BoneCast

CTF Edition

Glucocorticoid-Induced Osteoporosis: New Guidelines for Early Prevention and Treatment

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IOF International Osteoporosis Foundation

IOF CAPTURE the FRACTURE

GLUCOCORTICOID-INDUCED OSTEOPOROSIS: NEW GUIDELINES FOR EARLY PREVENTION AND TREATMENT

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IOF Webinar

IOF
International Osteoporosis Foundation

KEY LEARNING OBJECTIVES OF THIS WEBINAR

- Understanding the epidemiology and pathophysiology of GIOP

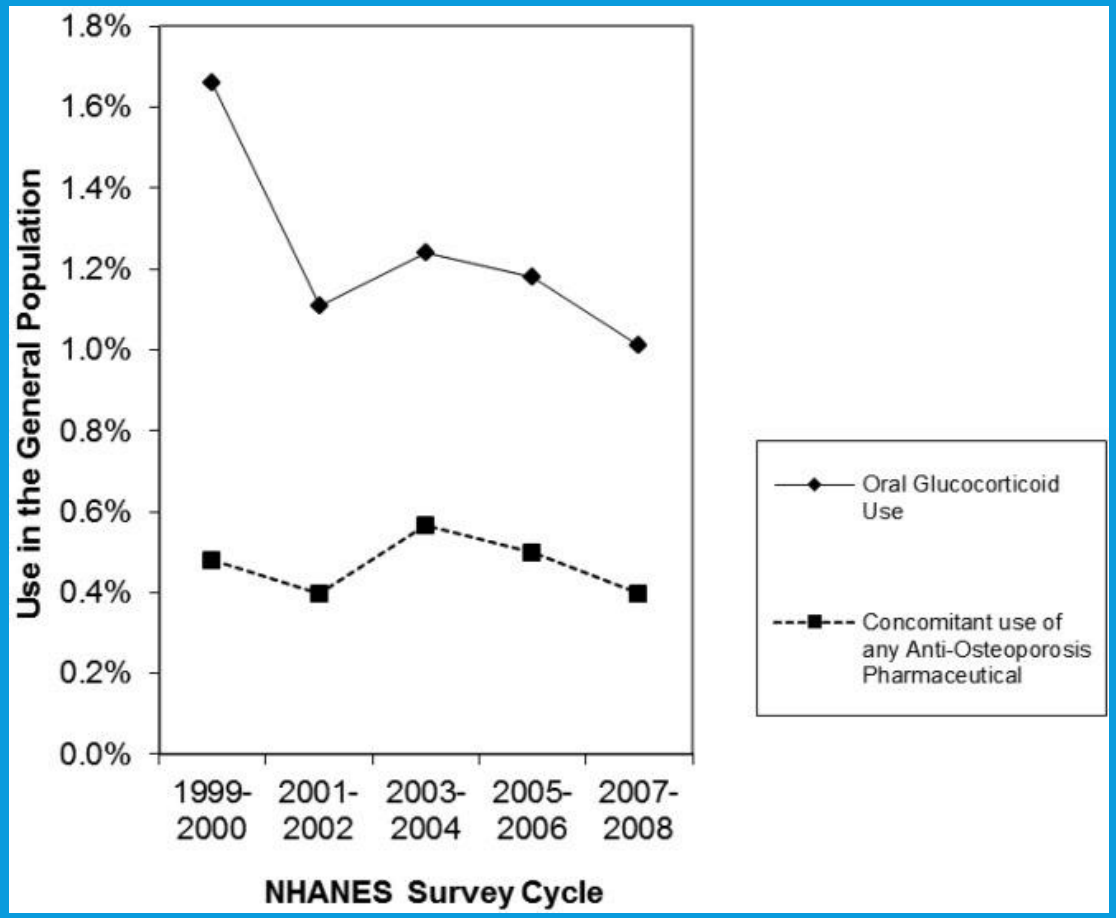
- Identify patients at risk of GIOP early, using clinical risk factors, glucocorticoid dose and duration, and BMD assessment

- Reviewing the latest recommendations for the prevention and treatment of GIOP

- Examining practical management strategies in routine care, including treatment selection, monitoring, and long-term follow-up to reduce fracture risk

ORAL GLUCOCORTICOIDS ARE WIDELY USED
PREVALENCE OF ORAL GC USAGE IN THE US

Prevalence of use from 5 NHANES* cycles (1999–2008)



- ✓ It is estimated that **1.2%** (1.1–1.4) of the US population (~2,513,259 persons) received an oral GC
- ✓ **28.8%** (22.2–35.4) reported use for ≥5 years
- ✓ Concomitant use of a bisphosphonate was reported by **8.6%** (5.1–11.7) of users

