Osteoporosis and Rheumatic Diseases

This is an area which is often neglected and is a burden too heavy to be carried by the weakened bones! There is an increased risk of osteoporosis (OP) in rheumatic diseases, a chronic inflammatory state, often warranting the use of steroids. Pathogenesis is multifactorial involving cross-talk between inflammatory cells and bone cells, disease complications, poor nutrition, medications, and decreased physical activity. Dickkopf-related protein 1 (DKK-1) and sclerostin, which are negative regulators of the Wnt signalling pathway, inhibit bone formation in rheumatic diseases.[1] Steroid use increases their expression besides augmenting osteoclastogenesis by inhibiting Osteoprotegerin (OPG) and increasing RANKL expression. Muscle wasting and changes in bone microstructure further compound the problem. Factors which increase the risk of OP have been outlined in Box 1. OP screening involves

Box 1: Risk Factors

1) Age
2) Previous h/o low trauma fractures
3) Low BMI, Significant weight loss
4) Current smoking and alcohol
5) Parental h/o hip fracture
6) Use of steroids
7) Rheumatic diseases
8) Secondary OP - Endocrine causes, IBD, malabsorption, Chronic liver disease
9) Malnutrition

1) A good history and examination to asses risk factors and h/o fracture and examination including BMI and loss of height, reduced space between lower ribs and pelvis, spinal tenderness.
2) Look for secondary causes
3) Addictions particularly tobacco use
4) Medications
5) Biochemistry including calcium, ALP
6) Bone mineral density (BMD) assessment within six months of initiation of glucocorticoid treatment. Most widely used tool is Dual-energy x-ray absorptiometry (DXA) thought newer techniques like pDXA (peripheral DXA), Quantitative Computerised Tomography (QCT) and peripheral QCT are available but needs validation and are costlier.
7) Biochemical biomarkers like C telopeptide, free deoxypyridinoline may independently predict fracture risk but are not routinely used

Fracture Risk Assessment Tool (FRAX) developed by University of Sheffield, estimates 10-year probability of hip and major OP fracture (hip, clinical spine, proximal humerus, or forearm) between 40-90 years using clinical risk factors with/without femoral neck BMD. [2] Besides age, gender, weight, height, it includes risk factors as defined in Box 1 where only Rheumatoid Arthritis is taken in rheumatic diseases, steroid use has been defined as ≥ 5mg for 3 or more months. There are however insufficient data to develop prediction tools for younger adults and children.

Although the greatest relative risk of fracture is in individuals with osteoporosis (OP), the absolute number of fractures in those with BMD T-scores in the low bone mass (osteopenia) range is the same or greater than in those with T-scores in the osteoporosis range, as more individuals belong to the latter category. At times BMD may give us a fall sense of hope and some patients who need preventive therapy may be missed.

