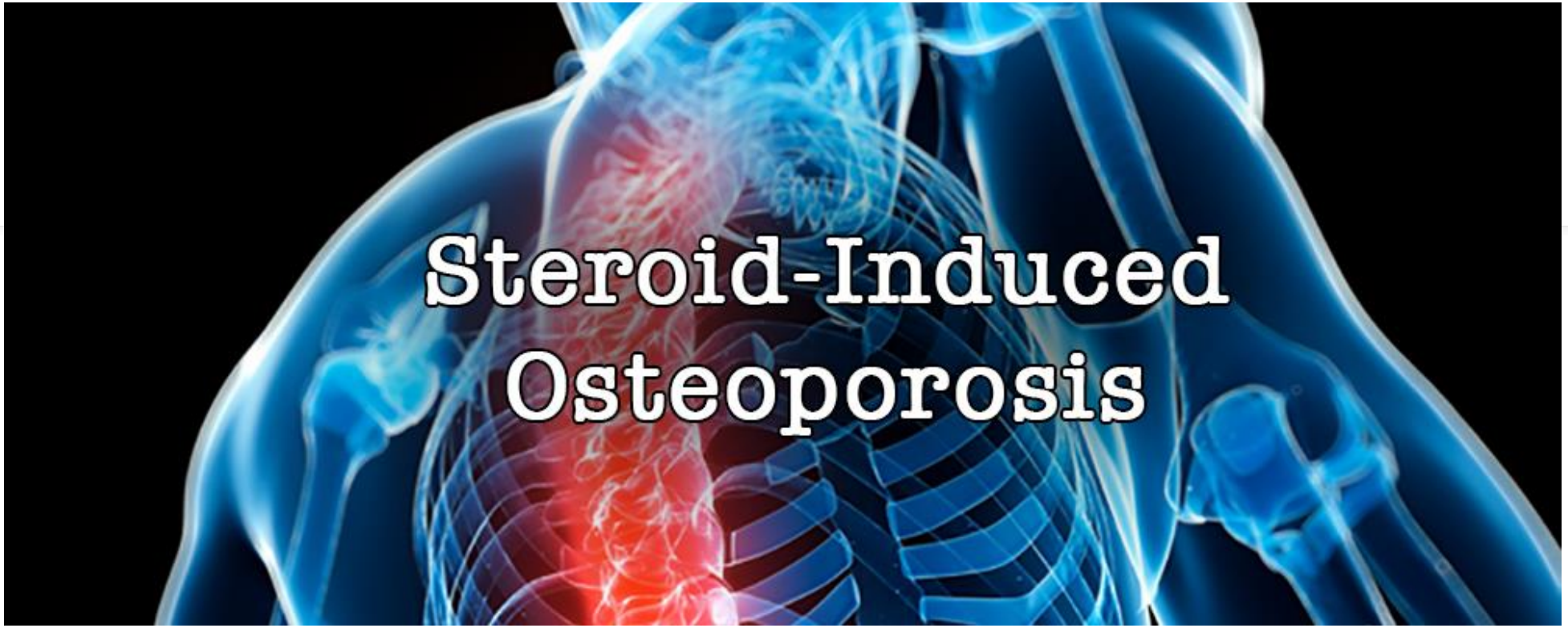

Dr. Ni Ni Hlaing

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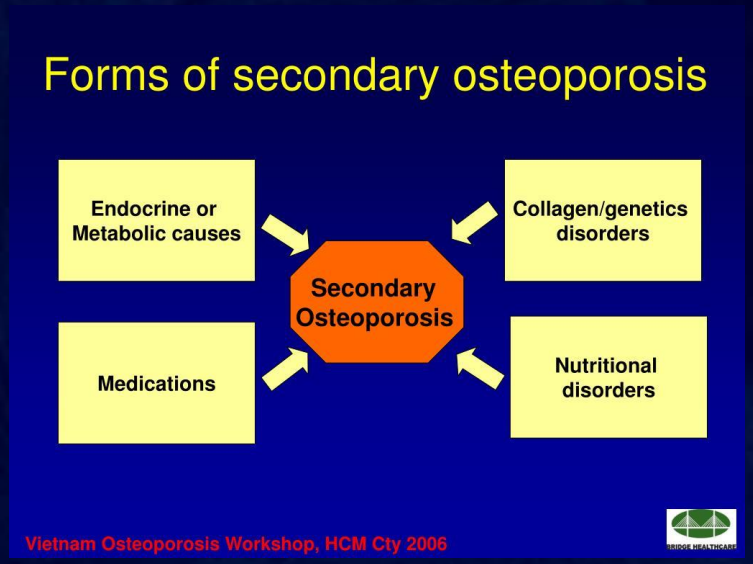
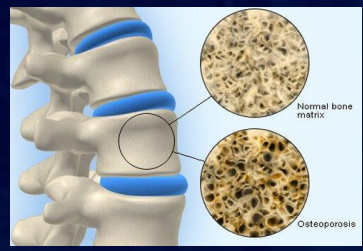
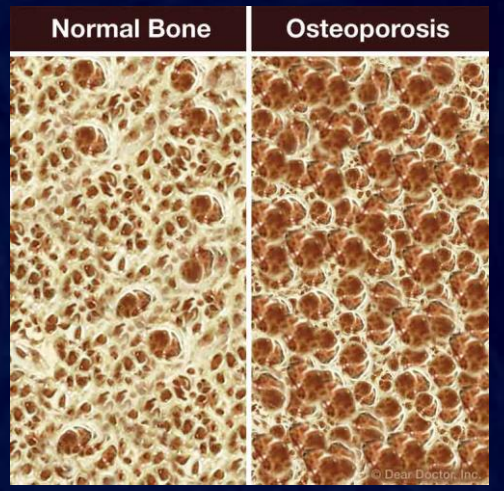
Steroid induced osteoporosis



- Most common form of secondary OP
- Affects all ages and ethnic groups
- Most fractures - Spine, proximal femur, and ribs
- Vertebral fracture, the most common due to the greater effects of GCs on trabecular bone than on cortical bone



- Highest rate of bone loss → within the first 3–6 months
- A slower decline continues with persistent use

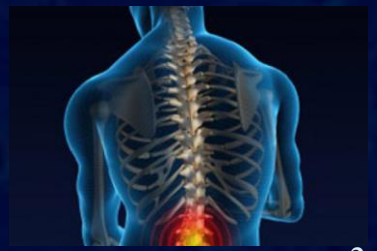


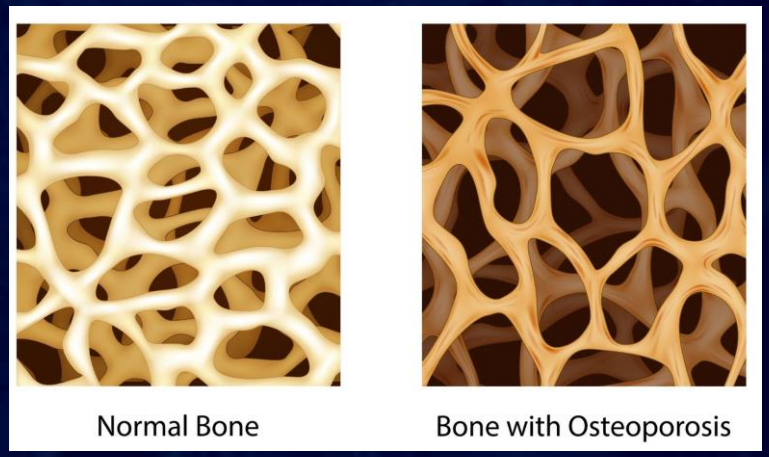
loss of trabecular bone

- first six months → 10%–20%
- subsequent years → 2% per year

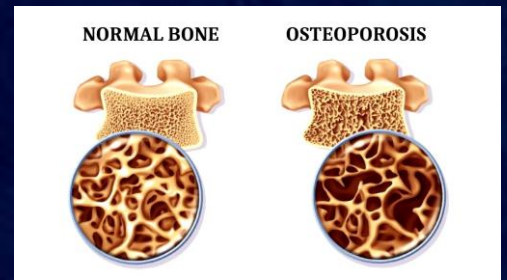
loss of cortical bone (at greater proportion in long bones)