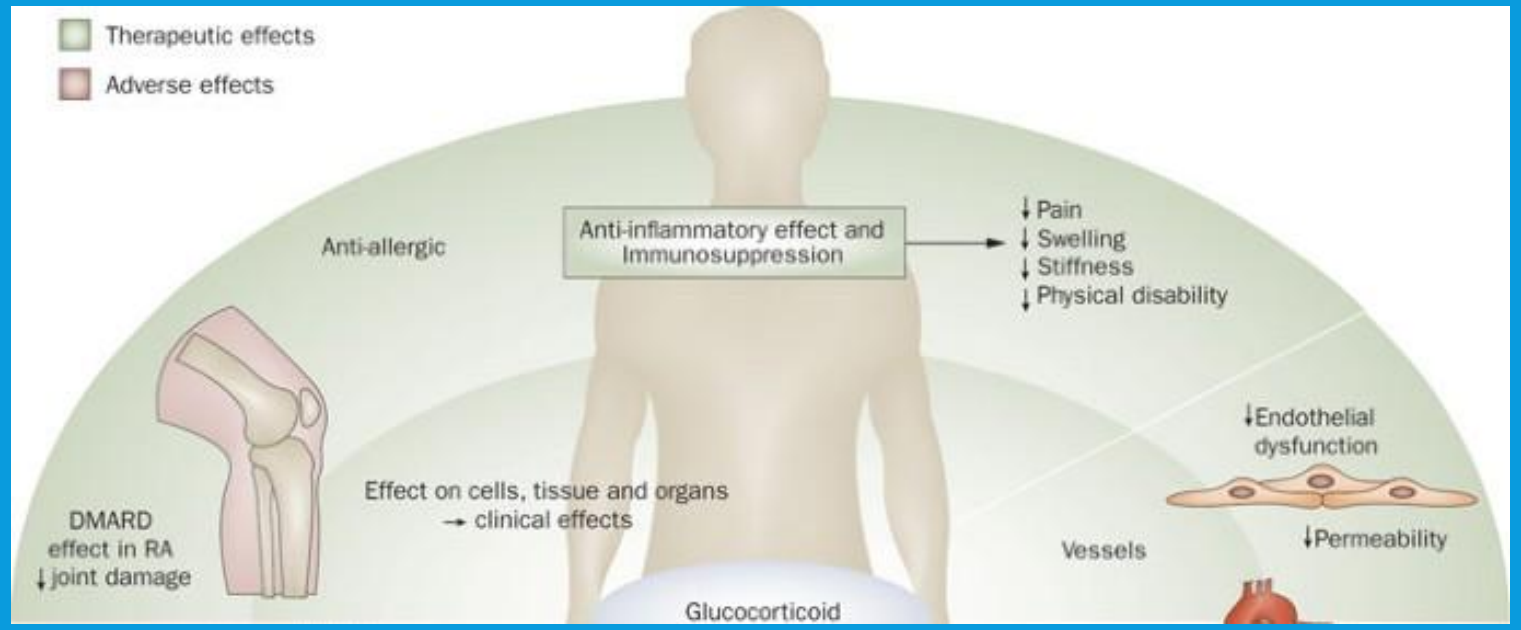
*National Health and Nutrition Examination Survey

Overman RA et al. Arthritis Care Res 2013;65:294-298

ORAL GLUCOCORTICOIDS ARE WIDELY USED

ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE EFFECTS

Glucocorticoids are widely used anti-inflammatory and immunosuppressive drugs (e.g., rheumatoid arthritis)

