Altres Efectes Adversos Sistèmics dels Glucocorticoides

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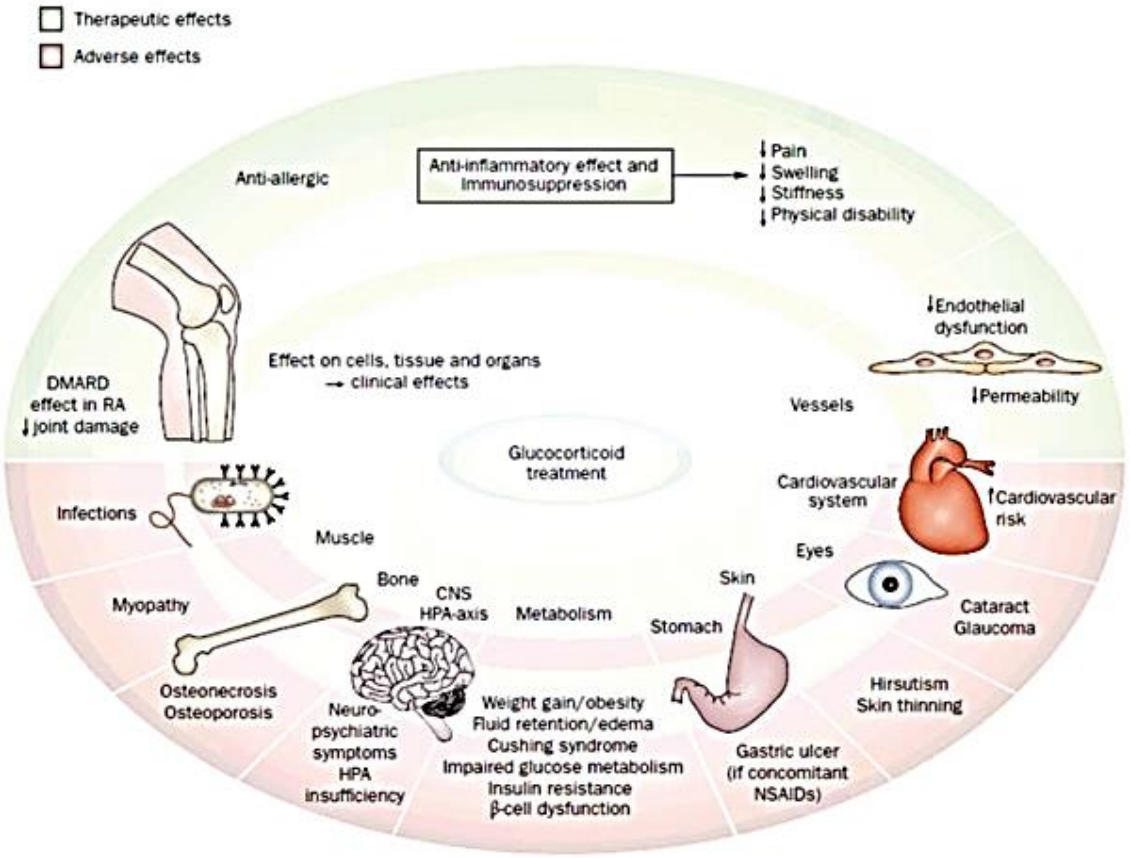
Introducció



Effects of glucocorticoids. Glucocorticoid therapy is associated with both beneficial effects (upper part) and adverse effects (lower part). CNS, central nervous system; DMARD, disease-modifying antirheumatic drug; HPA, hypothalamic-pituitary-adrenal; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis. Adapted from [127].

Major side effects associated with glucocorticoid therapy

Dermatologic and soft tissue
Skin thinning and purpura
Cushingoid appearance
Alopecia
Acne
Hirsutism
Striae
Hypertrichosis
Eye
Posterior subcapsular cataract
Elevated intraocular pressure/glaucoma
Exophthalmos
Cardiovascular
Arrhythmias (with intravenous pulse therapy)
Hypertension
Perturbations of serum lipoproteins
Premature atherosclerotic disease
Gastrointestinal
Gastritis
Peptic ulcer disease
Pancreatitis
Steatohepatitis
Visceral perforation

Renal
Hypokalemia
Fluid volume shifts
Genitourinary and reproductive
Amenorrhea/infertility
Intrauterine growth retardation
Bone
Osteoporosis
Avascular necrosis
Muscle
Myopathy
Neuropsychiatric
Euphoria
Dysphoria/depression
Insomnia/akathisia
Mania/psychosis
Pseudotumor cerebri
Endocrine
Diabetes mellitus
Hypothalamic-pituitary-adrenal insufficiency
Infectious disease
Heightened risk of typical infections
Opportunistic infections
Herpes zoster

Table 3 Risks of GC-related AEs based on placebo-controlled studies and studies without control group*

Placebo-controlled studies

AE	*Dose range and application*	*Events/100 patient-years for GC users*	*Events/100 patient-years for GC-naive patients*
Osteoporosis	chronic medium dose	16	3
	intramuscular	2	0
Cardiovascular disease (ie, myocardial infarction)	chronic medium dose	0–1	0–1
	step-down	1	0
	intramuscular	0–1	0–1
Diabetes	chronic medium dose	0–3	0–1
	intramuscular	1	0
Weight gain	intramuscular	0	1
Renal dysfunction	chronic medium dose	1–6	0
	step-down	0–17	0–1
Peptic ulcer disease	chronic medium dose	1–4	0–2
Hypertension	chronic medium dose	3–28	0–19
	step-down	0	0
	intramuscular	4	1

Duru N, van der Goes MC, Jacobs JWG, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. 2013

TABLE 4. Two-year difference in costs (2001 USD) and number of deaths of glucocorticoid users and non-users when selected adverse events are not considered—results from Monte Carlo simulations

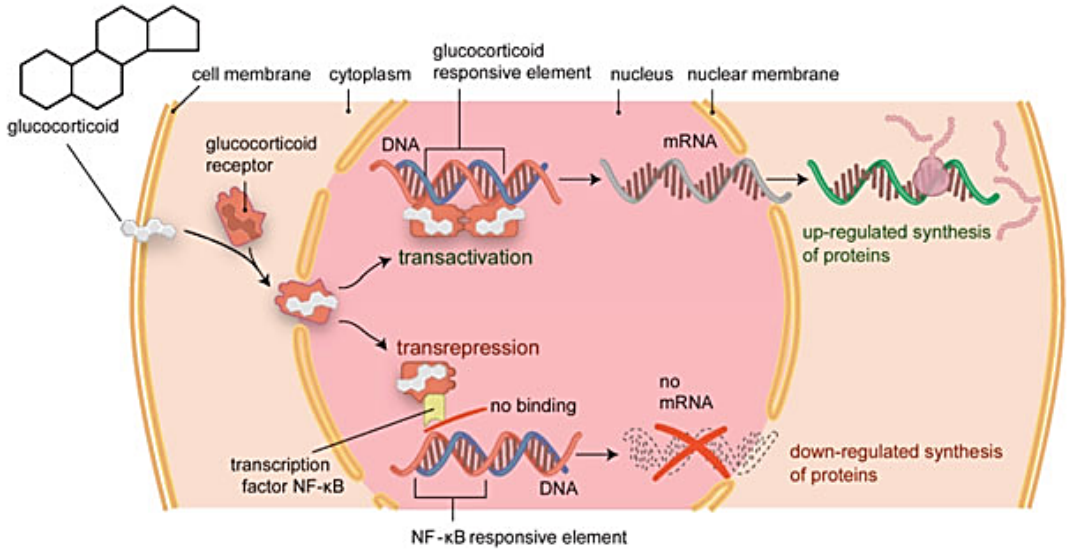
Adverse event not included	Cost in users	Δ[a]	G-ICF[b]	No of deaths in users	Δ[a]
Model without MI and stroke[c]					
Hip fracture (fx)	1021.0 (153.9)	407.8 (213.3)	1.42	0.038 (0.009)	0.006 (0.012)
Vertebral fx	1029.3 (147.6)	363.2 (212.8)	1.37	0.040 (0.009)	0.006 (0.012)
Pelvic fx	1094.1 (164.9)	400.0 (226.5)	1.41	0.040 (0.009)	0.006 (0.011)
GI complication	796.2 (157.4)	326.5 (189.2)	1.34	0.038 (0.009)	0.005 (0.012)
Pneumonia	953.2 (141.8)	401.3 (199.3)	1.41	0.020 (0.001)	0.001 (0.001)
UTI	1140.5 (166.8)	406.1 (250.6)	1.42	0.040 (0.009)	0.006 (0.011)
Cataract	1057.2 (136.4)	390.4 (225.2)	1.40	0.040 (0.009)	0.006 (0.012)
Hypertension	1018.6 (151.7)	421.4 (208.6)	1.43	0.040 (0.009)	0.006 (0.012)
Diabetes mellitus	1044.7 (223.6)	409.2 (223.6)	1.42	0.040 (0.009)	0.006 (0.012)
Model with MI and stroke[d]					
MI	1329.6 (176.9)	193.4 (303.6)	1.20	0.038 (0.007)	0.004 (0.012)
Stroke	1483.4 (177.1)	682.3 (236.8)	1.70	0.043 (0.009)	0.008 (0.012)
Hip fx	1546.6 (181.1)	393.3 (305.5)	1.40	0.043 (0.009)	0.005 (0.012)
Vertebral fx	1553.2 (174.8)	343.6 (302.0)	1.35	0.044 (0.009)	0.006 (0.012)
Pelvic fx	1621.8 (190.2)	386.3 (313.4)	1.40	0.045 (0.009)	0.006 (0.012)
GI complication	1322.0 (180.2)	308.2 (287.4)	1.32	0.042 (0.009)	0.005 (0.012)
Pneumonia	1483.0 (174.4)	386.6 (296.6)	1.40	0.025 (0.001)	0.001 (0.002)
UTI	1666.9 (189.8)	431.4 (310.8)	1.44	0.044 (0.009)	0.006 (0.012)
Cataract	1582.0 (189.0)	374.6 (310.3)	1.39	0.045 (0.009)	0.006 (0.012)
Hypertension	1556.3 (183.2)	403.9 (307.8)	1.42	0.044 (0.009)	0.006 (0.012)
Diabetes mellitus	1577.6 (186.3)	399.3 (309.8)	1.41	0.044 (0.009)	0.006 (0.012)