- the first year → 2%–3%
- then, a slow and continuous loss





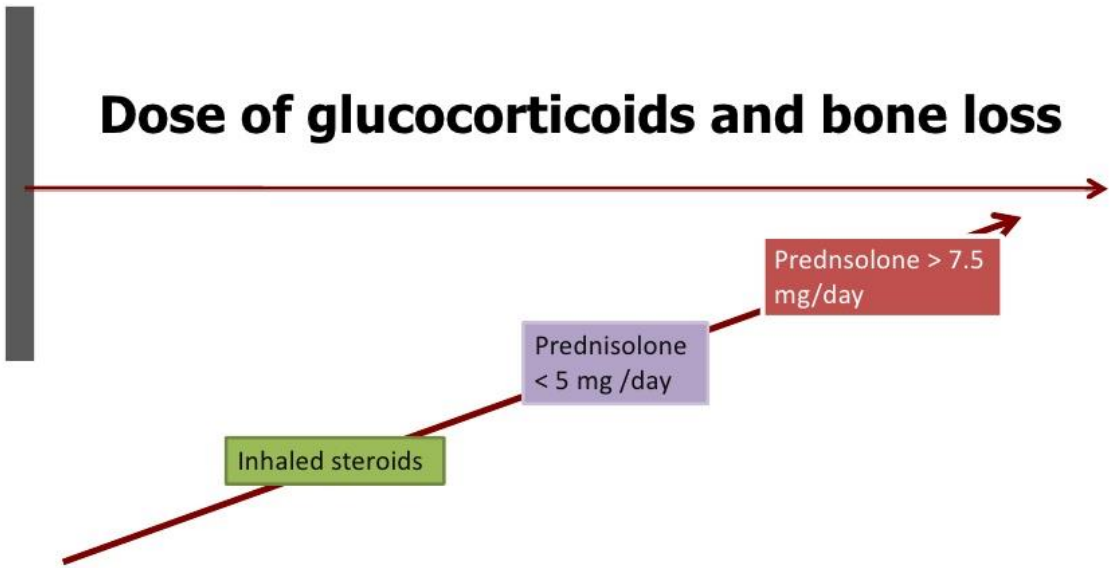
- potentially reversible risk factor for OP
- If GC treatment is terminated, BMD increases and fracture risk declines
- A prospective study showed clinically significant improvement in bone mineral density at the lumbar spine within 6 months after discontinuation of glucocorticoids



Both high daily and high cumulative GC doses increase risk of fracture

High-dose inhaled glucocorticoids and rarely high-dose topical glucocorticoids can lead to osteoporosis and increased fracture risk

Even alternate-day oral glucocorticoid Rx is no protection from GIOP



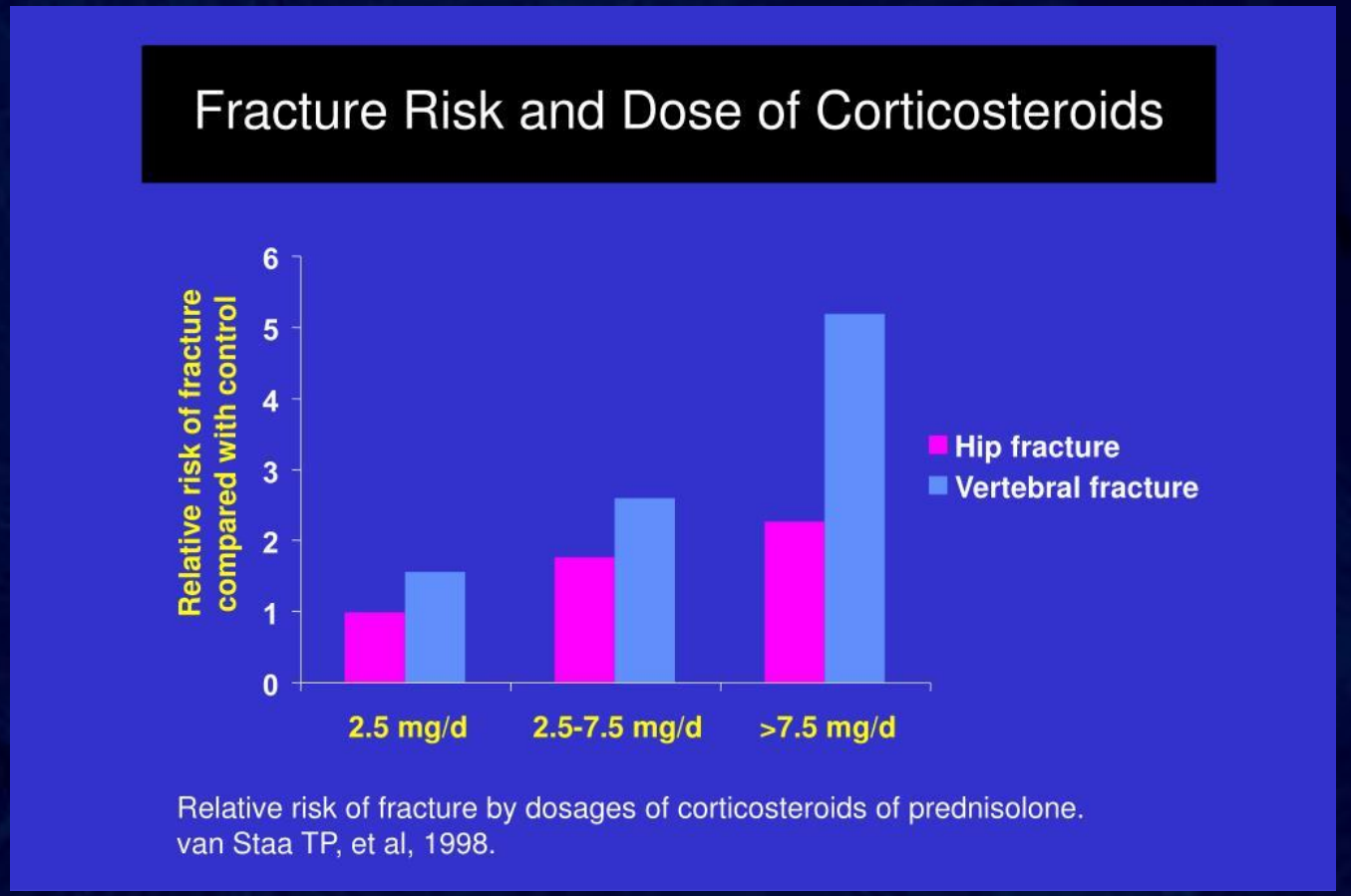
Wong CA, Walsh LJ, Smith CJ, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. Lancet 2000; 355:1399–1403

van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. QJM 2000; 93:105–111.