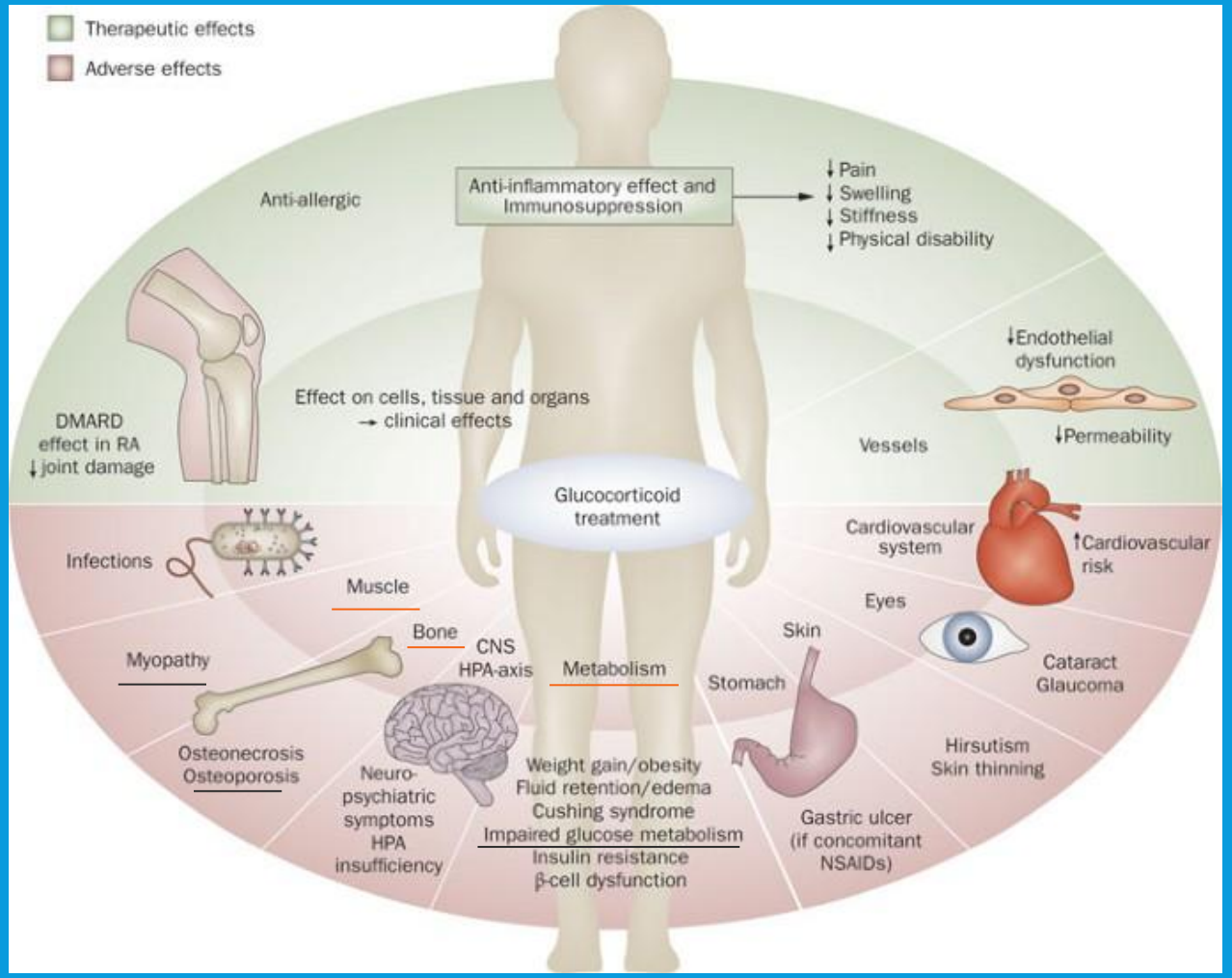


- ✓ Rheumatoid arthritis (RA),
- ✓ Asthma/chronic obstructive pulmonary disease (COPD),
- ✓ Inflammatory bowel disease (IBD),
- ✓ Multiple sclerosis (MS),
- ✓ Lupus,
- ✓ Sarcoidosis,
- ✓ …

Hoes JN et al. Nat Rev Rheumatol 2010;6:693-702.

ORAL GLUCOCORTICOIDS ARE WIDELY USED

CHRONIC GCS EXCESS INCREASES THE RISK OF ADVERSE EFFECTS



Especially bone loss and fractures, with up to 30-50% of GC-treated patients developing GIOP

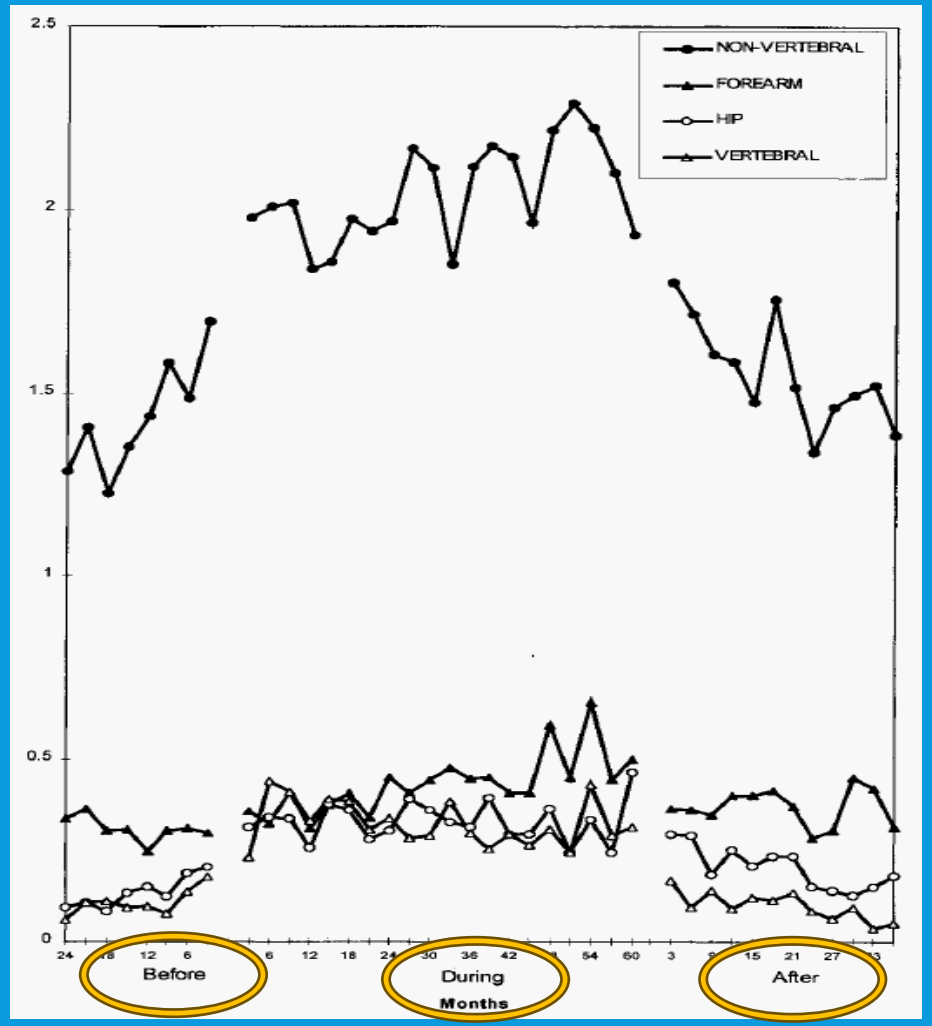
Most common drug-induced secondary osteoporosis

Hoes JN et al. Nat Rev Rheumatol 2010;6:693-702.
Compston J. European Journal of Endocrinology 2023;188:46-55.

