

## Indian rheumatology association guidelines for management of glucocorticoid-induced osteoporosis

Endorsed by: Endocrine Society of India and Indian Society for Bone & Mineral Research

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### INTRODUCTION

Glucocorticoids have revolutionized the treatment of inflammatory diseases in the past 60 years. The beneficial anti-inflammatory effects are associated with various side-effects. Osteoporosis resulting in fractures at spine and hips is one of the significant adverse effects with long-term use. Other adverse effects include precipitation of diabetes, hypertension, cataract formation, skin thinning, osteonecrosis and Cushingoid appearance. Around 1% of adult population chronically ingests glucocorticoids on long-term basis and the percentage is higher in the elderly. In one of the largest studies having included more than 250,000 glucocorticoid users and same number of age matched controls, the incidence of hip and vertebral fractures was increased 2–4 fold amongst patients taking daily doses of prednisolone more than 2.5 mg.<sup>1</sup> After discontinuation of glucocorticoids, the bone loss is at least partially reversed.<sup>2</sup>

### PATHOGENESIS

Bone is a dynamic tissue wherein pockets of resorption and formation are coupled under normal physiological conditions. These processes are uncoupled during glucocorticoid treatment, the bone formation being inhibited and resorption unchanged or accelerated. Trabecular bone is initially affected and with prolonged use the cortical bone such as femoral neck can also get involved. Glucocorticoids stimulate

apoptosis of osteoblasts and osteocytes, and they prolong the lifespan of osteoclasts.<sup>3</sup> Glucocorticoids preferentially stimulate the differentiation of mesenchymal stem cells into adipocytes pathway over the differentiation to osteoblasts. The intestinal absorption of calcium is also reduced and urinary calcium loss is increased.<sup>4</sup> Oral glucocorticoids inhibit follicle stimulating hormone-induced estrogen production in women and suppress testosterone levels in men. These negative effects on gonadal hormones contribute to increased bone resorption.<sup>4</sup> Other than these direct effects on bone, glucocorticoids induce muscle wasting and consequently muscle weakness and increased susceptibility to physical falls.

Although decline in bone mineral density is correlated with fracture risk, the glucocorticoid-induced micro-architectural changes of collagen content and cross-linking are also important determinants of fracture risk. Analysis of placebo groups from randomized trials indicate that for the same bone mineral density the incidence of vertebral fractures is higher in glucocorticoid patients than in no-users, suggesting that the increased fracture risk is only partly explained by measuring bone mineral density.<sup>5</sup>

The underlying disease for which the glucocorticoid is prescribed also contributes to the increased risk of fracture. Inflammatory processes, through pro-inflammatory cytokines contribute to systemic bone loss.<sup>5</sup> Although glucocorticoids reduce systemic inflammation, there is evidence of higher risks of fractures on oral glucocorticoid users compared to non-users with similar underlying disease.<sup>1</sup>

The relative contribution of the different mechanisms to development of fractures is not known, and there exists

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individual heterogeneity in response to oral glucocorticoids which is in turn dependent on genetic polymorphism in the glucocorticoid receptor that determines differences in body composition, insulin and cholesterol levels.<sup>5</sup>

## ASSESSMENT OF GIOP

Grade of recommendation are based on the evidence available. According to this it can be graded as tabulated below:

Grade of recommendation	Level of evidence	Type of evidence
A	Ia	Meta-analysis of RCTs
	Ib	At least one RCT
B	IIa	At least one well designed controlled trial without randomization
	IIb	At least one well designed experimental study
	III	At least one well designed descriptive study
C	IV	Expert committee report, opinion and or experience of respected authorities

## POINTS TO BE REMEMBERED WHILE ASSESSING PATIENTS FOR GLUCOCORTICOID-INDUCED OSTEOPOROSIS (GIOP)

1. Loss of BMD is greatest in first few months of GC use (grade A, level Ia).
2. The administration of GC is associated with a significant increase in fracture risk at the hip and spine. The risk of fracture increases two-fold for each SD reduction in BMD (grade A, level Ia).
3. Fracture threshold in GIOP is significantly lower than in postmenopausal osteoporosis, which means GC increase fracture risk over and above the effect of low BMD (grade A, level Ia). This emphasizes the importance of evaluating fracture risk in all individuals on GC.
4. No dose, route of administration or type of GC is safe from decreasing BMD, if used for prolonged periods (grade B, level IIa).

5. Bone loss is related to cumulative dose of GC. Start preventive measures in these individuals if planning long-term treatment with GC.
6. BMD measurement is not essential in all patients before starting them on GC.

## WHO SHOULD BE SUBJECTED TO BMD MEASUREMENT BEFORE STARTING ON GC?

1. Age more than 65 years.
2. History of fragility fracture.
3. Premature menopause including surgical (<45years).
4. Family history of fragility fracture.
5. BMI < 19 kg/m<sup>2</sup>.
6. Prolonged immobilization.

## WHAT SCREENING OR MONITORING MODALITIES SHOULD BE USED?

### Quantitative Ultrasound (QUS)

Assessment and monitoring of skeletal changes with QUS is not recommended because of limited experience and no availability of validated data on diagnostic thresholds for peripheral densitometry in GIOP.