Risk of fracture depends on the GC dose

- Prednisone dose

- ❑ up to 2.5 mg/day, RR 1.55
- ❑ 2.5–7.5 mg/day , RR 2.59
- ❑ > 7.5 mg/day, RR 5.18



Relative risk of fracture by dosages of corticosteroids of prednisolone.
van Staa TP, et al, 1998.

Rev Bras Reumatol 2012;52(4):569-593

- GC use into 2 categories:

1. low (prednisone ≤ 7.5 mg/day)
2. high (prednisone >7.5 mg/day)

(ACR,2017)

Risk factors for GC-induced fracture

Related to glucocorticoid use

- High daily dose of GC (e.g., >7.5 mg of prednisone daily)
- Cumulative dose of glucocorticoide >5 g
- Current or recent (<3 mth) use of glucocorticoid
- Glucocorticoid-associated myopathy that increases the risk of falls
- Glucocorticoid-induced hypogonadism

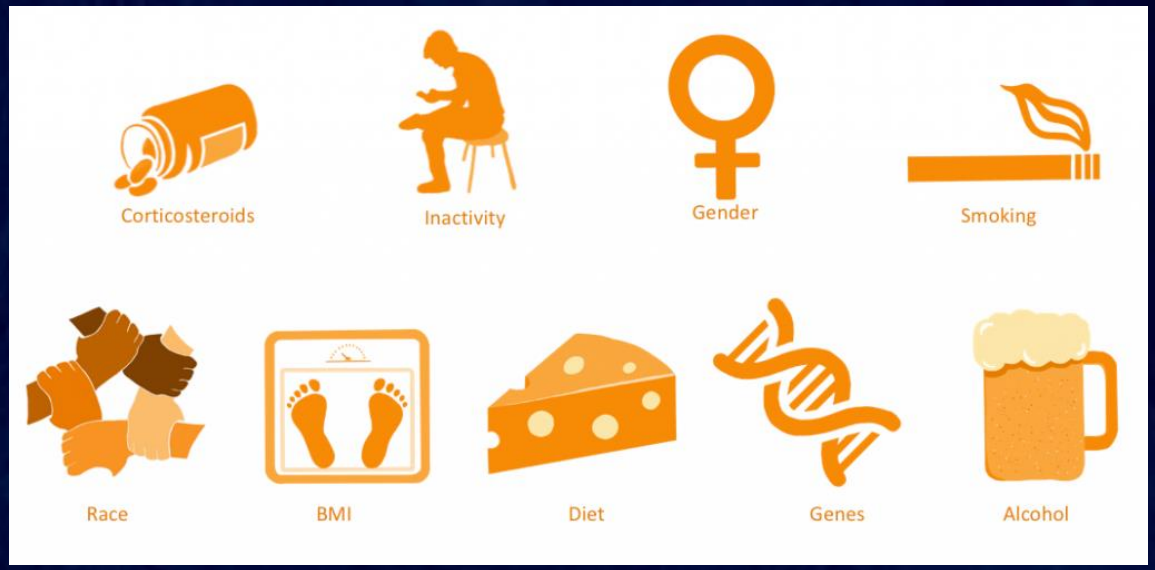
Risk factors for GC-induced fracture

Related to underlying condition

- Rheumatoid arthritis
- Ankylosing spondylitis
- Inflammatory bowel disease
- Biliary cirrhosis

Risk factors for GC-induced fracture

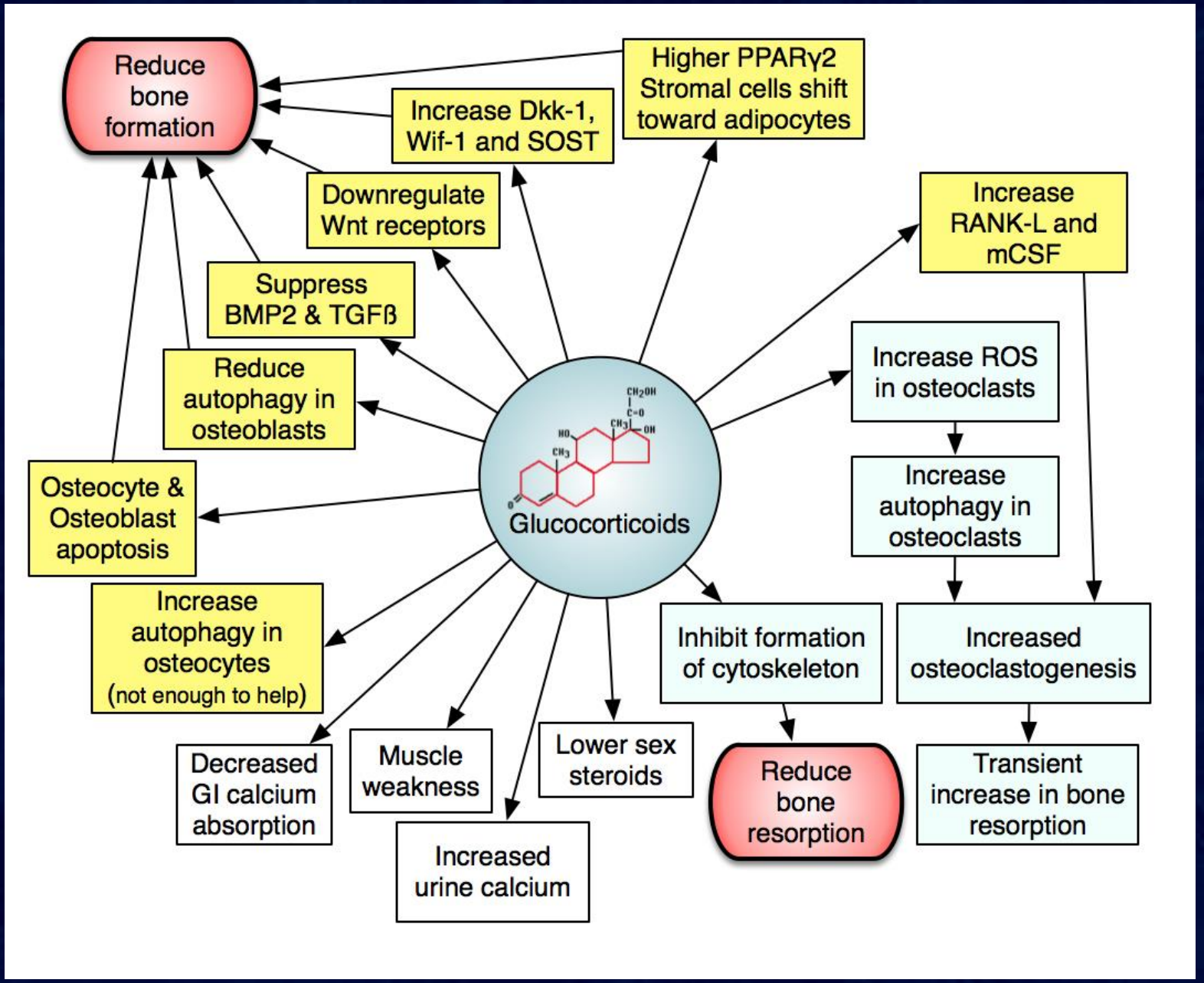
Related to risk of osteoporosis



- Age >55 years
- White race
- Female sex
- Menopause
- Smoking
- Excess alcohol use (>2 units per day)
- BMD T score < −1.5
- Endocrine disorders:
  - hypogonadism, hyperparathyroidism, or hypoparathyroidism
- Malabsorption
- BMI <18.5
- Previous fracture