CHRONIC GC EXCESS -THE RISK OF FRACTURE

RETROSPECTIVE COHORT STUDY USING DATA FROM THE GPRD

244,235 oral GC users and 244,235 controls (matched by age, sex, and medical practice)



+++ Seminal study on GIOP +++

Incidence of fragility fracture

Mean age 57.1 years – 58.6% women

(Respiratory diseases 40%)

The risk of fracture becomes apparent early, within the first 3 months of treatment, remains stable under treatment for years, and declined toward baseline rapidly after cessation of GCs

Van Staa et al. J Bone Miner Res 2010;15:993-1000

CHRONIC GC EXCESS -THE RISK OF FRACTURE

RETROSPECTIVE COHORT STUDY USING DATA FROM THE GPRD

244,235 oral GC users and 244,235 controls (matched by age, sex, and medical practice)

Increased fracture risk with GC exposure, including dose-response relationships

TABLE 2. INCIDENCE OF FRACTURES AMONG SUBJECTS USING ORAL CORTICOSTEROIDS AND CONTROLS

	Corticosteroid group (n = 244,235)		*Control group (n = 244,235)*			
	No. of cases	*Rate (%)*	*No. of cases*	*Rate (%)*	*Adjusted relative rate*	*95% confidence interval*
Nonvertebral	6395	2.0	8595	1.3	1.33	1.29–1.38
Forearm	1338	0.4	2190	0.3	1.09	1.01–1.17
Hip	1072	0.3	1102	0.2	1.61	1.47–1.76
Vertebral	1033	0.3	465	0.1	2.60	2.31–2.92

TABLE 3. FRACTURE RISK ACCORDING TO DOSE OF ORAL CORTICOSTEROIDS

	Low dose (n = 50,649)		*Medium dose (n = 104,833)*		*High dose (n = 87,949)*	
	No. of cases	*Adjusted relative rate (95% CI)*	*No. of cases*	*Adjusted relative rate (95% CI)*	*No. of cases*	*Adjusted relative rate (95% CI)*
Nonvertebral	2192	1.17 (1.10–1.25)	2486	1.36 (1.28–1.43)	1665	1.64 (1.54–1.76)
Forearm	531	1.10 (0.96–1.25)	526	1.04 (0.93–1.17)	273	1.19 (1.02–1.39)
Hip	236	0.99 (0.82–1.20)	494	1.77 (1.55–2.02)	328	2.27 (1.94–2.66)
Vertebral	191	1.55 (1.20–2.01)	440	2.59 (2.16–3.10)	400	5.18 (4.25–6.31)

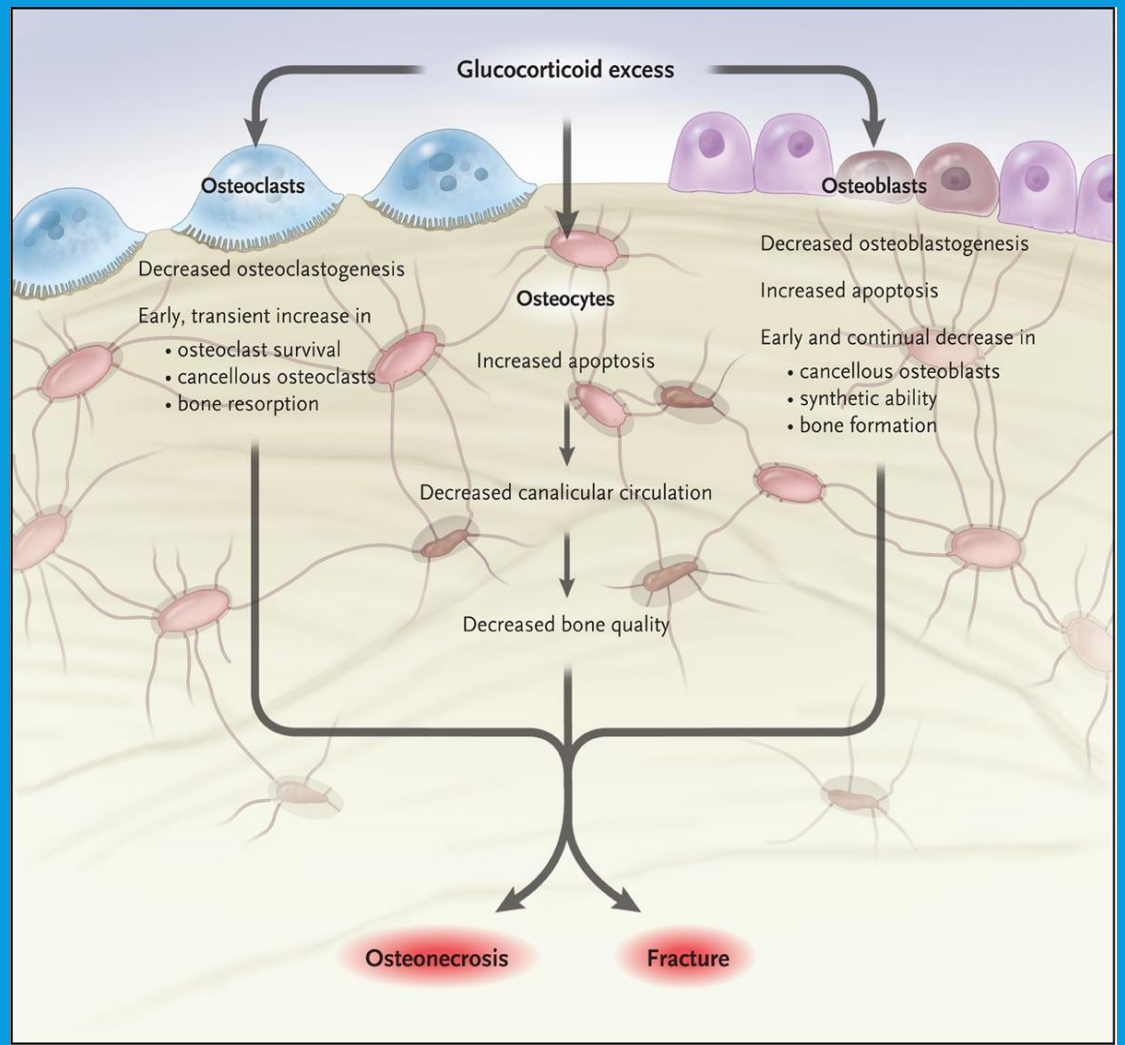
Low dose
<2.5mg/day
Medium dose
2.5-7.5mg/day
High dose
>7.5mg/day