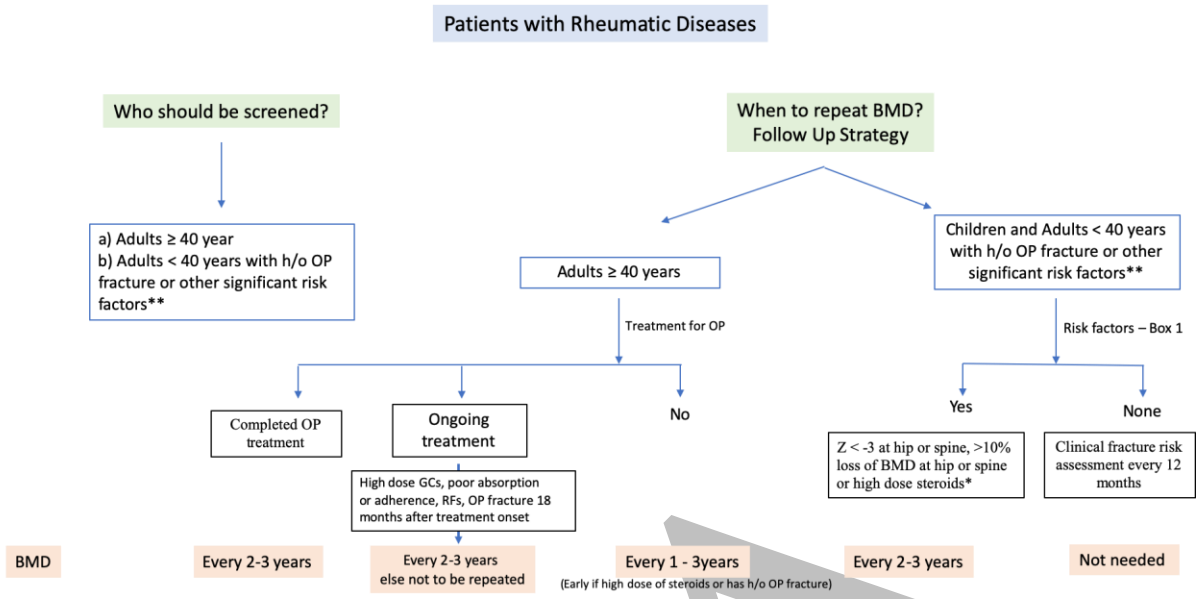

Figure 1 - highlights the candidates who should undergo screening and follow up strategy in such patients; h/o, history of; OP, Osteoporosis; RFs, Risk factors; *High dose steroids ≥30mg/d or 5g in last one year. BMD, Bone Mineral Density **as defined in box 1. (Modified from ACR 2017 guidelines[3])

Rheumatic Diseases

Various studies have looked at the prevalence of osteoporosis in rheumatic disease. [4,5] Prevalence and some of the associated risk factors have been mentioned in **Table 1.**

Table 1: Prevalence and Risk Factors of OP in rheumatic diseases [4,5]

	Osteoporosis	Additional Risk Factors
SLE	1.4 – 68%	Reduced sun exposure, high falls, renal involvement, longer disease duration No relation to disease activity
RA	18 – 56%	Longer disease duration, Disease activity, HAQ, RF/ACPA, High CRP
AS	19 – 62%	Older age, long-standing disease, syndesmophyte formation, associated IBD
PsA	11 – 47%	Association with disease duration is controversial
SSc	3 – 51%	Intestinal malabsorption, renal disease, subcutaneous calcinosis, no difference in lcSSc and dcSSc
IIM	25%	Correlation with disease activity unclear
JIA	40-52% of adult patients with JIA	Disease Activity and duration

It is important to remember that osteoarthritis, syndesmophytes, new bone formation, atherosclerosis may falsely increase BMD measurement.[6,7] Management strategy should include FRAX score calculation and risk stratification and the use of OP medications accordingly. Moderate to high risk patients should be treated with OP medications even if steroids are not used. (**Table 2 and Figure 1)**

GIOP (Glucocorticoid induced Osteoporosis)

Long-term glucocorticoid therapy causes osteoporotic fractures in about 10-12% of treated adult patients and 30–40% of them have radiographic evidence of vertebral fractures, in view of higher effects of steroids on trabecular bone [8,9] Daily doses of ≤5 mg prednisolone have been shown to increase fracture risk by ~20%, rising to 60% for doses of ≥20 mg per day.[7,10] **Fracture risk is highest particularly within first the 3-6 months and correlates with cumulative dose and daily dose**. [10] Still the preventive care is suboptimal and less than a quarter undergo OP assessment and often the therapy is instituted once a fracture occurs.

Whom to Treat?

In GIOP, the terms 'prevention' and 'treatment' distinguish between the initiation of anti-osteoporosis intervention at the start of glucocorticoid therapy or after >3 months, respectively.

Table 2: OP Risk Stratification as per ACR 2017 guidelines

	Adults ≥ 40 years			**Adults < 40 years**	
	Prior OP #	T score	FRAX	Prior OP #	Z score
High Risk	Yes	≤ 2.5 in men ≥ 50 years and post menopausal women	≥ 20% * ≥ 3% **	Yes	
Moderate Risk			10-19 % * 1-3% **		< - 3 (Hip or Spine) or rapid bone loss ≥ 10%/year and continued GC > 7.5 mg/day for ≥ 6 months
Low Risk			< 10% * <1% **		None of above risk factors other than GC treatment

*GC adjusted 10 year risk of major OP #, ** GC adjusted 10 year hip # risk
Increase the risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid (GC) treatment is 7.5 mg/day (e.g., if hip fracture risk is 2.0%, increase to 2.4%).
Major osteoporotic fracture includes fractures of the spine (clinical), hip, wrist, or humerus
OP, Osteoporosis; #, Fracture; FRAX, Fracture Risk Assessment Tool. Visit https//www.shef.ac.uk/FRAX/tool.jsp.