[a]Difference between glucocorticoid users and non-users.
[b]Glucocorticoid-attributable iatrogenic cost factor.
[c]The baseline cost of glucocorticoid users was $1142 (Δ = $445.4), and the number of deaths was 0.04 (Δ = 0.006).
[d]The baseline cost of glucocorticoid users was $1667 (Δ = $429.6), and the number of deaths was 0.045 (Δ = 0.006).

Pisu M et al. The cost of glucocorticoid-associated adverse events in rheumatoid arthritis. 2005

- Ús dels Corticoesteroids
  - Inflamatòries
  - Al·lèrgiques
  - Immunològiques
  - Neoplàstiques (hematològiques)
- EA: Pocs estudis de Causalitat (prospectius)
- EA: Influència d'altres factors:
  - Malaltia de base (naturalesa i severitat)
  - Tractaments concomitants
  - Dosi
  - Durada

Mecanisme d'Acció Genòmic



Genomic action of glucocorticoids. Glucocorticoid binds to the glucocorticoid receptor (GCR) in the cytoplasm. This complex migrates into the nucleus. Activation of transcription (transactivation) by binding of GCR-glucocorticoid complex dimers to glucocorticoid-responsive elements of DNA upregulates synthesis of regulatory proteins, thought to be responsible for metabolic effects and also some anti-inflammatory/ immunosuppressive effects. Interaction of GCR-glucocorticoid complex monomers with proinflammatory transcription factors, such as activator protein-1, interferon regulatory factor-3 and nuclear factor (NF)-κB, leads to inhibition of binding of these transcriptional factors to their DNA consensus sites (for NF-κB: NF-κB-responsive elements). The transcription of these proinflammatory transcription factors is thus repressed. This process is called transrepression and downregulates synthesis of predominantly inflammatory/immunosuppressive proteins. Adapted from [128].

Mecanisme Genòmic

- Transactivació: augment de l'expressió de proteïnes reguladores i proinflamatòries: Majoria d'Efectes Adversos:
  - Hiperglicèmia
  - Miopatia
- Transrepressió: disminució de la producción de proteïnes proinflamatòries: Majoria d'Efectes Terapèutics:
  - supressió eix hypotàlam-hipofisari-adrenal
- Transactivació + Transrepressió:
  - Osteoporosi

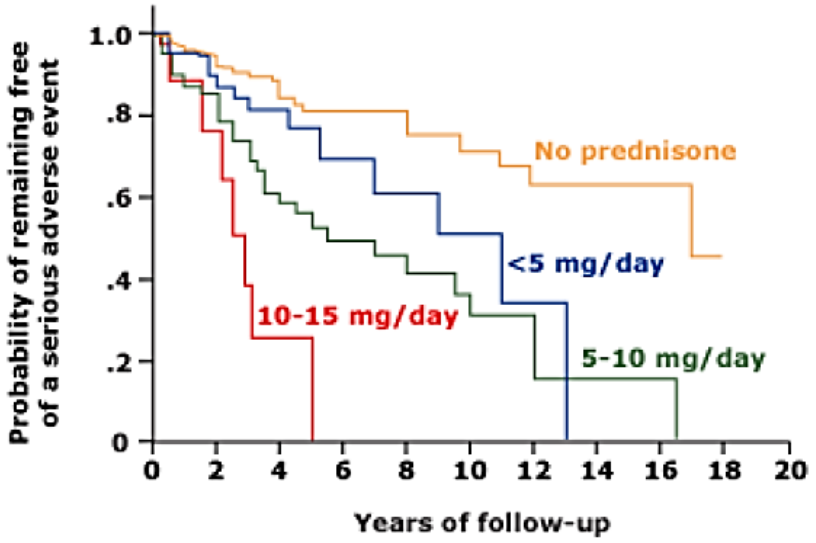
Mecanisme No-Genòmic

- Interaccions ràpides i inespecífiques amb membranes cel·lulars
- Efectes mediats per receptors citosòlics
- Interaccions específiques amb receptors de membrana

Ramamoorthy S et al. 2016. Vandevyver S et al. 2013. Sundahl N et al. 2015.

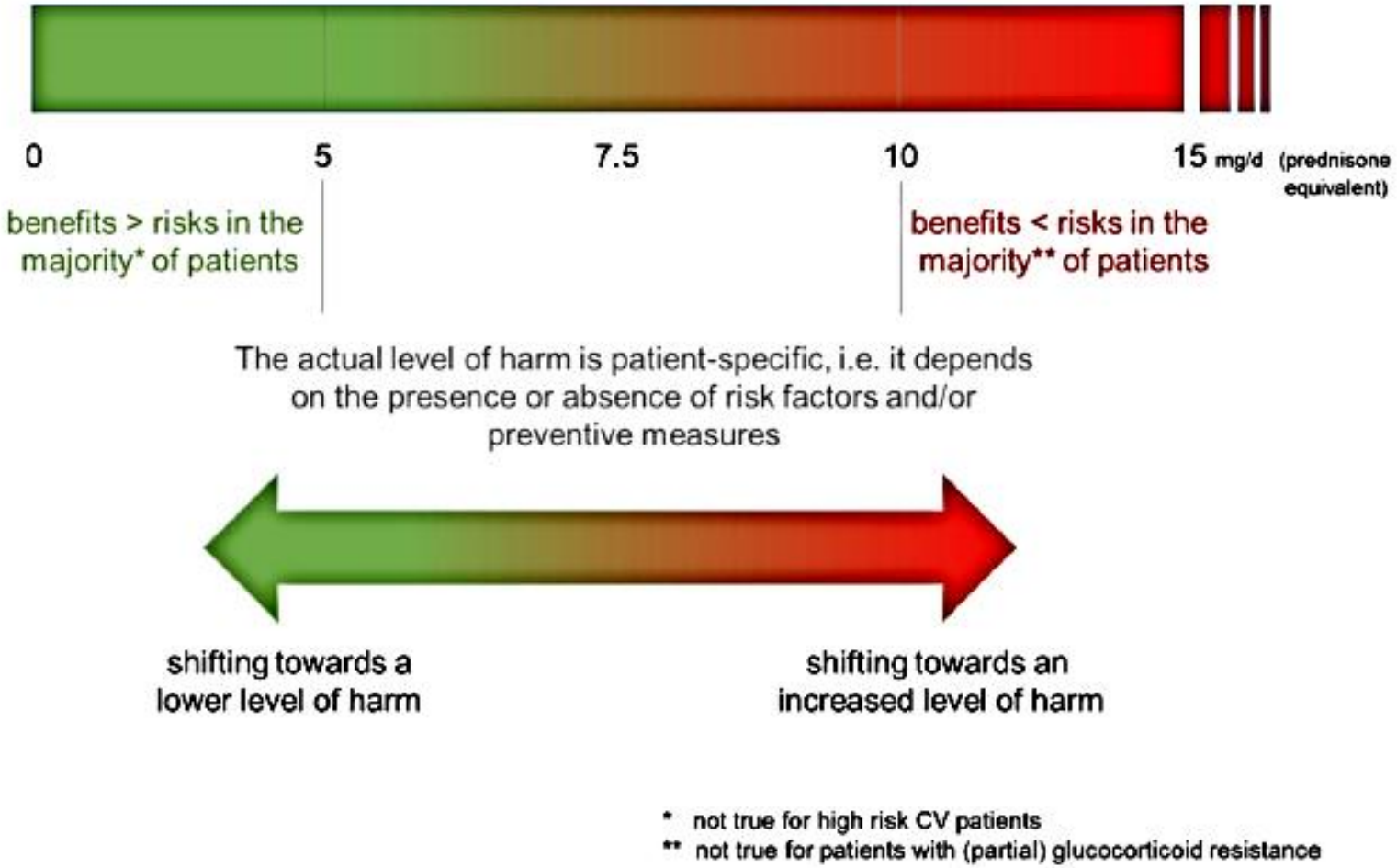
Efecte de la Dosi i Durada

Time course of steroid side effects



Survival curves demonstrating the time to development of the first serious adverse event (ie, the probability of remaining free of an adverse event) in patients with rheumatoid arthritis treated with no or different doses of prednisone. There is a clear dose-dependence of side effects: odds ratio 4.5 for 5 to 10 mg/day, and 32.3 for 10 to 15 mg/day.