Increased risk of fracture found at daily doses as low as 2.5 mg

Van Staa et al. J Bone Miner Res 2010;15:993-1000

THE PATHOPHYSIOLOGY OF GIOP IS COMPLEX

DIRECT EFFECTS OF GLUCOCORTICOIDS ON BONE CELLS

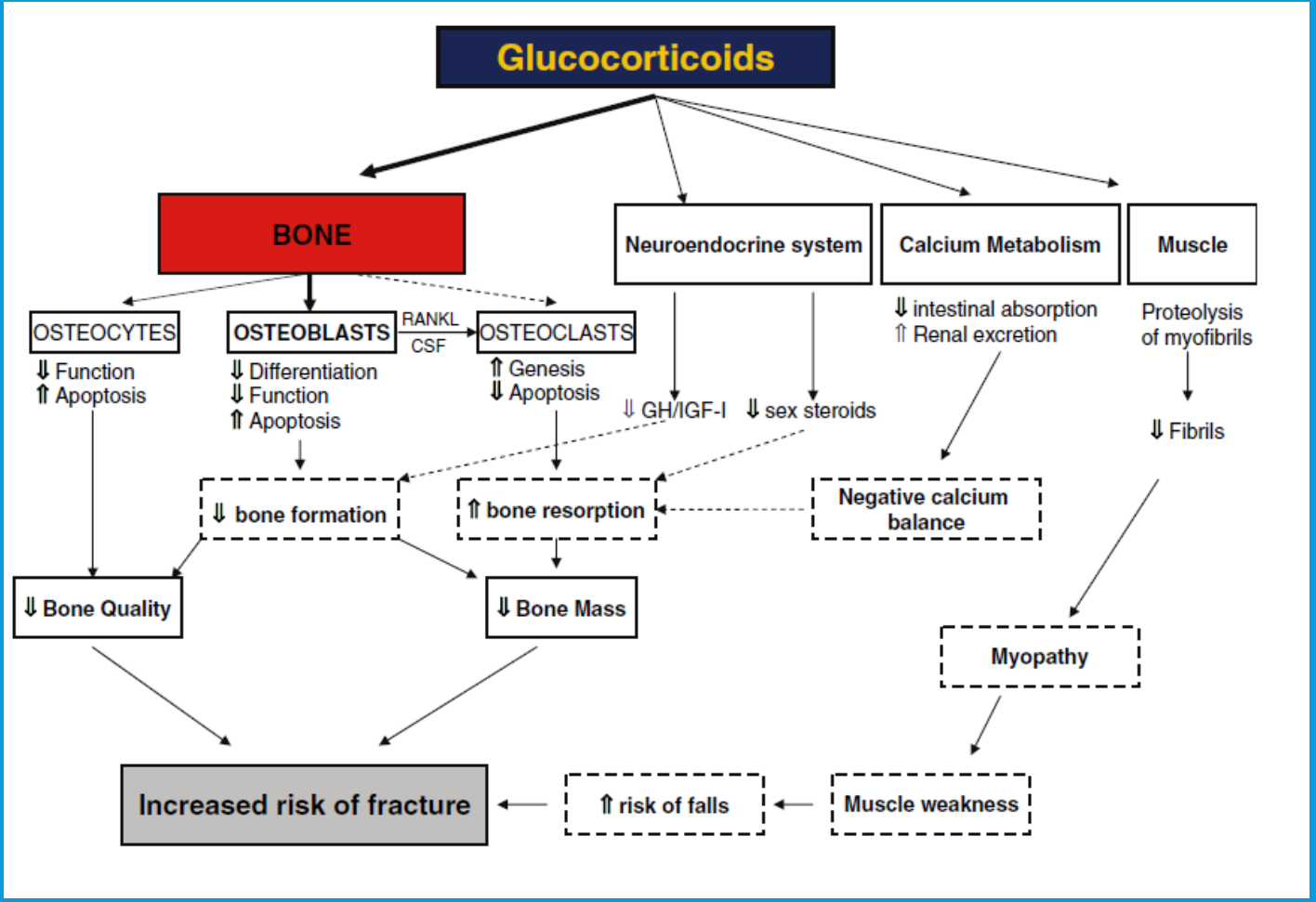


The highest rate of bone loss occurs within the first 3 to 6 months of GC treatment, due to early osteoclast activation!

Weinstein RS. N Engl J Med 2011;365:62-70.

THE PATHOPHYSIOLOGY OF GIOP IS COMPLEX

DIRECT AND INDIRECT EFFECTS OF GLUCOCORTICOIDS ON BONE



Changes in body composition