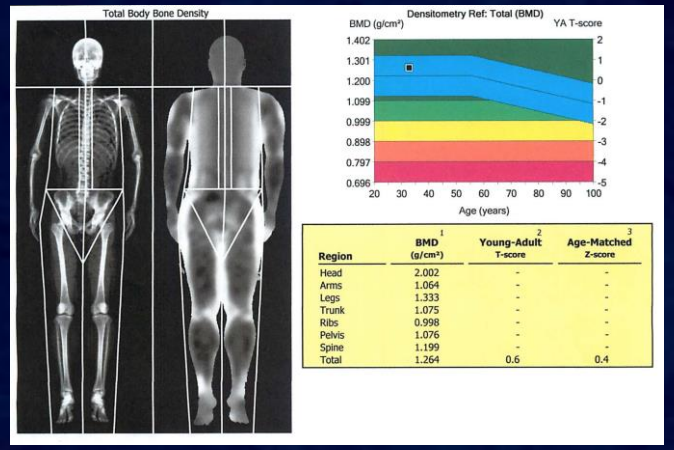
Table 1. Mechanisms of Glucocorticoid-Induced Osteoporosis

Rapid decrease in bone formation
Possible increase in bone resorption
Decreased gut aborption of calcium
Increased urinary excretion of calcium
Secondary hyperparathyroidism
Decreased muscle mass
Decreased bone matrix
Suppression of gonadal function
Suppression of adrenal androgen secretion
Patient inactivity from underlying disorder
Possible effects of inflammatory conditions


Reduce bone formation
Higher PPARγ2 Stromal cells shift toward adipocytes
Increase Dkk-1, Wif-1 and SOST
Downregulate Wnt receptors
Increase RANK-L and mCSF
Suppress BMP2 & TGFß
Increase ROS in osteoclasts
Reduce autophagy in osteoblasts
Glucocorticoids
Osteocyte & Osteoblast apoptosis
Increase autophagy in osteoclasts
Increase autophagy in osteocytes (not enough to help)
Inhibit formation of cytoskeleton
Increased osteoclastogenesis
Decreased GI calcium absorption
Muscle weakness
Lower sex steroids
Reduce bone resorption
Transient increase in bone resorption
Increased urine calcium

Indications for DEXA in steroid induced OP

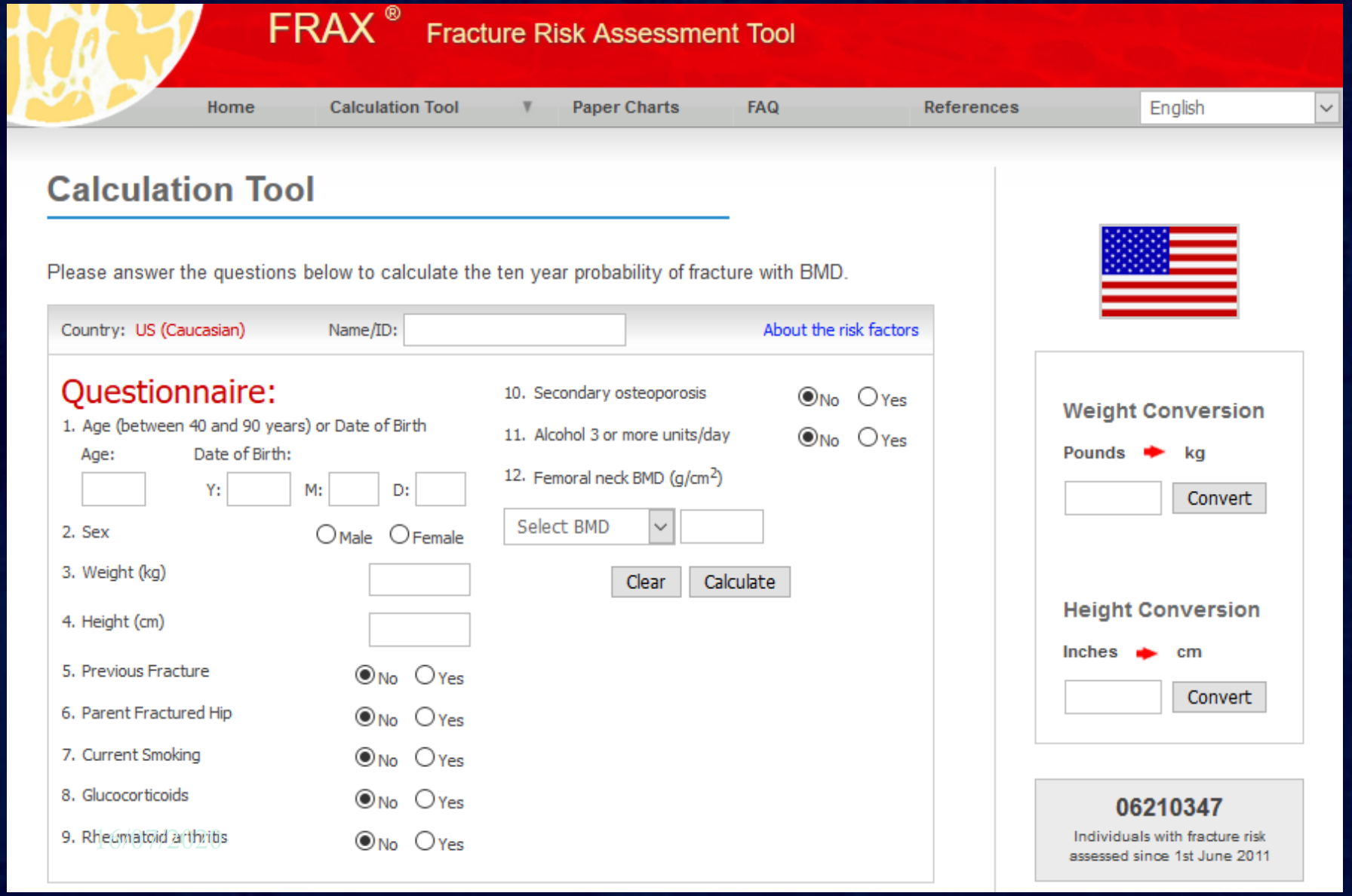
- ‘Before starting treatments that may have a rapid adverse effect on bone density’ (NICE CG146)
- All women on GC (USPSTF, NOF)
- All men on GC (US Surgeon General’s Report on Bone Health)