Prevention:

Depending on risk stratification, all adults irrespective of age, not of childbearing age or childbearing age but not planning a pregnancy during treatment, with moderate to high risk as defined in **Table 2**, should receive oral Bisphosphonate. Second line therapies include IV bisphosphonate, teriparatide, denosumab and raloxifene (for post-menopausal women only) in that order except in women of childbearing potential where teriparatide is preferred over oral bisphosphonate. IV bisphosphonate and denosumab lack safety data in pregnancy and hence should be used only in high risk patients whereas raloxifene is not recommended. Some authorities do no rate bisphosphonates over teriparatide due to lack of head to head comparisons. Denosumab, though not a first line therapy, but is a good alternative particularly in patients with renal failure. **Some experts recommend upfront teriparatide in patients with T-score < -3.5 or T-score of -2.5 or below plus a fragility fracture**. Romosozumab**,** sclerostin inhibitor, is another new emerging therapy yet to find a place in guidelines. Refer to table 3 for dosing, side effects and monitoring.

Other essential recommendations including for those with low risk of fracture are

1) **Daily calcium and vitamin D 1,000–1,200 mg and 600–800 IU respectively**
2) **Lifestyle modifications** like cessation of smoking, limiting alcohol intake to 1-2/day,
3) Balanced diet and weight and daily exercises.

4) **Figure 1** summarises the prevention strategy and follow up treatment [11] In case of moderate to high risk, continue oral Bisphosphonate for ten years and Zoledronic acid for five years. There is no concept of drug holiday in such cases. Besides GCs, Methotrexate, Cyclophosphamide, heparin, oral anticoagulants, anti-convulsant are some of the medications which have been implicated in OP.

Drug	Dose	Pre-requisites or monitoring	Side effects and Contra-indications
Oral Bisphosphonate	Alendronate 70mg/week Risedronate 35mg/week or 150mg/month	Avoid oral calcium supplements, antacids, magnesium supplements/laxatives, and iron preparations for at least 60 minutes after drug administration Check serum calcium	GERD/Reflux oesophagitis Osteonecrosis of Jaw (ONJ) - 1 in 10,000 to 1 in 100,000 patient-years Atypical Femur Fracture (AFF) Hypersensitivity GFR < 30ml/min Hypocalcemia achalasia, esophageal stricture, esophageal varices, Barrett's esophagus) or with an inability to follow the dosing requirements (eg, stay upright for at least 30 minutes) Pregnancy and breastfeeding
IV Bisphosphonate	Zoledronic 4mg every year	Can have flu like symptoms, give Paracetamol before IV administration Check calcium and correct before drug administration	Transient hypocalcemia, Flu like symptoms within 24-72 hours of infusion; Treat with Paracetamol or NSAIDs ONJ, AFF Hypersensitivity GFR < 30ml/min Hypocalcemia Pregnancy and breastfeeding
Teriparatide	20 mcg s.c every day upto 2 years		Hypercalcemia, Dizziness, arthralgia, rhinitis Osteosarcoma Hypersensitivity, hypercalcemia and related conditions
Denosumab	60mg s.c every six months	Check calcium and vitamin D and in deficient – correct same before administering Denosumab Higher risk in CKD pts, eGFR < 30 and in those with malabsorption and hence more prone to hypocalcemia. Check calcium level 10 days after administration of Denosumab	Infections Skin Rash Immediate risk of fractures on stopping the drug – add bisphosphonate if denosumab needs to be stopped Hypersensitivity Hypocalcemia

CKD, Chronic Kidney Disease; GERD, Gastro-esophageal reflux disease; GFR, Glomerular filtration rate; s.c, subcutaneous