Data from Saag, KG, Koehnke, R, Caldwell, JR, et al. Am J Med 1994; 96:115.



Strehl C et al. EULAR task force 2016.

Osteoporosi

- Forma més freqüent d'osteoporosi
- Fractures 30-50% (a sovint assimptomàtiques)
- Fractures Vertebrals:
  - Precoces 3-6 mesos (disminució ràpida de la DMO)
  - En dones amb DMO superiors que en dones amb osteoporosi post-menopàusica
- La fase de disminució ràpida de la DMO es segueix d'una fase de descens lent i progressiu

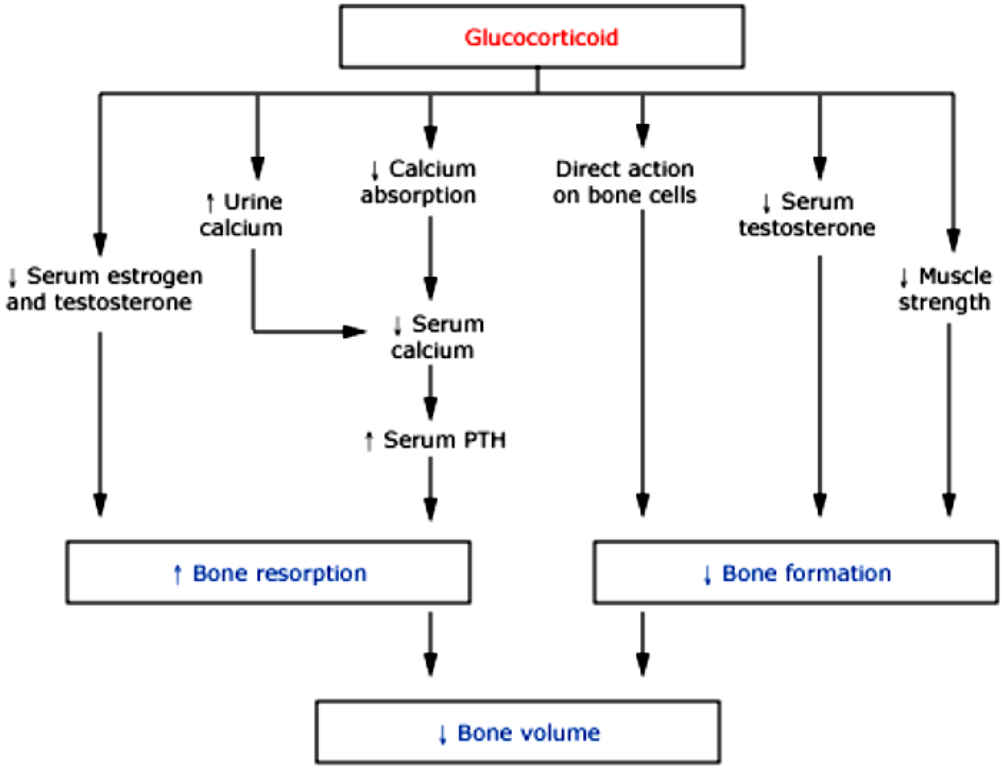
TABLE 3. RISK RATIO OF ANY FRACTURE AND 95% CIs ASSOCIATED WITH EVER USE OF CORTICOSTEROIDS ACCORDING TO AGE AND ADJUSTED FOR BMD

	Any fracture		*Osteoporotic fracture*		*Hip fracture*	
Age (years)	*Risk ratio**	*95% CI*	*Risk ratio*	*95% CI*	*Risk ratio*	*95% CI*
50	1.98	1.35–2.92	2.63	1.68–4.13	4.42	1.26–15.49
55	1.83	1.35–2.47	2.32	1.63–3.30	4.15	1.50–11.49
60	1.67	1.33–2.09	2.00	1.52–2.62	3.71	1.67–8.23
65	1.56	1.29–1.88	1.81	1.43–2.27	2.98	1.55–5.74
70	1.55	1.30–1.86	1.76	1.42–2.19	2.44	1.37–4.36
75	1.64	1.37–1.97	1.70	1.36–2.11	2.22	1.35–3.63
80	1.62	1.31–2.00	1.59	1.26–2.02	2.13	1.39–3.27
85	1.66	1.26–2.17	1.71	1.29–2.28	2.48	1.58–3.89
All ages	1.57	1.37–1.80	1.66	1.42–1.92	2.25	1.60–3.15
All ages†	1.53		1.61		2.13	

* Ever use vs. no use.
† Ever use vs. population risk.

Kanis JA et al. A Meta-Analysis of Prior Corticosteroid Use and Fracture Risk 2004

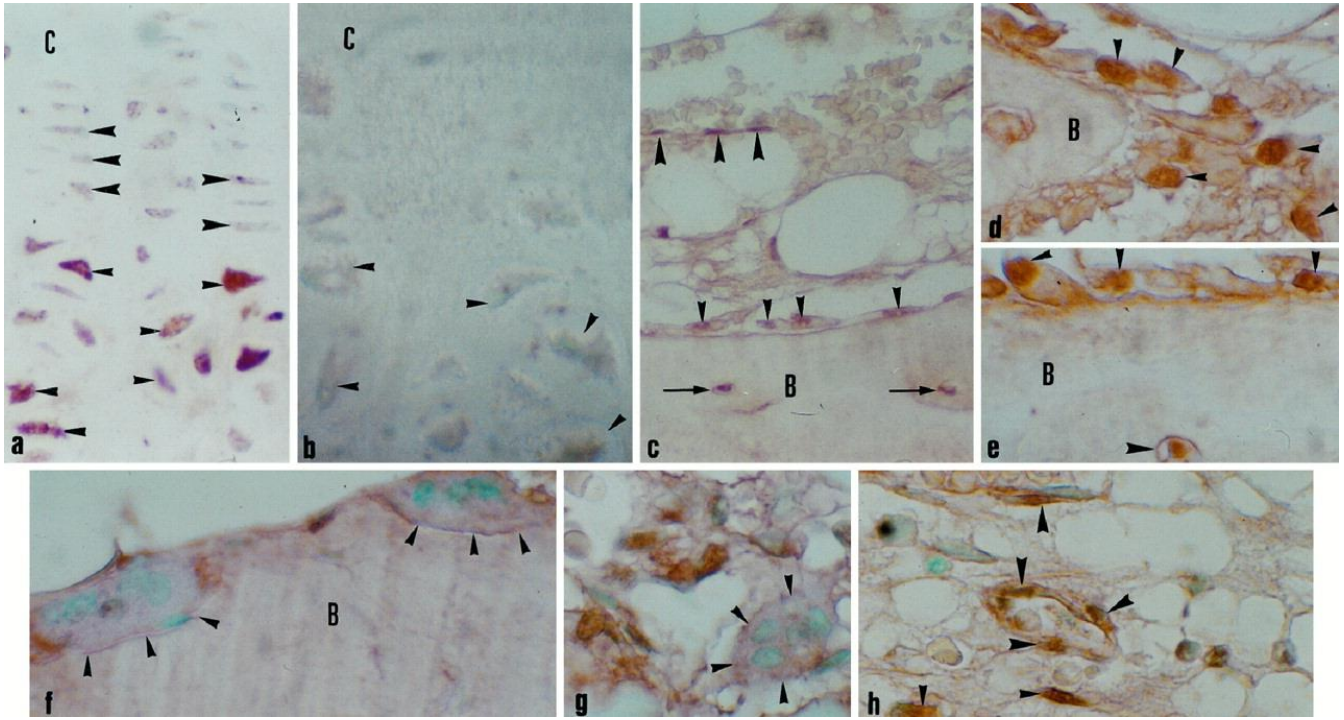
Glucocorticoid-induced osteoporosis: Mechanisms of bone loss



Schematic representation of the mechanisms of bone loss in patients with glucocorticoid-induced osteoporosis.