Limitations of DEXA

- **May underestimate fracture risk**
  - Fractures occur despite good BMD
  - Quality vs. quantity
- **Positive predictive value:**
  - Fracture risk higher with lower BMD

FRAX Tool



The FRAX tool was developed to be used those patients who have low bone mass to determine their 10-year risk

Limitations of FRAX

- Risk factors not considered include falling rate of bone loss, bone turnover
- Medications other than glucocorticoids
- Family history of fractures other than parental hip fracture

limitation of the FRAX score

- fracture estimates reflect the risk associated with prednisone at a dose of 2.5 to 7.5 mg per day

- U.K. General Practice Database suggests that among patients who receive more than 7.5 mg of prednisone daily,

➢ major osteoporotic fracture ⟶ increased by 15%
➢ risk of hip fracture ⟶ increased by 20%

(eg, if hip fracture risk is 2.0%, increase to 2.4%)

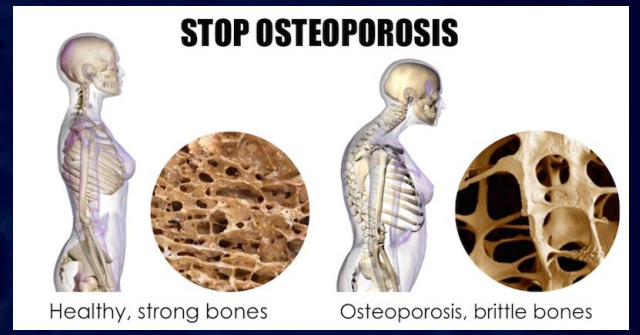
limitation of the FRAX score

- However, among patients who receive very high doses of prednisone (>30 mg per day or cumulative doses to >5 g per year), this adjustment may underestimate the risk of fracture

- use of bone mineral density at the hip instead of at the lumbar spine, since glucocorticoids have the greatest negative effect on trabecular bone in the spine

Management of Steroid induced OP

- **Minimise steroid exposure:**
  - Lowest dose/shortest time
- **Treat/control the underlying condition:**
  - May not be possible: e.g. COPD
- **Physical activity:**
  - Weight-bearing activities to strengthen bone
  - Strength-training to improve muscle strength
- **Prevent falls**



Calcium and vitamin D

- Adequate dietary intake of calcium (1000 mg per day) & vitamin D (600 to 800 IU)
- more important than for general population as steroids increase the excretion of urinary calcium

- Randomized trials

✓ prevented decreases in BMD in the spine during long-term use of low-dose prednisone (mean dose, 5 mg per day)

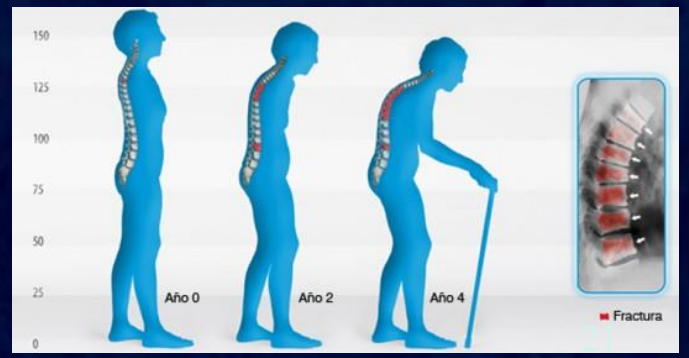
✓ not completely prevent bone loss in patients who were beginning to receive high-dose treatment (mean dose, 23 mg per day)

- Calcium alone is not effective in preventing bone loss

Pharmacologic Treatment

- 2017 guidelines of the American College of Rheumatology recommend pharmacologic treatment

1. In any patient with a previous osteoporotic fracture who is receiving GC (prednisone dose >2.5 mg per day)
2. Among patients who are receiving glucocorticoids and have a bone mineral density T score of −2.5 or less at either the spine or the femoral neck
3. for men who are 50 years of age or older
4. for postmenopausal women



Pharmacologic Treatment

- 5. Adults ≥ 40 years who do not meet the above criteria, pharmacologic treatment is recommended if

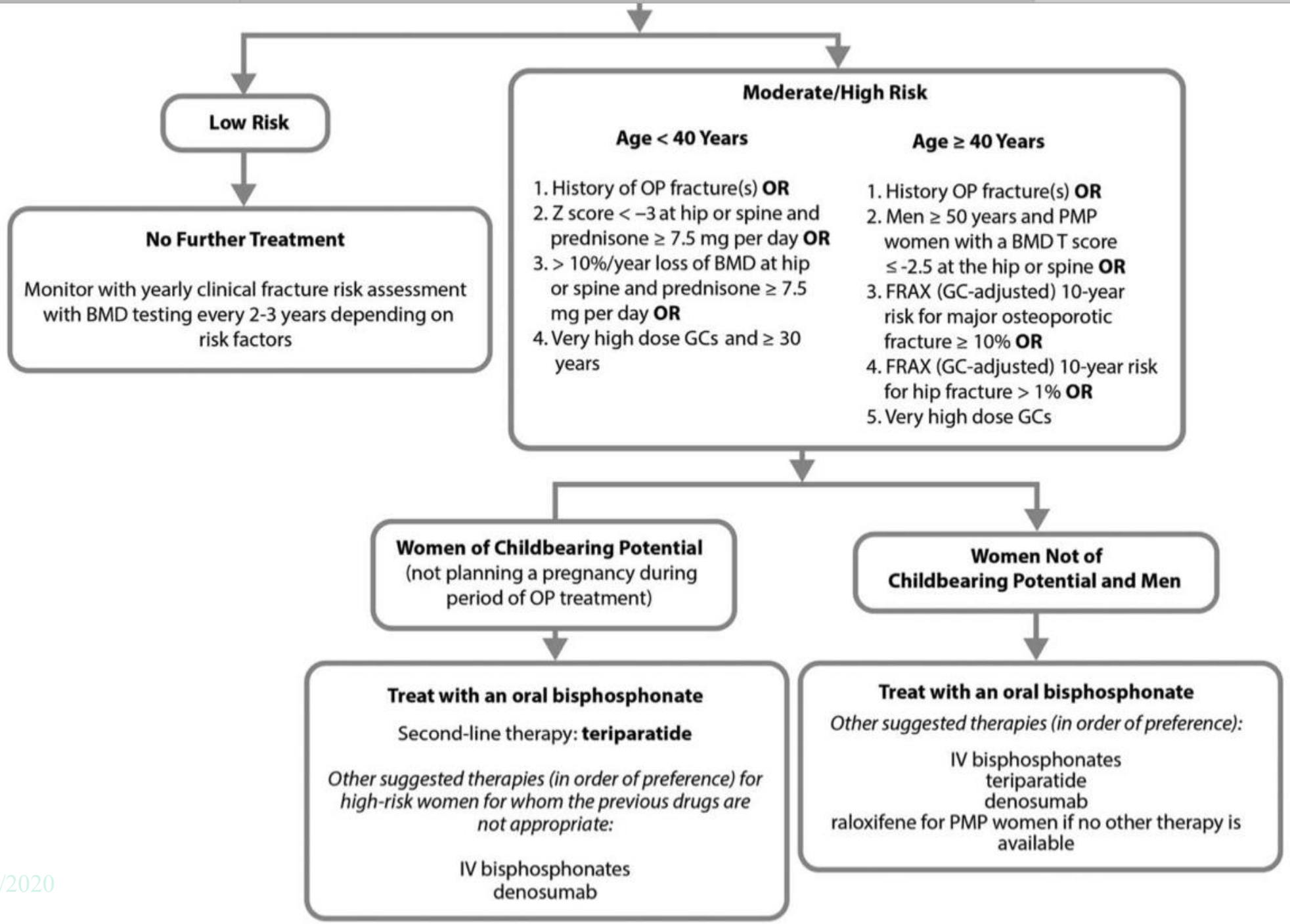
  ✓ the 10-year risk of major osteoporotic fracture is at least 20% or