↘ lean mass and ↗ fat mass

↓

Sarcopenia
Sarcopenic obesity

Canalis E et al. Osteoporosis Int 2007;18:1319-1328.

GIOP REMAINS UNDER-DIAGNOSED AND UNDER-TREATED

RECOMMENDATIONS ARE REGULARLY PUBLISHED

- **Year 2022:**

❖UK clinical guideline for the prevention and treatment of osteoporosis (2022)

❖American College of Rheumatology (ACR) (2022)

❖Consensus Recommendations from the Belgian Bone Club (2022)

❖Latin American Guidelines (2022)

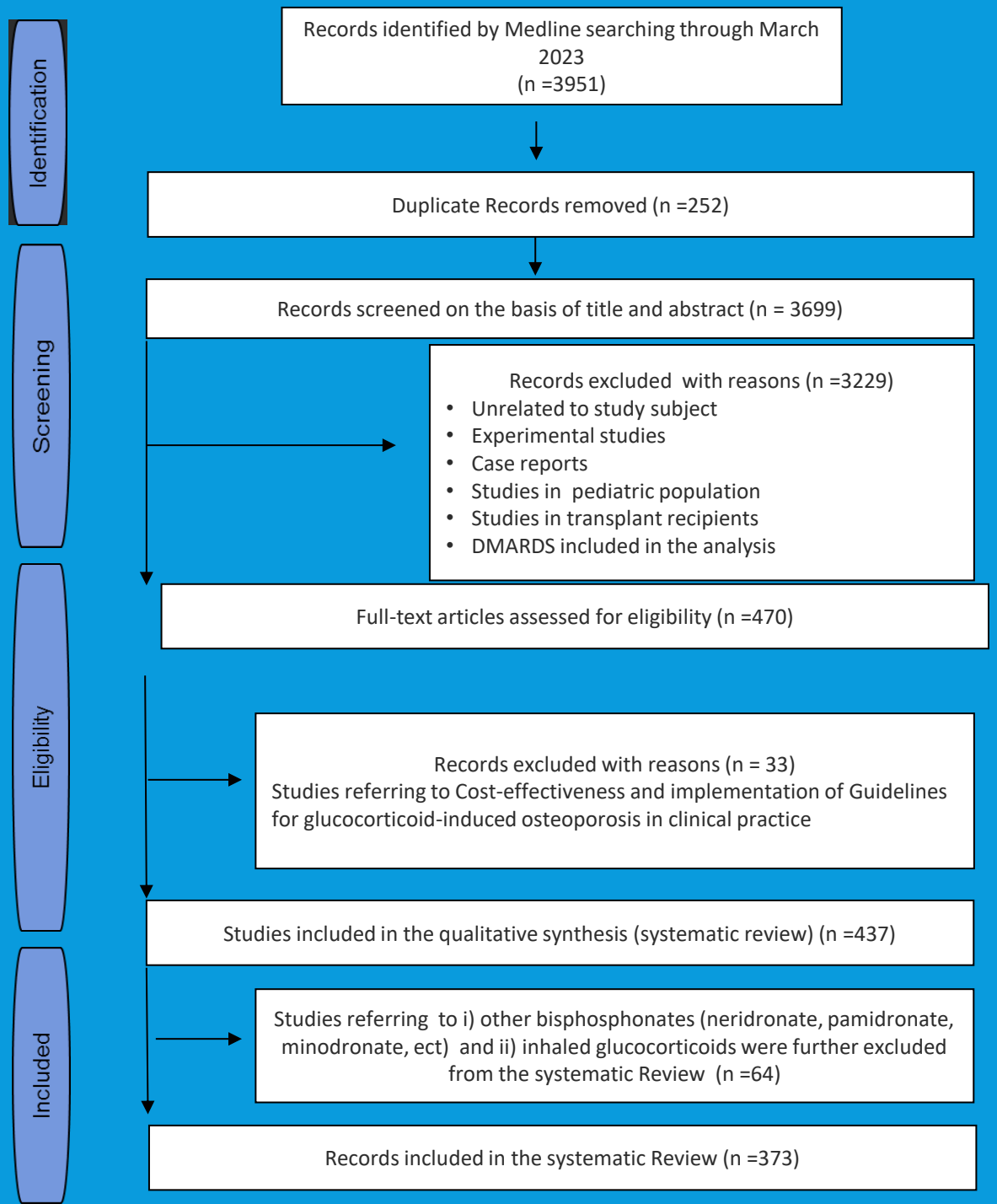
EUROPEAN CALCIFIED TISSUE SOCIETY (ECTS)