PTH: parathyroid hormone.

Adapted from Libanati CS, Baylink DJ. Prevention and treatment of glucocorticoid-induced osteoporosis: A pathogenetic perspective. Chest 1992; 102:1426.



EXPRESSIÓ RECEPTOR CITOPLASMÀTIC GLUCOCORTICOIDES
a i b. Cartílag: condròcits hipertròfics i alguns immadurs.
c. Zones Remodelat Ossi: osteoblastes i cèls. Endotelials
d i e. ídem magnificat
f i g. Zones Remodelat Ossi: no s'observen en osteoclastes
h. Vasos: Mononuclears i cèls. endotelials

Abu EO et al. 2000.

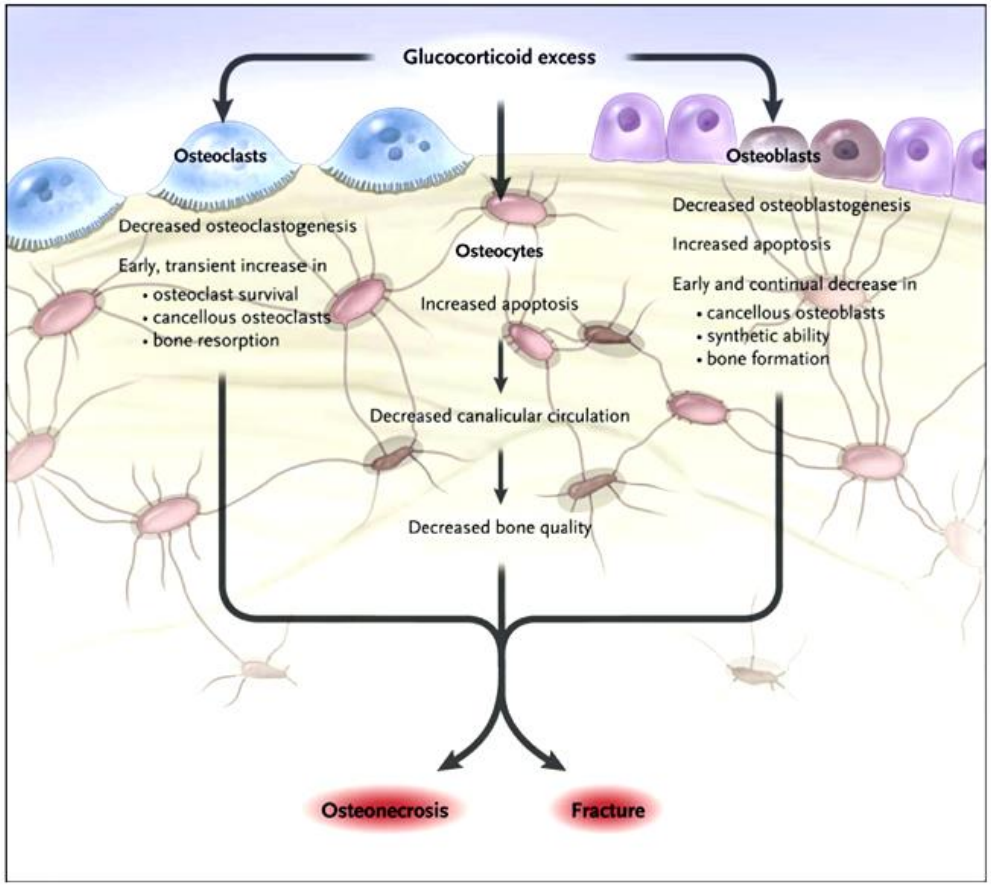


FIG 1. Direct effects of glucocorticoids on bone cells. Shown are the adverse skeletal changes that result from an excess of glucocorticoids and lead to osteoporosis and osteonecrosis. The *brown* condensed cells are apoptotic osteoblasts and osteocytes. Apoptotic osteocytes disrupt the osteocyte-lacunar-canalicular network. Reproduced with permission from Weinstein.[7]

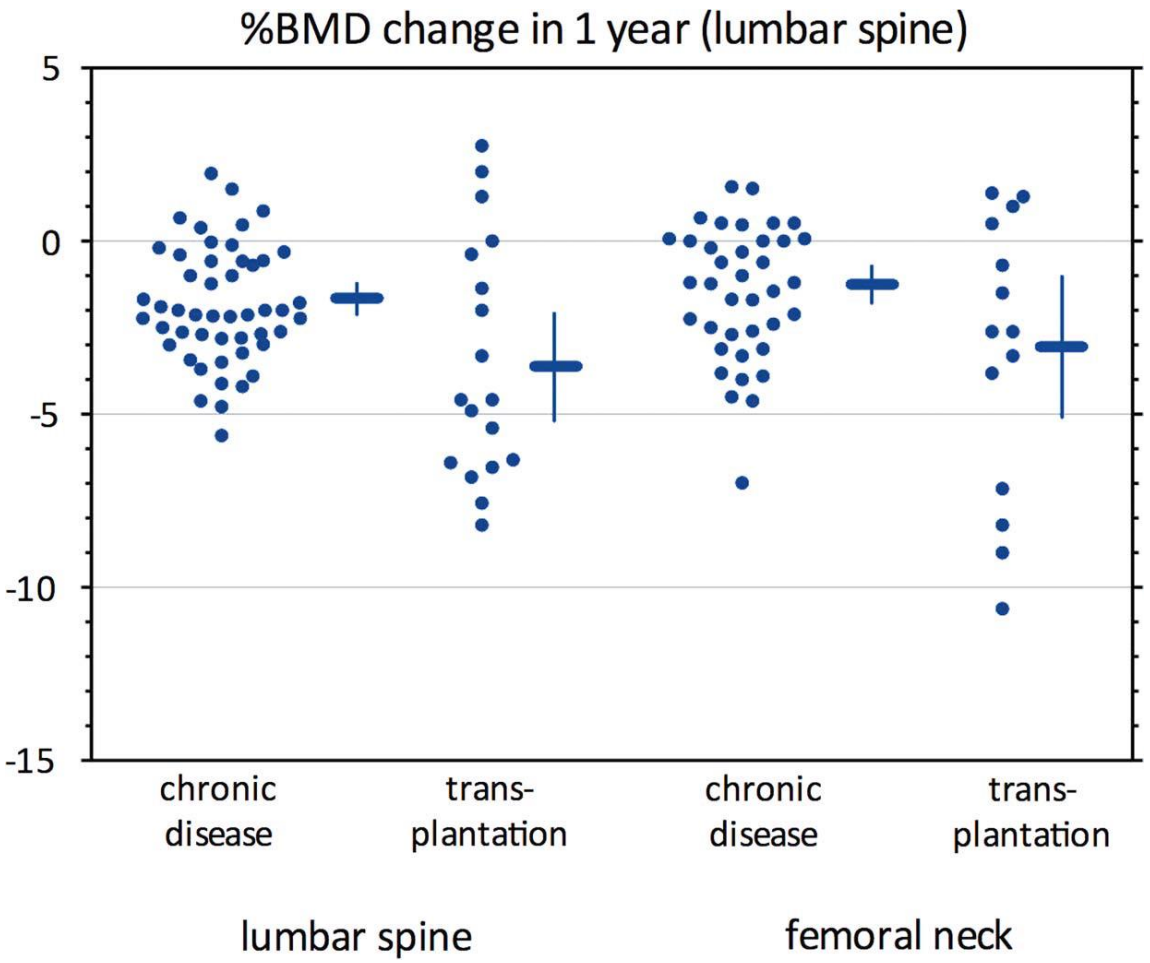
Buehring B et al. 2013.

Table 1 Characteristics of included studies

	Chronic Inflammatory disease		Transplantation	
Cohorts		49		18
RCT arms		34		9
Patients (n, n with follow-up)		1818, 1519		635, 571
Diagnosis	RA	313	Kidney	450
	SLE	200	Heart	78
	PMR	91	Lung	18
	Mixed	915	Liver	25
Women (%)		71		34
Mean age (years)		51		46
Starters (% patients)		32		87
Patients on Ca/D (%)		67		72
Mean GC dose (mg/day)		9.3		15.7
range		1.2–16.4		6.0–52.7
1–year change in BMD (% of baseline)				
Lumbar spine mean*		– 1.7		– 3.6
95% CI		–2.2 to –1.2		–5.2 to –2.0
Femoral neck mean*		– 1.3		– 3.1
95% CI		–1.8 to –0.7		–5.1 to –1.1

*All within-group changes, $p<0.001$.
BMD, bone mineral density; Ca/D, use of calcium or vitamin D; GC, glucocorticoids; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; RCT, randomised controlled trial; SLE, systemic lupus erythematosus.

