility caused by active disease or joint destruction. The rapid and strong anti-inflammatory effect of GCs in patients with rheumatoid arthritis seem to balance the negative effects of GCs on bone in the early, active phase of the disease."
(Güler-Yüksel et al. *Calcified Tissue International* 2018)
- c. "In fact, treatment of chronic inflammatory disease with glucocorticoids may have a beneficial effect on bone in some cases."
(Epsley et al. *Front Physiol*, 2021)
- d. "Regarding therapeutic agents for RA, GC therapy deserves a special mention. Indeed, GCs suppress osteoblast bone formation, which is associated with a rapid suppression of procollagen type 1 N-terminal pro-peptide (PINP, a biomarker of bone formation), leading to an early reduction in trabecular bone. Interestingly, GCs also suppress osteoclast activity, certainly increased in active arthritis patients, which might have a protective effect in some cases. In fact, some studies show that GC use in RA could even be beneficial, with a low impact on BMD due to their anti-inflammatory and suppressive effect on arthritis activity.

Therefore, low doses of GCs could provide protection from inflammatory bone loss during polyarthritis flares and might counteract their unfavorable effects on bone resorption leading to neutral or even positive net skeletal balance). The cumulative GC dose (long-term or high dose) as well as the continuous vs. alternative GC dosage strategy are correlated with an increased risk of fracture or a reduced BMD in juxta-articular bone, spine and femoral neck. In addition, GCs induce muscle wasting which secondarily increases the risk of falls and fractures. However, a daily dose below 5 mg may have a relatively small impact on BMD in RA patients.” **(Llorente et al. Front Med, 2021)**

Supplemental Box S2

Indication for osteoporosis screening in this patient population were according to the German Osteoporosis Guidelines as provided by the Dachverband Osteologie (DVO): <https://dv-osteologie.org/osteoporose-leitlinien>

Here is short and focused summary of the screening rules:

Screening is recommended by the DVO if the estimated 10-year risk for vertebral and femoral fractures is 20% or higher (or was as high in the past two years). This includes both males and females regardless of age and is applicable also if the structured screening is expected to yield a therapeutic consequence.

Generally, all men above 80 years and women above 70 years are recommended to undergo an osteoporosis screening. Furthermore, all patients from the age of 50 years onwards with a history of fragility fractures or a glucocorticoid therapy with a daily dose of ≥ 7.5 mg per day for 3 months or longer.

The guideline also recommends a structured osteoporosis screening in postmenopausal women (≥ 50 years of age) and men (≥ 60 years) with following risk factors:

Use of medications linked with osteoporosis (oral glucocorticoids > 2.5 mg/day for more than 3 months, proton pump inhibitors, opioids, anti-epileptic drugs, antidepressants, inhaled glucocorticoids, aromatase-inhibitors and medications linked to a higher risk of falls)

- low impact vertebral fracture (Genant 2°) or multiple vertebral fractures (Genant 1°)
- clinically relevant low-impact vertebral fracture
- low-impact non-vertebral fractures
- rheumatic diseases such as rheumatoid arthritis, ankylosing spondylitis and systemic lupus erythematoses
- father or mother with a history of femoral fractures
- endocrine diseases such as hyperthyroidisms, hypogonadism, diabetes type 1 or 2, factitious hyperthyroidism, (sub-)clinical hyperthyroidisms, Cushing syndrome
- neurologic/psychiatric diseases such as epilepsies, depression and others
- other diseases like heart failure
- active smoking or alcohol consumption