- A working group of the European Calcified Tissue Society (ECTS) performed an updated review of existing literature on GIOP
- The goal was to provide Recommendations From the European Calcified Tissue Society on Prevention and Treatment of GIOP <u>in adults</u>

<u>Clinical Action Group</u>
- Willem Lems
- Athanasios Anastasilakis
- John Carey
- Anda Naciu
- Tim Rolvien
- Maria Yavropoulou
- Julien Paccou

<u>External experts</u>
- Manju Chandran
- Osvaldo Messina
- Kenneth Saag

The target = non-bone specialists



Of the 373 remaining abstracts, original articles of larger studies and systematic reviews with meta-analyses were prioritized for review

CHALLENGES IN THE DIAGNOSIS AND MANAGEMENT OF GIOP IN ADULTS

- Who to assess?
- How to assess?
- Who to treat?
- How to treat?
- When to do a reassessment?
- When to stop antiosteoporosis medication?

Follow-up and monitoring

Assessment of fracture risk in patients with an indication for or who have already started oral glucocorticoids for at least 3 months

General measures: For whom?

Any patient on long-term oral GC treatment (≥3 months)

(i) Inform the patient on the risk of GIOP, (ii) check for height loss, back pain and history of fragility fractures, (iii) Assess dietary calcium intake, (iv) Laboratory testing

Who to assess? (long-term oral GC treatment ≥3 months)

- ✓ Postmenopausal women and men ≥ 50 years
- ✓ Patients at high risk of fracture* (regardless of age, GCs dosage, and underlying disease)

How to assess?

- ✓ Measurement of BMD by DXA
- ✓ Systematic vertebral imaging
- ✓ Osteoporosis risk factors including history of fragility fracture
- ✓ GCs dose-adjusted FRAX® AND Fall risk

*Patients at high risk of fracture are:
- History of fragility fracture during the adulthood;
- Comorbidities/medications that are frequently associated with osteoporosis.

Who to treat? Non-pharmacological measures

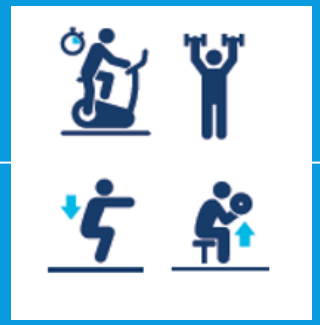
Any patient on long-term oral GC treatment (≥3 months)

- Use oral GC at the lowest possible dosage and as short as possible
- Lower dosage of oral GC with concomitant use of immunosuppressive drugs such as methotrexate and/or biologics
- Administering GCs locally (topical, inhaled, intra-articular) rather than systemically when this may be equally effective
- Optimal treatment of the underlying disease
- Adequate calcium intake (~1000mg per day)

Who to treat? Non-pharmacological measures

Any patient on long-term oral GC treatment (≥3 months)

- Normalize the intake of protein (at least 60 g/day)
- Vitamin D ideally per day throughout the year (25-OH vitamin D ≥ 20 ng/ml or ≥ 50 nmol/l) and not only during fall or winter
- Prevention of falls
- Promote weight-bearing physical activity and progressive resistance training program
- No smoking - Limited alcohol intake



Who to treat? Pharmacological treatment

Postmenopausal women and men ≥ 50 years

on long-term oral GC treatment (≥3 months)

- In the presence of a fragility fracture, OR
- T-score ≤ -1.5, OR
- GCs dosage ≥ 7.5 mg/day, OR
- Age ≥ 70, OR
- GCs dose-adjusted FRAX© (with 10-year probability risk of MOF or hip fracture above the country specific thresholds)

Who to refer?
(to a specialist in bone diseases)

In premenopausal women and men < 50 years

✓ If previous history of bone fragility fractures, OR

✓ if Z-score ≤ -2 (in the absence of fractures)

How to treat? Pharmacological treatment

Post-menopausal women and men ≥ 50 years on long-term oral GC treatment (≥3 months)

Treatment should be tailored according to patient preference, safety and level of fracture risk

- **Bisphosphonates**
- Data support beneficial effects of bisphosphonates on BMD in the spine and hip but also on vertebral and non-vertebral fractures, including hip fracture
- No head-to-head studies have compared **fracture outcomes** between anti-resorptive agents

Adachi et al., Arthritis Rheum 2001, Axelsson et al., JAMA 2017, Bergman et al., J Clin Endoc Metab 2018, Lems et al., Osteoporosis Int 2006, Saag et al., N Engl J Med 1998, Reid et al., Lancet 2009