Lems WF et al. One-year effects of glucocorticoids on bone density: a meta-analysis in cohorts on high and low dose therapy. 2016



Lems WF et al. One-year effects of glucocorticoids on bone density: a meta-analysis in cohorts on high and low dose therapy. 2016

Box 1
American College of Rheumatology (ACR) recommendations on counseling for lifestyle modification and assessment of patients starting on glucocorticoids at any dose with an anticipated duration greater than or equal to 3 months

Assessments

Fall risk assessment

Baseline dual x-ray absorptiometry

Serum 25-hydroxyvitamin vitamin D level

Baseline height

Assessment of prevalent fragility fractures

Consider radiographic imaging of the spine or vertebral fracture assessment for patients initiating or currently receiving prednisone greater than or equal to 5 mg/d or its equivalent

Recommendations

Weight-bearing activities

Smoking cessation

Avoidance of excessive alcohol intake (>2 drinks per day)

Nutritional counseling on calcium and vitamin D intake

Calcium intake (supplement plus oral intake) 1200–1500 mg/d

Vitamin D supplementation

Whittier X and Saag KG 2016

Table 2
Comparison of guidelines for prevention and treatment of GIOP for postmenopausal women and men more than 50 years of age

	ACR[8]	IOF-ECTS[57]
Bone density and/or FRAX score requiring treatment	Determination made based on FRAX and overall clinical risk incorporating BMD	BMD T-score and FRAX with country-specific thresholds
Minimum glucocorticoid dose and duration requiring treatment	Low risk: ≥7.5 mg/d for at least 3 mo[a] Medium risk: any dose for at least 3 mo use[b] High risk: any dose for at least 1 mo use[c]	≥7.5 mg/d for ≥3 mo
Other indications for treatment	—	Previous fracture Age ≥70 y
Calcium and vitamin D supplementation	Calcium 1200–1500 mg/d Vitamin D 800–000 IU/d	Recommended but doses not specified
Pharmacotherapy	Alendronate or risedronate for all low-risk, medium-risk, and high-risk patients Zoledronic acid for low-risk and medium-risk patients taking ≥7.5 mg/d and all high-risk patients Teriparatide for high-risk patients taking ≥5 mg/d for ≤1 mo or any dose used for >1 mo	Alendronate, etidronate, risedronate, zoledronic acid, and teriparatide all options

Abbreviations: ACR, American College of Rheumatology; IOF-ECTS, International Osteoporosis Foundation and the European Calcified Tissue Society.

[a] Low risk: FRAX less than 10% for 10-year major osteoporotic fracture.

[b] Medium risk: FRAX 10% to 20% for 10-year major osteoporotic fracture.

[c] High risk: FRAX greater than 20% for 10-year major osteoporotic fracture.

Whittier X and Saag KG 2016

Infeccions

- Augment dosi depenent
- Efectes dels GC en el sistema immunològic
- Neutrofília
- Impacte en vacunacions (virus vius: triple vírica, varicela)

- Antagonisme diferenciació macròfags
- Supressió producció de IL 1, IL 6, TNF i prostaglandines i leucotriens proinflamatoris.
- Supressió activitat tumoricida i microbicida dels macròfags activats
- Supressió adhesió dels neutròfils a la cèl. endotelial
- Limfopènia (totes les subpoblacions)
- Inhibició activació cèl-T per inhibició IL 2, 3, 4 i 6
- Defecte en la maduració de limfòcits T amb doble positivitat (timòcits,CD41 CD81). Apoptosis.
- Supressió maduració cèls. dendrítiques (presentadores d'antigen)

Coutinho AE and Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Molecular and Cellular Endocrinology 335 (2011) 2–13

Table 2
Recent observational studies evaluating risk of infections in patients with rheumatoid arthritis treated with systemic corticosteroids

Author, Year, Country, Duration, Study Type	Population	Prednisone or Prednisone Equivalent Dose	Infections	Results	Risk Ratios[a]
Wolfe et al,[32] 2006, US, 2001–2004, prospective	RA, n = 16,788	PEQ ≤5 PEQ 5–10 PEQ >10	Pneumonia requiring hospitalization	Increased risk of infection; dose dependent	HR of hospitalization for pneumonia: • Any PEQ, HR 1.7 (95% CI, 1.5–2) • PEQ ≤5, HR 1.4 (95% CI, 1.1–1.6) • PEQ 5–10, HR 2.1 (95% CI, 1.7–2.7) • PEQ >10, HR 2.3 (95% CI, 1.6–3.2)
Curtis et al,[35] 2007, US, 5/1998–12/2003, retrospective	Patients with RA: n = 2393 on TNF, n = 2933 on MTX	PEQ ≤5 PEQ 5–10 PEQ >10	Hospitalization with confirmed bacterial infection	Increased risk of infection in patients on PEQ >10 mg daily	Adj HR of confirmed infections: • PEQ ≤5, HR 1.49 (95% CI, 0.82–2.72) • PEQ 5–10, HR 1.46 (95% CI, 0.84–2.54) • PEQ >10, HR 1.85 (95% CI, 1.21–2.85)
Franklin et al,[37] 2007, NOAR, 1990–1999, prospective	Patients with inflammatory polyarthritis, n = 2108	Ever use	SBI	Increase risk of SBI	RR of SBI in patient on CS: • Univariate analysis, RR 2.3 (95% CI, 1.6–3.5) • Multivariate analysis, RR 2.2 (95% CI, 1.5–3.4)
Schneeweiss et al,[33] 2007, US, 1/1995–12/2003, prospective	RA >65 y old, n = 15,597	PEQ ≤5 PEQ 6–9 PEQ 10–19 PEQ ≥20	SBI	Increased risk of infection; dose dependent	ARR of SBI as per PEQ: • PEQ ≤5 mg, ARR 1.34 (95% CI, 0.85–2.13) • PEQ 6–9, ARR 1.53 (95% CI, 0.95–2.48) • PEQ 10–19, ARR 2.97 (95% CI, 1.89–4.68) • PEQ ≥20, ARR 5.48 (95% CI, 3.29–9.11)
Smitten et al,[14] 2008, US, 1/1999–7/2006, retrospective	RA patients (n = 24,530) compared with 500,000 non-RA patients	PEQ ≤5 6–10 >10	Any infection requiring hospitalization	Increased risk of infection; dose dependent	RR of hospitalization for infection risk as per PEQ: • PEQ ≤5, RR 1.32 (95% CI, 1.06–1.63) • PEQ = 6–10, RR 1.94 (95% CI, 1.53–2.46) • PEQ >10, RR 2.98 (95% CI, 2.41–3.69)
Greenberg et al,[38] 2010, US, CORRONA, 10/2001–9/2006, prospective	Patients with RA on DMARDs, n = 7971	PEQ <10 PEQ >10	Overall infections (includes both Opportunistic and non-OIs)	Increased risk of overall infections with PEQ >10	IRR of overall infections as per PEQ: • Any dose, IRR 1.05 (95% CI, 0.97–1.15) • PEQ >10, IRR 1.30 (95% CI, 1.11–1.53) IRR of OIs: Any CS dose, IRR 1.63 (95% CI, 1.20–2.21)
Dixon et al,[31] 2012, Quebec, 1985–2003, nested case-control	RA >65 y old, n = 16,207	PEQ <5 PEQ 5–9.9 PEQ 10–14.9 PEQ 15–19.9 PEQ ≥20	Nonserious infections	Increased risk of nonserious infections if PEQ >5; dose dependent	ARR of nonserious infections: • PEQ <5, RR 1.1 (95% CI, 0.99–1.22) • PEQ 5–9.9, RR 1.1 (95% CI, 1.04–1.16) • PEQ 10–14.9, RR 1.25 (95% CI, 1.17–1.34) • PEQ 15–19.9, RR 1.26 (95% CI, 1.12–1.42) • PEQ ≥20, RR 1.85 (95% CI, 1.68–2.05)
Dixon et al,[20] 2011, N/A, up to 1/2010, meta-analysis	21 RCTs 42 Observational studies	Any dose	Any Infection	CS therapy was associated with increased risk of infection in observational studies, not in RCTs	RR of increased infection risk as per PEQ: • In RCTs, RR 0.97 (95% CI, 0.69–1.36) • In observational studies, RR 1.67 (95% CI, 1.49–1.87)
Grijalva et al,[30] 2011, US, 1998–2007, retrospective	1—RA, n = 10,484 2—Pso or SpA, n = 3215	Any dose	Infection requiring hospitalization In patients on DMARDs	Increased risk of infection; dose dependent in RA group and Pso/SpA group	HR of serious infection risk as per PEQ: • RA group: PEQ 0–<5, HR 1.32 (95% CI, 1.10–1.58) PEQ 5–10, HR 1.78 (95% CI, 1.47–2.15) PEQ >10, HR 2.95 (95% CI, 2.41–3.61) • Pso and SpA group: 0–<5, 1.15 (0.75–1.77) 5–10, 2.01 (1.08–3.73) >10, 2.77 (1.44–5.32)
Xie et al,[39] 2012, China, 1/2009–2/2011, retrospective	RA, n = 2452	Any dose	Nosocomial infections	Increased risk of infection	OR of nosocomial infections by multivariate analysis: 1.02 (95% CI, 1.01–1.03)
van Dartel et al,[40] 2013, DREAM, 2005–2010, prospective	Patients with RA, n = 2044	Any dose	SBI	Increased risk of infection	• HR of SBI by multivariate analysis: HR 1.54 (95% CI, 1.08–2.20) • HR of SBI by univariate analysis: HR 1.78 (95% CI, 1.26–2.53)
Widdifield et al,[34] 2013, Ontario, 1992–2010, nested case control	RA ≥66 Y/O, n = 86,039	PEQ ≤5 PEQ 6–9 PEQ 10–19 PEQ ≥20	Serious infections	Increased risk of infection; dose dependent	Adj OR of serious infections as per PEQ: • PEQ ≤5, OR 3.96 (95% CI, 3.67–4.27) • PEQ 6–9, OR 4.28 (95% CI, 3.70–4.96) • PEQ 10–19, OR 5.98 (95% CI, 5.42–6.59) • PEQ ≥20, OR 7.57 (95% CI, 6.87–8.34)