  ✓ if the risk of hip fracture is at least 3% according to the FRAX tool

(after increasing the risk by 15% and 20%, respectively, for a prednisone dose >7.5 mg daily)

Fracture risk categories in GC-treated patients

	Adults ≥40 years of age	Adults <40 years of age
High fracture risk	Prior osteoporotic fracture(s) Hip or spine bone mineral density T score ≤−2.5 in men age ≥50 years and postmenopausal women FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ ≥20% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≥3%	Prior osteoporotic fracture(s)
Moderate fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ 10–19% FRAX* (GC-adjusted†) 10-year risk of hip fracture >1% and <3%	Hip or spine bone mineral density Z score <−3 **or** rapid bone loss (≥10% at the hip or spine over 1 year) **and** Continuing GC treatment at ≥7.5 mg/day for ≥6 months
Low fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ <10% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≤1%	None of above risk factors other than GC treatment


Low Risk
No Further Treatment
Monitor with yearly clinical fracture risk assessment with BMD testing every 2-3 years depending on risk factors
Moderate/High Risk
Age < 40 Years
1. History of OP fracture(s) OR
2. Z score < –3 at hip or spine and prednisone ≥ 7.5 mg per day OR
3. > 10%/year loss of BMD at hip or spine and prednisone ≥ 7.5 mg per day OR
4. Very high dose GCs and ≥ 30 years
Age ≥ 40 Years
1. History OP fracture(s) OR
2. Men ≥ 50 years and PMP women with a BMD T score ≤ -2.5 at the hip or spine OR
3. FRAX (GC-adjusted) 10-year risk for major osteoporotic fracture ≥ 10% OR
4. FRAX (GC-adjusted) 10-year risk for hip fracture > 1% OR
5. Very high dose GCs
Women of Childbearing Potential (not planning a pregnancy during period of OP treatment)
Women Not of Childbearing Potential and Men
Treat with an oral bisphosphonate
Second-line therapy: teriparatide
Other suggested therapies (in order of preference) for high-risk women for whom the previous drugs are not appropriate:
IV bisphosphonates
denosumab
Treat with an oral bisphosphonate
Other suggested therapies (in order of preference):
IV bisphosphonates
teriparatide
denosumab
raloxifene for PMP women if no other therapy is available

Approved Pharmacological Agents for the Management of GIO

Intervention	Dosing regimen	Route of administration
Alendronate	5 or 10 mg once daily 70 mg once weekly*	Oral
Etidronate‡	400 mg daily for 2 weeks every 3 months	Oral
Risedronate	5 mg once daily 35 mg once weekly*	Oral
Zoledronate	5 mg once yearly	Intravenous infusion
Teriparatide	20 µg once daily	Subcutaneous injection
*Only once-daily dosing regimens are approved for GIO. ‡Etidronate is only approved in Europe and Canada. Abbreviation: GIO, glucocorticoid-induced osteoporosis.		

Nat Rev Rheumatol. 2010;6(2):82-88

Bisphosphonates

- Numerous randomized trials have shown that bisphosphonates (alendronate, risedronate, zoledronate, and ibandronate) increase BMD in patients who receive glucocorticoids

- Due to their low cost and good safety profile, first-line agents unless there are contraindications or unacceptable side effects

- Intravenous bisphosphonates preferred
  - not adherent to oral bisphosphonates or
  - who cannot safely take the oral formulation

Bisphosphonates

- Caution, if at all, in patients with reduced kidney function (**GFR <30 mL/min for risedronate and ibandronate or <35 mL/min for alendronate and zoledronic acid)**

Oral bisphosphonates

	Advantages	Disadvantages
Oral bisphosphonates: Alendronate 70 mg/week (or 10 mg/d) Risedronate 35 mg/week (or 5 mg/d) Ibandronate 150 mg/mo.	• Affordable, cost effective • Osteoclast inhibition • Stops osteocyte apoptosis (ALN)	• GI side effects • Pill burden • Poor adherence • Contraindicated in poor renal function (eGFR < 30-35) • No data on hip fracture reduction in GIO • Non-anabolic

IV Zoledronate

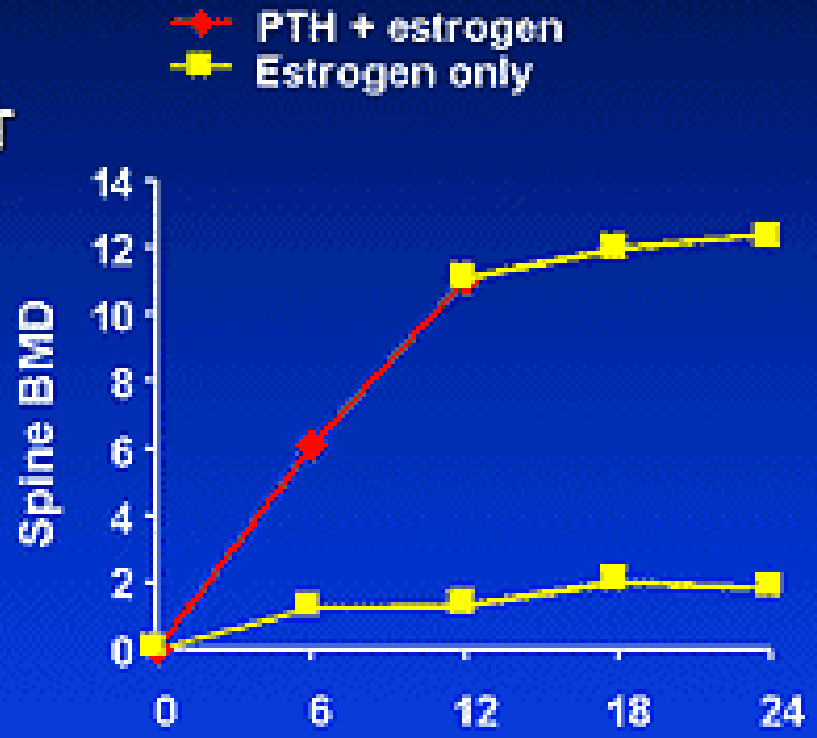
	Advantages	Disadvantages
Zoledronate 5mg/year	• Cost effective • Better compliance • More convenient • Avoids GI side effects	• Requires attendance to health facility Contraindicated in poor renal function (eGFR <30-35) • Risk of hypocalcaemia esp. if low vitamin D <50 nmol/L • Acute phase reaction • Risk of ONJ • Risk of atypical femoral fractures • Non-anabolic