Summary of prospective head-to-head comparator studies in the prevention and treatment of glucocorticoid-induced osteoporosis

Comparators	Reference	Duration of study	Population and number randomised	BMD outcome	Fracture outcome
Zoledronate vs risedronate	Reid et al.	12 months	Men and women n = 833	Significantly greater increases in spine and hip BMD in zoledronate treated group in prevention and treatment populations	N/A
Denosumab vs risedronate	Saag et al.	24 months	Men and women n = 795	Significantly greater increases in spine and hip BMD in denosumab treated group in prevention and treatment Populations	N/A
Teriparatide vs alendronate	Saag et al.	24 months with further analysis at 36 months	Men and women n = 428	Significantly greater increases in spine and hip BMD at 24 and 36 months in teriparatide group	Significantly fewer vertebral fractures at 24 and 36 months in teriparatide group

How to treat? Pharmacological treatment
Post-menopausal women and men ≥ 50 years

Treatment should be tailored according to patient preference, safety and level of fracture risk

Medium risk of fractures: adults without recent history of fracture*
Alendronate or risedronate as the first-line of treatment

High risk of fractures: adults with recent history of fracture*
Zoledronic acid or denosumab as the first-line of treatment

Very high risk of fractures: adults aged ≥ 70 years with recent* hip and/or pelvis and/or vertebral fracture
Teriparatide as the first-line of treatment

*Less than 2 years

How to treat? Pharmacological treatment
Post-menopausal women and men ≥ 50 years

Treatment should be tailored according to patient preference, safety and level of fracture risk

Medium risk of fractures: adults without recent history of fracture*
Alendronate or risedronate as the first-line of treatment

In those adults starting oral GCs ≥ 7.5 mg/day and without a recent history of fracture*, we recommend to start immediately alendronate or risedronate as the first-line of treatment without waiting for the DXA-result

(DXA-VFA should be ordered as baseline value, to compare changes in BMD and to differentiate incident from prevalent vertebral fractures)

*Less than 2 years

FOLLOW-UP AND MONITORING

- It is imperative that sequential therapy be implemented in individuals receiving denosumab or teriparatide as their first-line treatment regimen

- What therapy to switch to after the completion of the first line treatment should be decided upon the initiation of the first-line medication

FOLLOW-UP AND MONITORING

- **Follow-up in patients receiving anti-osteoporosis treatment**

a) Annual clinical and biological follow-up
b) Fall risk
c) Systematic vertebral imaging
d) Lowering the GC dosage should be evaluated
e) BMD every 1-2 years initially and then every 2 years or more thereafter

FOLLOW-UP AND MONITORING

- **Follow-up in patients <u>not receiving treatment and still under GC</u>**

a) Fracture risk reassessment every 1 to 2 years,

b) Depending on the initial level of risk and the presence of new CRFs

c) Clinical and biological follow-up

d) Fall risk

e) BMD and systematic vertebral imaging

FOLLOW-UP AND MONITORING

- **<u>Treatment Failure</u> in patients receiving anti-osteoporosis treatment**

a) ≥ 2 fragility fractures

b) ≥ 12 months after starting anti-osteoporosis treatment

c) Significant loss of BMD* after 1-2 years of anti-osteoporosis treatment

d) Ensure good compliance

e) Then, switch to another class or switch to another route of administration (subcutaneous or intravenous) if taken orally

*Least significant BMD change according to their DXA machine

FOLLOW-UP AND MONITORING

- **Discontinuation of GCs in patients receiving treatment**

a) Re-evaluation of fracture risk to guide the decision,

b) In patients with no new fragility fracture, no new CRFs, and a current BMD T-score ≥ −1.5,

c) Stopping current anti-osteoporosis treatment,

d) Bisphosphonates (orally or intravenously) should be administered following the discontinuation of denosumab for at least 1 year,

e) Continuing non-pharmacological management.

FOLLOW-UP AND MONITORING

- **<u>Discontinuation of anti-osteoporosis treatment</u> in patients still receiving GC**

a) Anti-osteoporosis treatment for ≥ 3-5 years for GIOP, and

b) Continuing GCs < 7.5 mg/day,

c) No evidence of a new fragility fracture,

d) No new clinical risk factors,

e) No significant BMD loss and a current BMD T-score ≥ −1.5

f) Bisphosphonates (orally or intravenously) should be administered following the discontinuation of denosumab for at least 1 year,

SUMMARY

- **ECTS recommendations on GIOP**

- Everyday practice

- Specificity of this secondary osteoporosis

- There is still a need to improve its management

- We have the wish to provide recommendations useful for non-bone specialists

WHAT IS NEW?

- **Systematic vertebral imaging (VFA)**
- **To start immediately alendronate or risedronate as the first-line of treatment without waiting for the DXA-result** (In adults starting oral GCs ≥ 7.5 mg/day and without a recent history of fracture)
- **To prioritize teriparatide, zoledronic acid or denosumab over oral bisphosphonates in patients at (very) high risk of fracture**

QUESTIONS

- Questions?
- Now welcome/possible, but also 1 week after by email
- Julien.paccou@chu-lille.fr

THANK YOU

On behalf of IOF, we thank you for your participation
in this webinar