Abbreviations: adj, adjusted; ARR, adjusted rate ratio; CS, corticosteroids; DREAM, Dutch Rheumatoid Arthritis Monitoring Registry; IRR, incidence rate ratio; MTX, methotrexate; N/A, not applicable; NOAR, Norfolk Arthritis Register; PEQ, PEQ dose measured by mg/d; Pso, psoriasis; SBI, serious bacterial infections; SpA, spondyloarthritis; TNF, tumor necrosis factor inhibitors; Y/O, years old.

[a] HR, OR, and IRR where indicated.

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Table 3
Prevention strategies

Disease	Prevention Strategies
Influenza	Annual vaccination in those with rheumatic diseases[88]
HZ	Vaccine in all patients with rheumatic diseases ages ≥50[75,77,78]
Pneumococcal pneumonia	In patients without prior vaccination, 1 dose of PCV13 in those on chronic steroid therapy should be given followed by PPSV23 ≥8 wk later. A second dose of PPSV23 is indicated 5 y after first dose.[88]
PJP	Treat with TMP/SMX (160 mg/800 mg) 3 times a week if on PEQ >16 mg daily for more than 8 wk.[45]
TB	Screen for latent TB using either TSTs or IGRAs[a] in those anticipated to start long-term corticosteroid therapy (10 mg for at least 1 mo) and treat for latent TB if positive.[81] If already on chronic steroid therapy, screen with IGRA and be aware of risk of false-negative results with TSTs or IGRAs.

Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

[a] IGRA is preferred if patient has a history of bacille Calmette-Guérin vaccine.

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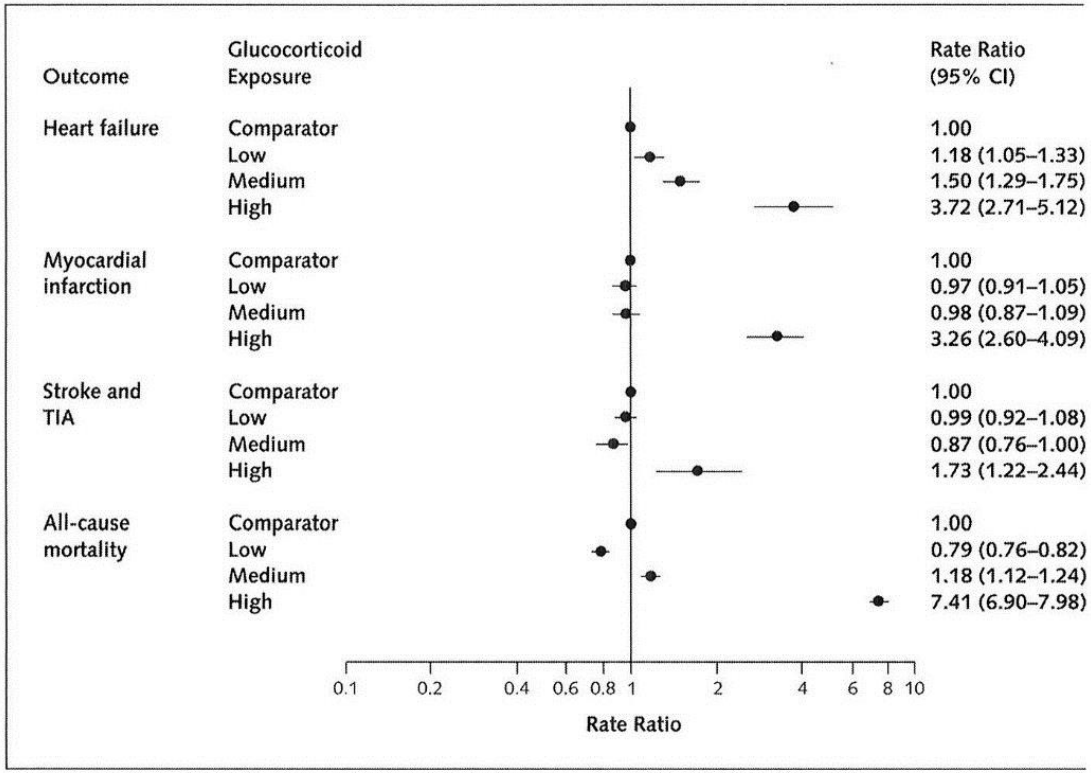
Cardiovasculars

- Dosi depenent (>7,5 mg/dia)
- Efectes
  - Infart de miocardi
  - Insuficiència cardiaca
  - Ictus
  - Augment de mortalitat de qualsevol causa
- Sobretot en Cushing: esdeveniments cardiovasculars (incidencia 15,1/100 persones.any)
  - Respecte a No Cushing HR 2,74 (2,06-3,62)
  - Respecte a No Corticoides HR 4,16 (2,98-5,82)

Table 2. Influence of Dose of Glucocorticoids on All Cardiovascular Events **(68 781 glucocorticoid users and 82 202 nonusers)**

Steroid Exposure	Events, *n*	Unadjusted Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)*	Adjusted Rate Ratio (95% CI)†
Comparator	4383	1.00	1.00	1.00
Low dose	3521	1.30 (1.24–1.36)	1.00 (0.95–1.05)	1.00 (0.95–1.05)
Medium dose	1380	1.60 (1.50–1.70)	1.03 (0.96–1.10)	1.04 (0.95–1.14)
High dose	167	4.50 (3.86–5.25)	2.56 (2.18–2.99)	3.09 (2.51–3.80)

Figure. Glucocorticoid use with different cardiovascular diseases.



TIA = transient ischemic attack.

Li, W et al. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Annals of Internal Medicine,141(2004) 764-70