Teriparatide

- anabolic and increase bone formation
- In a trial involving 428 patients who were receiving glucocorticoids, patients received either teriparatide or alendronate for 36 months
- Teriparatide was associated with
  - ✓ greater increases in BMD at the spine than alendronate (11% vs. 5.3%, P<0.001) and
  - ✓ a lower rate of radiographic vertebral fractures (1.7% vs. 7.7%, P = 0.007)

PTH in Glucocorticoid-Induced Osteoporosis Increased Spine BMD in Postmenopausal Women on HRT

- 51 postmenopausal women on HRT
- Chronic prednisone 5–20 mg
- 12-month spine BMD:
  - QCT ↑ 35%
  - DXA ↑ 11%
- 24-month F/U, BMD maintained off PTH



QCT=quantitative computed tomography
DXA=dual-energy x-ray absorption

Nancy Lane. *J Clin Invest.* 1998;102:1627.
Nancy Lane. *J Bone Miner Res.* 2000;15:944.

Teriparatide

	Advantages	Disadvantages
Teriparatide 20 µg SC daily for 2 years	• **The only anabolic agent** • Reduces vertebral fractures • Quick onset • Analgesic effect	• Cost (US$ 8547.90 for 2 year, list price) • Licensed for treatment for 2 years • Daily SC injections • No hip fracture data • Uncertain effect where PTH is raised (SHPT, CKD)

- Because of its higher cost and need for daily SC injection, teriparatide is generally regarded as a second-line option in the prevention and treatment of steroid induced OP.

Denosumab

- Inhibits bone resorption by binding to RANKL and interfering with the development of osteoclasts

- A noninferiority trial comparing denosumab with risedronate

- long-term showed superiority of denosumab with respect to
  - ✓ increases in BMD at the spine at 12 months
  - ✓ noninferiority with respect to rates of fracture

- Some but not all studies have shown a higher risk of infection

Denosumab

	Advantages	Disadvantages
Denosumab 60 mg SC every 6 months	• Potent anti-resorptive • **Not contraindicated in low renal clearance (eGFR ≤30)** • **Rapid onset/offset**	• Requires administration by a health professional • Strict 6-month schedule • Risk of hypocalcaemia esp. if low vitamin D <50 nmol/L • Risk of ONJ (0.001 to 0.15%) • Risk of atypical femoral fracture • Non-anabolic

Given the limited available safety data, denosumab is generally not recommended as the first line treatment in patients taking multiple immunosuppressive drugs or a biologic treatment

Raloxifene (Third-Line Agent)

- A selective estrogen-receptor modulator in postmenopausal women or
- with calcitonin, another antiresorptive agent,
- reserved for patients in whom
  - other treatments are contraindicated or
  - such treatments have failed

Treatment in Women of Childbearing Age

- Pharmacologic treatment to prevent fractures is not recommended in pregnant women

- A summary of 15 case reports and case series involving 65 women who received a bisphosphonate before or in the first few months of pregnancy showed no clinically significant adverse effects in the fetus

- But more data are needed

Treatment in Women of Childbearing Age

- When treatment is needed (e.g. with previous fracture or a high risk of fracture while receiving glucocorticoids)

  ✓ agents such as risedronate and teriparatide that have a shorter half-life and less retention in bone are generally recommended

- Animal studies shown that denosumab has teratogenic effects

- used with caution and with birth control

FOR PREMENOPAUSAL WOMEN AND FOR MEN YOUNGER THAN 50 yr

Younger patients with no prevalent fracture,

- Data were considered inadequate to make a recommendation, and no votes were taken

Prevalent fracture in premenopausal women of nonchildbearing potential

- Treatment is recommended with any of the four medications in patients with a fracture and treated with glucocorticoids for more than 3 months

(alendronate, risedronate, zoledronic acid, or teriparatide)

- For shorter-duration glucocorticoid use (1–3 months) at 5 mg/day or higher, only alendronate and risedronate are recommended

- If the dose is 7.5 mg/day or higher, any bisphosphonate is recommended

Prevalent fracture in women of childbearing potential

- For short term GC therapy at any dose and for therapy longer than 3 months at less than 7.5 mg, no consensus

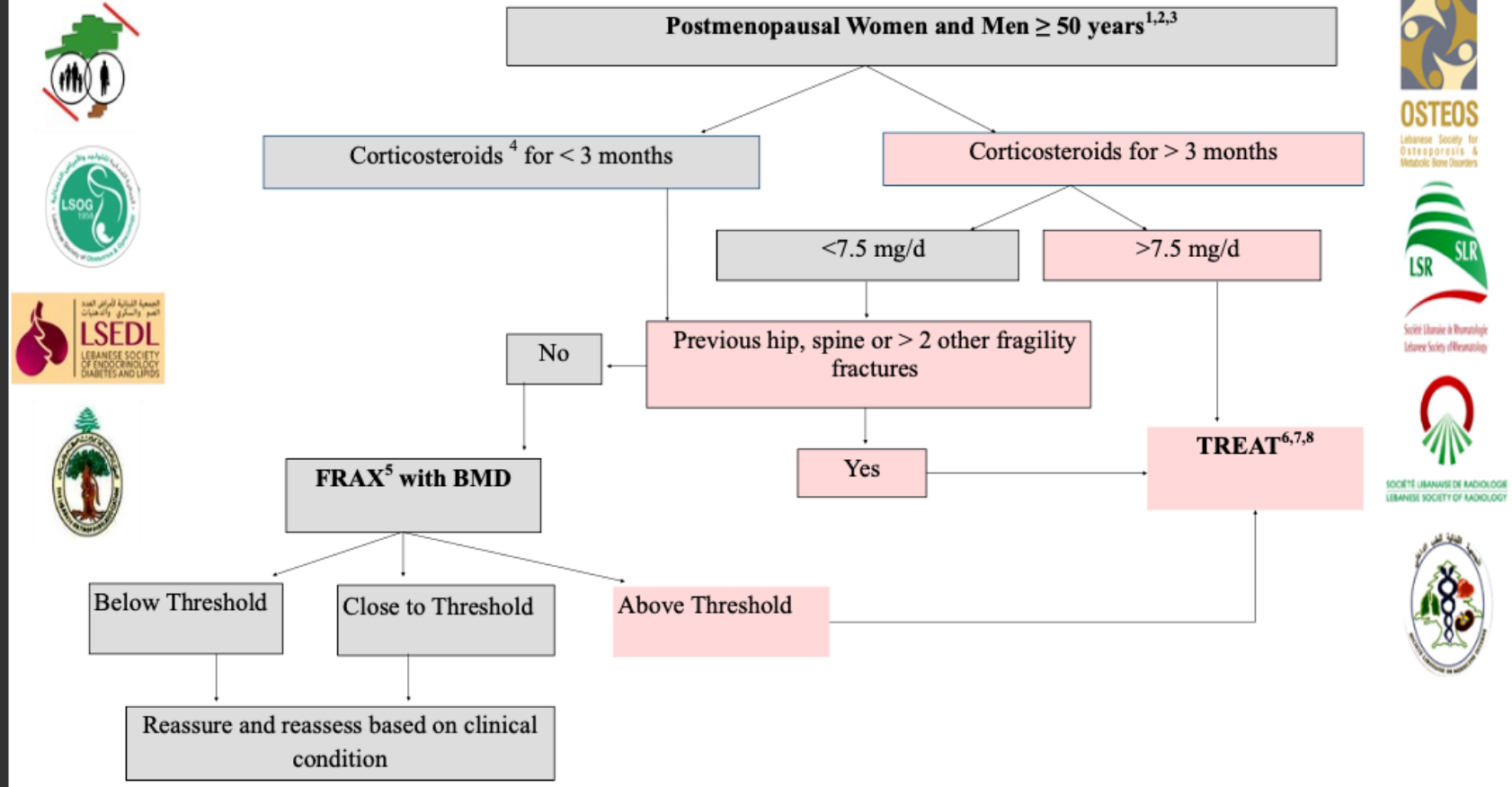
For therapy longer than 3 months and with 7.5 mg/day or higher, treatment is recommended