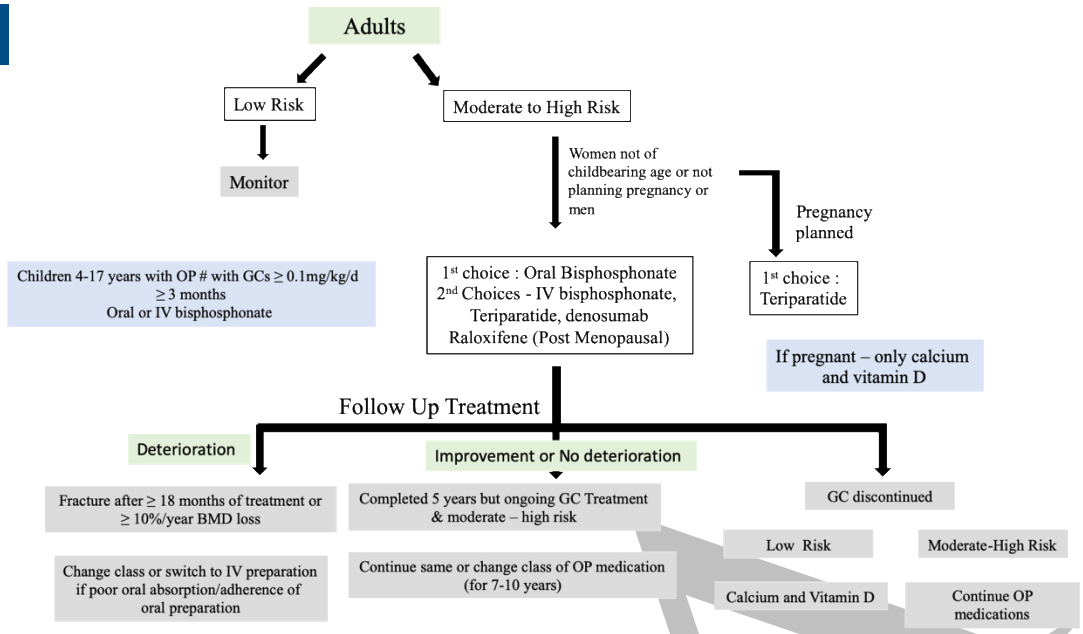

Fig 1: Prevention of GIOP in patients beginning long term GC treatment - ≥ 2.5 mg for ≥ 3months; Calcium 1- 1.2 g/d and vitamin D 600-800IU/d should be given to everyone; BMD, Bone Mineral Density; GC, Glucocorticoid: OP, Osteoporosis. For risk stratification see table 2

Osteoporosis is a potentially preventable complication which needs to be taken care of by a rheumatologist considering an increasing prevalence of OP in rheumatic diseases. Good control of disease and hence inflammation, minimising steroid use, emphasis on dietary and lifestyle modifications, calcium and vitamin D supplementation and use of OP medications when indicated will help in reducing this complication. "Prevention is always better than cure! Action is better than procrastination."

Summary

1. Osteoporosis is a common but neglected issue, amenable to therapy or prevention in patients with rheumatic diseases particularly on steroids.
2. 10-12% patients on steroid suffer from fracture or 30-50% have radiological evidence of vertebral fracture with maximum loss occurring in 3-6 months.
3. Do not forget secondary causes which further increase the risk of osteoporosis.
4. All patients with rheumatic diseases, age 40 years or more, and children with risk factors should undergo BMD within six months of initiation of glucocorticoid.
5. FRAX score, with correction for steroid dose, can be used in patients aged ≥ 40 years for fracture risk prediction with/without BMD. (https//www.shef.ac.uk/FRAX/tool.jsp)
6. Treatment should be started for those falling in moderate to high risk.
7. There is no role of follow up BMD adults population on treatment unless there are risk factors and/or development of fracture despite ≥ 18 months of therapy or poor adherence/compliance.
8. There is no concept of drug holiday at end of 3-5 years if there is moderate to high risk and therapy should be continued for additional 3-5 years.
9. Upfront Teriparatide maybe considered in T-score < -3.5 or T-score of -2.5 or below plus a fragility fracture or a contra-indication for bisphosphonate except pregnancy

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