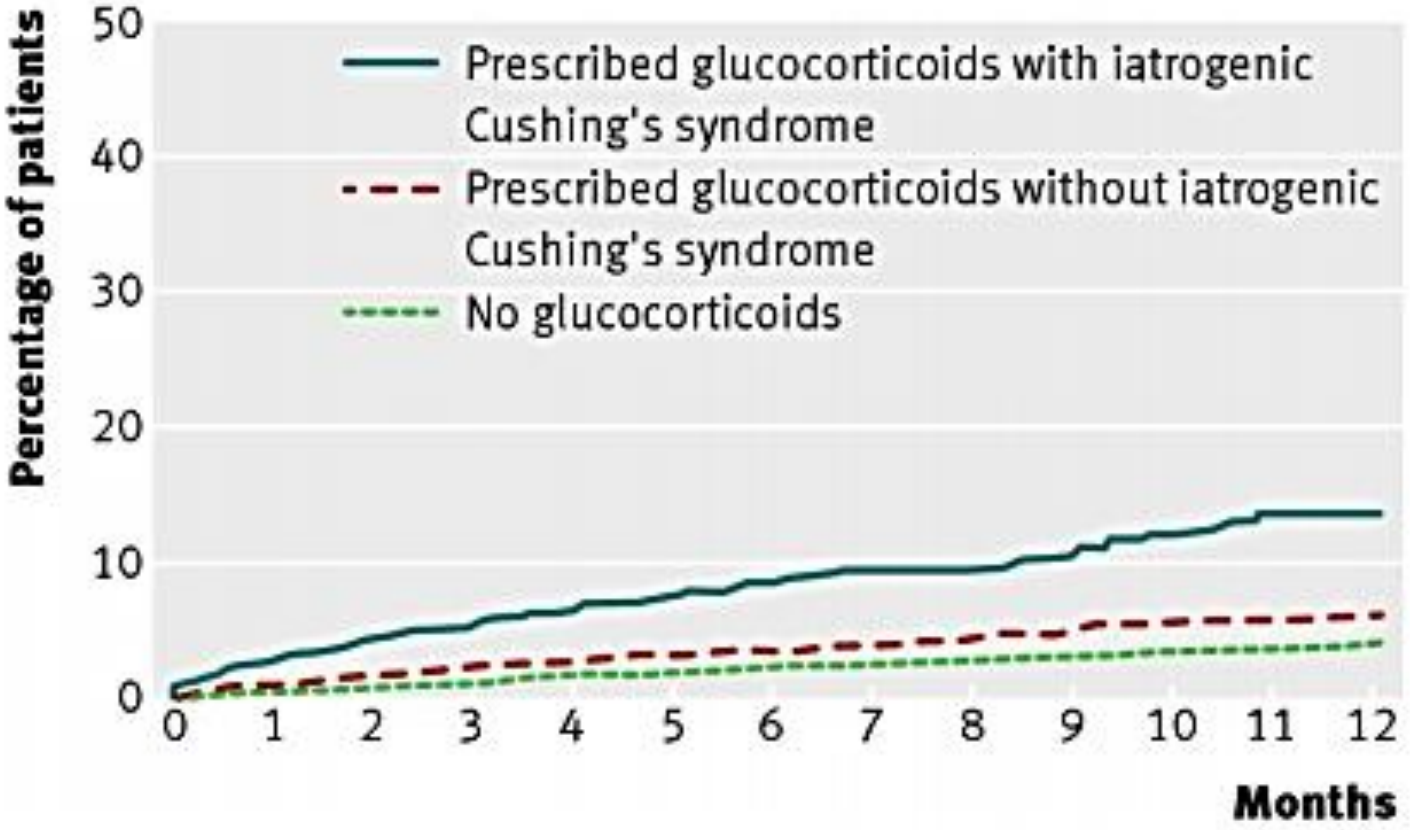
Table 5| **Adjusted hazard ratios (95% confidence intervals) of cardiovascular events in patients with iatrogenic Cushing's syndrome** **(n 547)**

	Compared with patients without iatrogenic Cushing's syndrome (n=3231)				Compared with patients not prescribed glucocorticoids (n=3282)			
Cardiovascular events	Crude hazard ratio (95% CI)	P value	Adjusted hazard ratio* (95% CI)	P value	Crude hazard ratio (95% CI)	P value	Adjusted hazard ratio† (95% CI)	P value
All (n=341)	2.33 (1.73 to 3.14)	<0.001	2.74 (2.06 to 3.62)	<0.001	3.70 (2.63 to 5.22)	<0.001	4.16 (2.98 to 5.82)	<0.001
Coronary heart disease (n=177)	1.96 (1.29 to 2.97)	0.002	2.27 (1.48 to 3.47)	<0.001	2.97 (1.91 to 4.64)	<0.001	2.68 (1.62 to 4.44)	<0.001
Cerebrovascular event (n=63)	2.26 (1.06 to 4.81)	0.02	2.23 (0.96 to 5.17)	0.07	1.79 (0.85 to 3.76)	0.12	2.14 (0.97 to 4.73)	0.06
Heart failure (n=101)	2.97 (1.82 to 4.84)	<0.001	3.77 (2.41 to 5.90)	<0.001	9.74 (4.98 to 19.06)	<0.001	13.31 (7.24 to 24.51)	<0.001

*Adjusted for age, sex, initial dosage of glucocorticoids and duration of use, underlying disease, smoking status, and use of aspirin, oral anticoagulants, diabetes drugs, antihypertensive drugs, and cholesterol lowering drugs.

†Adjusted for age, sex, underlying disease, smoking status, and use of aspirin, oral anticoagulants, diabetes drugs, antihypertensive drugs, and cholesterol lowering drugs.

Fardet L et al. Risk of cardiovascular events in people prescribed glucocorticoids with iatrogenic Cushing's syndrome: cohort study. BMJ 345 (2012) e4928



Kaplan-Meier survival curves showing cumulative incidence of cardiovascular events over time in the three study group

Fardet L. 2012

Table 3| **Initiation of treatments within year after index date (up to date of cardiovascular event). Values are numbers (percentages) of participants unless stated otherwise**

Treatments	Glucocorticoids		No glucocorticoids (n=3282)	P values
	Iatrogenic Cushing's syndrome (n=547)	No iatrogenic Cushing's syndrome (n=3231)		
Antihypertensive drugs	81 (14.8)	295 (9.1)	211 (6.4)	<0.001
Lipid lowering drugs	20 (3.7)	76 (2.3)	79 (2.4)	0.18
Diabetes drugs	14 (2.6)	19 (0.6)	9 (0.3)	<0.001

Fardet L. 2012

Oftalmològics

- Cataractes (>10 mg/dia x >1 any):
  - Subcapsulars posteriors
  - Bilaterals
  - Atenció nens
- Glaucoma
  - Antecedents familiars
  - Miopia
  - Antecedent Glaucoma (angle obert o tancat)
- Exoftalme, Edema palpebral
- Corioretinopatia serosa central

Cutanis

- Aprimament cutani
- Púrpura i Hemorràgies superficials
- Càncer de pell (escatós – OR 2,3- i basocel·lular – OR 1,5-)
- Acné

SNC

- Transtorns de l'humor
  - Sensació benestar
  - Eufòria
  - Ansietat
  - Hipomania (precoç)
  - Depressió (tardana)
- Acatísia
- Alteracions del son
- Psicosi (>20 mg/dia de llarga durada)
- Alteració de la memòria

Gastrointestinals

- Combinació amb AINEs (profilaxi)
  - x2 respecte a AINEs sols
  - x4 respecte a no AINEs i no Corticoesteroids
- Esteatosi Hepàtica
- Enmascarament Peritonitis
- Pancreatitis OR 1,53 (1,27-1,84)

Renals i Hemodinàmics

- Retenció hídrica (en nefropatia de base)
- HTA
- Augment de la Kaliuresi (hipokalièmia i alcalosi rars)

Miopatia

- Clínica:
  - Gradual
  - Musculatura proximal (aixecar-se, pujar escales, tasques per damunt del cap)
  - No miàlgies
  - EEII abans i més severa
- Dosi i Durada (>10 mg/dia)
  - > 40 to 60 mg/dia indueix debilitat clínicament important en 2 setmanes
  - > 40 to 60 mg/dia indueix miopatia en 1 mes
- Diagnòstic Clínic
- Relació amb Miopatia del Pacient Crític

Altres Musculesquelètics

- Fractures vertebrals no osteoporòtiques
- Osteonecrosi
- Alteració creixement

Maneig i Prevenció

Patient specific factors shifting towards a lower level of harm

	Factors	References
General	early diagnosis, low disease activity, low cumulative glucocorticoid dosage, healthy life style (especially cessation of smoking, low alcohol consumption), monitoring and treatment of risk factors and co-morbidities	[1] [21] [37]
Glucocorticoid-induced osteoporosis	sufficient vitamin D & calcium intake, exercise, muscle strengthening, prescription on indication: bisphosphonates, osteoanabolic drugs, selective oestrogen receptor modulators	[36] [39] [40] [41] [42]
Infections	screening for infections, vaccination, usage of risk scores before therapy, follow rules of conduct (avoiding infected persons, appropriate wound care, washing hands, good sleep)	[44] [50] [52]
Carbohydrate metabolism	healthy diet, appropriate exercise, weight loss for obese patients, prescription on indication: hydroxychloroquine, diuretics	[58] [59]
Cardiovascular	diet in low saturated fat & calories, physical activity, weight normalization, sodium restriction, follow the EULAR-recommendations for cardiovascular risk management (including medications like statins or angiotensin-converting enzyme inhibitors on indication)	[2] [60] [70] [75] [76] [77]

Strehl C et al. 2016.

Patient specific factors shifting towards an increased level of harm

	Factors	References
General	high disease activity, high cumulative glucocorticoid dosage, lifestyle (especially bad nutrition, smoking, high alcohol consumption)	[17] [26] [66]
Glucocorticoid-induced osteoporosis	age > 60 years, female sex, low body weight, low bone mineral density, family history of osteoporosis, prevalent fractures, low calcium intake	[23] [35] [36] [37] [38]
Infections	age > 60, male sex, comorbidities (e.g. chronic lung disease, coronary heart disease, heart failure, peripheral vascular diseases, diabetes mellitus, hepatitis C, chronic renal diseases, leukopenia, neurological disease) high number of treatment failures, prior serious infections	[28] [43] [46] [47] [48] [49] [50] [51]
Carbohydrate metabolism	higher age, high body mass index, genetic predisposition, long disease duration	[54] [55]
Cardiovascular	higher age, male sex, severe extra-articular disease manifestation, RF positivity, ACPA positivity, comorbidities (e.g. hypertension, diabetes, dyslipidaemia, obesity, Cushing´s syndrome)	[29] [47] [65] [67] [72] [73] [74]

Strehl C et al. 2016.