Glucocorticoid Induced Osteoporosis

Developed by the Lebanese National Task Force for Osteoporosis and Metabolic Bone Disorders*

Endorsed by:

Lebanese Society for Osteoporosis and Metabolic Bone Disorders, Lebanese Society of Endocrinology, Lebanese Society of Obstetrics and Gynecology, Lebanese Society of Rheumatology, Lebanese Orthopedics Society, Lebanese Society of Radiology, Lebanese Society of Family Medicine, Lebanese Society of Internal Medicine, Lebanese Society of General Practitioners.



[1] Osteoporosis Canada guidelines 2010.
[2] ACR 2010 guidelines.
[3] IOF-ECTS 2012 guidelines.
[4] Prednisone or prednisolone.
[5] 10-year risk for MOF adjustment: dose <2.5 mg/day, decrease FRAX by 20% ; dose 2.5-7.5 mg/day: no adjustment; Dose ≥ 7.5 mg/day: increase FRAX by 15%.
[6] FDA approved therapies for GIOP: alendronate, risedronate, zoledronic acid and teriparatide.
[7] Teriparatide is indicated in high risk individuals. High risk individuals are defined as postmenopausal women and men ≥ 50 years with high FRAX estimate as defined by FRAX Lebanon treatment thresholds, or premenopausal women and men < 50 years who have a history of fragility fracture and on a prednisone dose ≥7.5 mg daily for more than 3 months.
[8] Treat for the duration of steroid therapy.

*** Lebanese National Task Force for Osteoporosis and Metabolic Bone Disorders Members**

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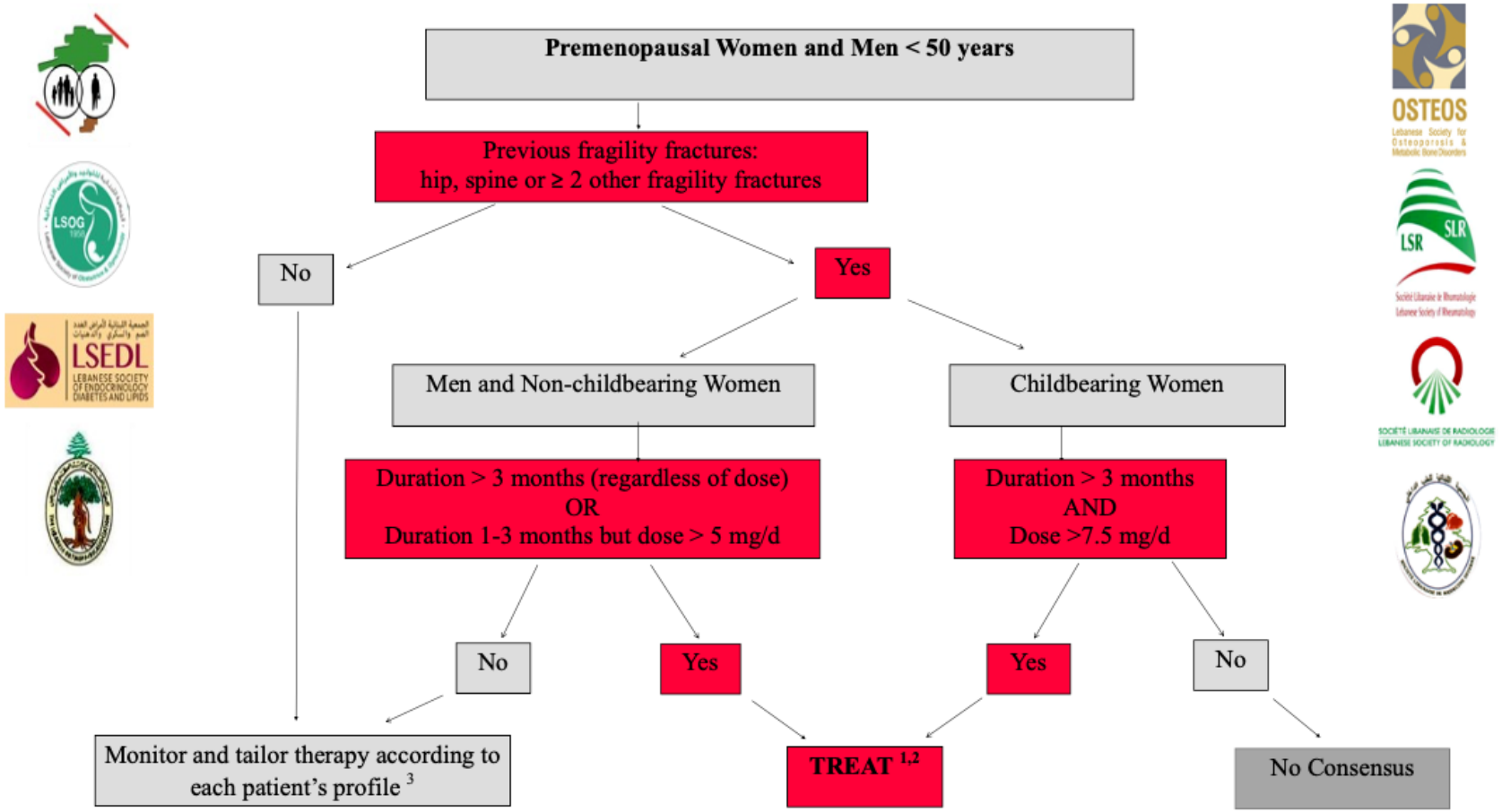

1 American College of Rheumatology (ACR) 2010 guidelines

2 Treat for the duration of steroid therapy.

3 If no previous fragility fracture, no recommendation was made by ACR. In a young individual with low bone mineral density and significant bone loss and who requires long term systemic glucocorticoid therapy, osteoporosis therapy may be suggested; expert opinion, Hansen et al, JBMR 2011.

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Key messages

- Steroid induced OP is common
- Risk is high at 3-6 months after starting, even at low doses
- Risk factors: fracture(s), age, dose-duration, BMI, BMD, underlying conditions
- Post-menopausal women or men >50: low threshold to treat
- Individualise decision in pre-menopausal women or younger men

Thank You