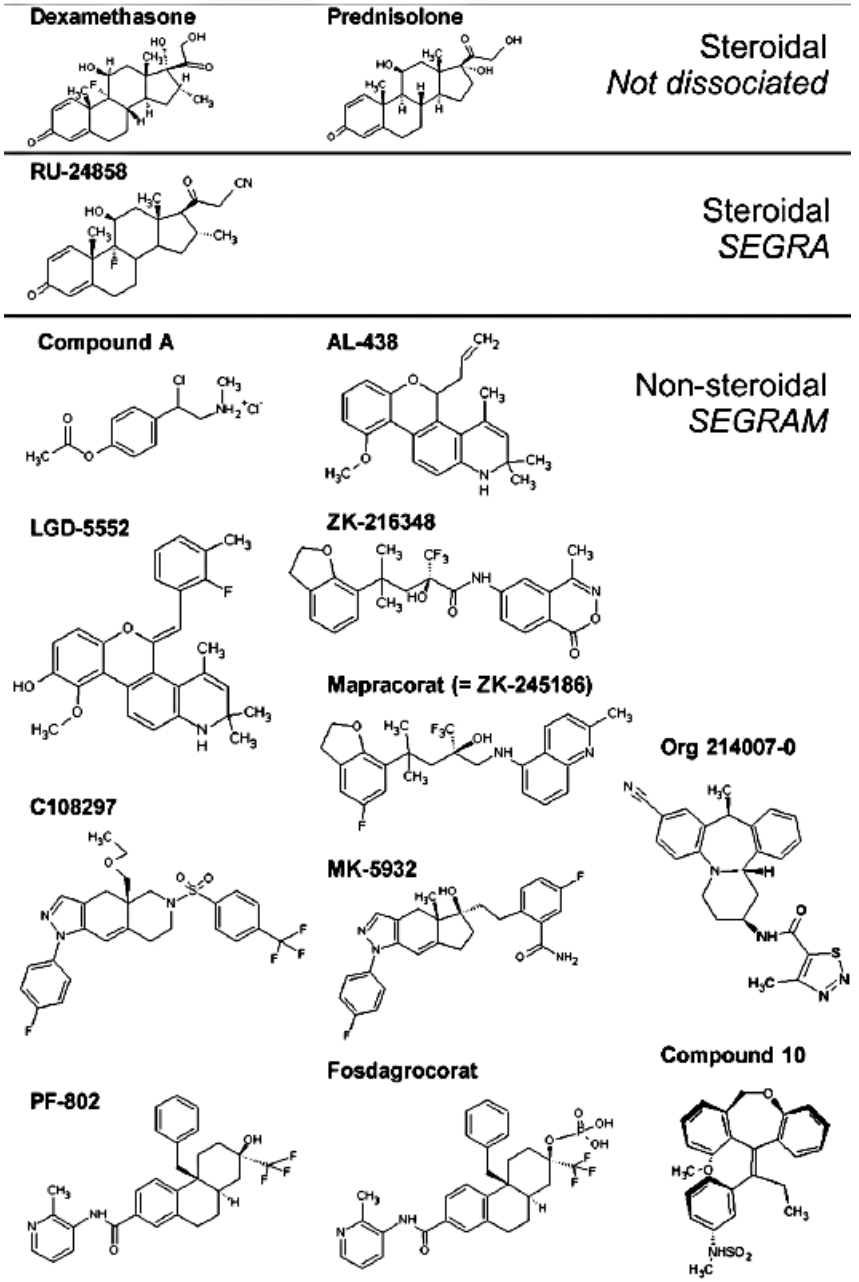
Table 2 The recommendations with strength of recommendation and level of evidence

	Proposition	SOR VAS; mean (95% CI)	A+B %	LoE
	Education and prevention			
1	Explain to patients (and their family and/or carers, including healthcare professionals) the aim of medium/high-dose GC treatment, and the potential risks associated with such therapy	91 (81 to 101)	100	III
2	Discuss measures to mitigate such risks, including diet, regular exercise and appropriate wound care	75 (57 to 93)	75	III/IV
3	Patients with, or at risk of, GC-induced osteoporosis should receive appropriate preventive/therapeutic interventions	91 (84 to 99)	100	I-A
4	Patients and the patients' treatment teams should receive appropriate, practical advice on how to manage with GC-induced hypothalamic-pituitary-adrenal axis suppression	84 (67 to 101)	92	IV
5	Provide an accessible resource to promote best practice in the management of patients using medium/high-dose GCs to general practitioners	80 (69 to 91)	75	IV
	Dosing/risk-benefit			
6	Before starting medium/high-dose GC treatment consider comorbidities predisposing to AEs. These include diabetes, glucose intolerance, cardiovascular disease, peptic ulcer disease, recurrent infections, immunosuppression, (risk factors of) glaucoma and osteoporosis. Patients with these comorbidities require tight control to manage the risk/benefit ratio	85 (76 to 94)	83	IV
7	Select the appropriate starting dose to achieve therapeutic response, taking into account the risk of undertreatment	85 (76 to 95)	92	I-A/IV
8	Keep the requirement for continuing GC treatment under constant review, and titrate the dose against therapeutic response, risk of undertreatment and development of AEs	82 (72 to 94)	92	IV
9	If long-term medium/high-dose GC therapy is anticipated to be necessary, actively consider GC-sparing therapy	REJECTED		
	Monitoring			
10	All patients should have appropriate monitoring for clinically significant AEs. The treating physician should be aware of the possible occurrence of diabetes, hypertension, weight gain, infections, osteoporotic fractures, osteonecrosis, myopathy, eye problems, skin problems and neuropsychological AEs	85 (79 to 92)	75	IV

A+B %, percentage of the task force members that strongly to fully recommended this proposition based on an A—E ordinal scale (A, fully recommended, B, strongly recommended); AEs, adverse effects; CI, confidence interval; GC, glucocorticoid; LoE, level of evidence (table 1); SOR, strength of recommendation; VAS, visual analogue scale (0–100 mm 0= not recommended at all, 100, fully recommended).

Duru N et al. EULAR evidence-based and consensus-based recommendations. 2013

Agonistes i Moduladors Selectius del Receptor dels Glucocorticoides (SEGRAMs)



Sundahl N et al. 2015.

Bibliografia

- Abu EO et al. The Localization of the Functional Glucocorticoid Receptor α in Human Bone. The Journal of Clinical Endocrinology & Metabolism 85 (2000) 883-889
- Buehring B et al. Glucocorticoid-induced osteoporosis: An update on effects and management. J Allergy Clin Immunol 132 (2013) 1019-30.
- Coutinho AE and Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Molecular and Cellular Endocrinology 335 (2011) 2–13
- Duru N, van der Goes MC, Jacobs JWG, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 72 (2013) 1905–1913.
- Fardet L et al. Risk of cardiovascular events in people prescribed glucocorticoids with iatrogenic Cushing's syndrome: cohort study. BMJ 345 (2012) e4928
- Kanis JA et al. A Meta-Analysis of Prior Corticosteroid Use and Fracture Risk. J Bone Miner Res 2004;19:893– 899
- Lems WF et al. One-year effects of glucocorticoids on bone density: a meta-analysis in cohorts on high and low dose therapy. RMD Open 2016;2:e000313.
- Li, W et al. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Annals of Internal Medicine,141(2004) 764-70
- Pisu M et al. The cost of glucocorticoid-associated adverse events in rheumatoid arthritis. Rheumatology 44 (2005) 781–788
- Ramamoorthy S, Cidlowski JA. Corticosteroids Mechanisms of Action in Health and Disease. Rheum Dis Clin N Am 42 (2016) 15–31.
- Saag KG and Furst DE. Major side effects of systemic glucocorticoids. Up toDate accredit 03/11/2016 17:41.
- Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, Kohler JA, Furst DE. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 96 (1994) 115-23.
- Strehl C, Bijlsma JWJ et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. Ann Rheum Dis 75 (2016) 952–957.
- Sundahl N, Bridelance J, Libert C, De Bosscher K, Beck IM. Selective glucocorticoid receptor modulation: New directions with non-steroidal scaffolds. Pharmacology & Therapeutics 152 (2015) 28–41
- Vandevyver S, Dejager L, Tuckermann J, and Libert C. New Insights into the Anti-inflammatory Mechanisms of Glucocorticoids: An Emerging Role for Glucocorticoid-Receptor-Mediated Transactivation. Endocrinology 154 (2013) 993–1007
- Whittier X and Saag KG. Glucocorticoid-induced Osteoporosis. Rheum Dis Clin N Am 42 (2016) 177–189
- Youssef J et al. Infection Risk and Safety of Corticosteroid Use. Rheum Dis Clin N Am 42 (2016) 157-176