### DUAL ENERGY X-RAY ABSORPTIOMETRY (DXA)

Measurement by DXA gives an accurate reflection of bone mass. BMD results are reported as T-score (comparison with young adult mean) and Z-scores (comparison with the mean of individuals of the same age). It is important to use race specific reference ranges when available. Preferably, same machine should be used each time for measuring BMD in a patient to ensure consistency in values. Prediction of fracture risk is site specific.

Measurement of BMD at hip and lumbar spine using DXA is currently recommended for assessment of fracture risk and monitoring treatment response in individuals on GC (grade C, level IV). If BMD measurement facility is not available, preventive treatment for GIOP should be started in individuals with risk factors (grade C, level IV).

### **Peripheral DXA (Phalanges/Distal Radius/Calcaneum)**

It is useful for site specific fracture risk prediction but predictive capacity for hip fracture appears to be less than that of DXA of spine and hip. It should not be used for screening for GIOP or monitoring response to therapy.

### **SINGLE ENERGY X-RAY ABSORPTIOMETRY (SXA)**

It measures BMD of peripheral skeleton (distal radius and calcaneum), therefore the predictive capacity for hip and vertebral fracture is less than that of DXA. It should not be used for assessment of GIOP or monitoring response to treatment.

### **QUANTITATIVE CT (QCT)**

It measures BMD at axial skeleton. The main limitation is very limited availability in India and a high radiation exposure compared to DXA. It has a role in assessment of bone mineral density in ankylosing spondylitis where DXA may give a false high values due to ligament calcification.

### **BIOCHEMICAL MARKERS**

They should not be used in the diagnosis of osteoporosis. Bone resorption markers (N-telopeptide, C-telopeptide of type I collagen) can be used in addition to a BMD assessment to identify high risk patients for future fracture and monitoring of response to treatment (grade B, level Ia).

The identification of pre-existing fracture is very important in patients who are taking GC as fracture may be asymptomatic. Consequently, a radiological approach with morphometric analysis (X-ray dorsolumbar spine lateral and anteroposterior view) is useful for the identification of vertebral deformities.

Secondary causes of osteoporosis should be excluded in individuals with prior fracture. Laboratory evaluation for secondary causes of osteoporosis in GIOP has not been evaluated. However, a general evaluation (haemogram, liver function test, renal function test, Calcium, phosphate, serum alkaline phosphatase, TSH, PTH, serum and urine electrophoresis, testosterone in males) is warranted in patients with unusual clinical features.

### **MONITORING OF THERAPY**

DXA (hip and lumbar spine L1–L4) should be performed at 1–2 years intervals. Bone resorption markers (N-telopeptide, C-telopeptide of type I collagen) along with DXA can be used to monitor treatment response if feasible. Two separate baseline values followed by repeat measurement at 3 months after starting GC should be done. Bone resorption markers can be repeated every year if needed (grade C, level IV).

### **NON PHARMACOLOGICAL INTERVENTIONS IN GIOP**

#### **Prevention of falls in elderly with or without GCs**

Ninety percent of hip fractures result from a fall especially in the elderly with osteoporosis.<sup>6</sup> Fall prevention should be an integral part of fracture prevention since many of the risk factors for falls and fractures are the same.<sup>7</sup> Deficiency of calcium and vitamin D contribute to myopathy and falls.<sup>8</sup> Reduced muscle strength and mass (sarcopenia) and poor balance are risk factors for falls and they can be improved by exercises such as progressive resistance training.<sup>9</sup> Physical activity has positive effect on BMD. Weight bearing exercises are more beneficial than non-weight bearing exercises.<sup>10</sup> Other interventions to prevent falls include gradual withdrawal of psychotropic drugs, home hazard assessment (floor, carpets, poor lighting, steps, etc.) improving the sight (cataract surgery), use of walking aids and foot wear improvement. Alcohol intake and smoking should be discouraged.

#### **Exercises**

Strength training exercises include using free weights, weight machine, resistant bands, or water exercises to strengthen muscles and bones of arms and upper spine. Weight-bearing aerobic activities includes walking, dancing, low impact aerobics and activities such as gardening. They improve the strength of muscles and bones of lower limbs and lower spine. However, adherence to the exercises is a major challenge in long-term interventions.

### **PHARMACOLOGICAL INTERVENTIONS**

The different treatment strategies which have been used for prevention and treatment include life style modification,

oral calcium and vitamin D supplementation, hormone replacement therapy, bisphosphonates, fluorides, calcitonin and PTH analogues. The pharmacological options include the following.

### Calcium and vitamin D

All patients taking GCs should be considered candidate for preventive therapy of osteoporosis regardless of dose and duration.<sup>11</sup> Calcium and vitamin D supplementation should be given to patients who have no risk of bone loss and are on lower doses of steroids for short duration (5 mg or less for less than 3 months). It is a relatively low cost way of reducing the risk of fracture in GIOP. It forms a basis for further pharmacotherapy. Patients who have associated risk factors, pre-existing bone loss and who are on higher doses of GCs for longer duration should be considered for anti-resorptive therapy in addition.

Despite the adequate sun light in our country, most individuals are vitamin D insufficient suggesting inadequate sun exposure or dark skin preventing adequate vitamin D synthesis. Low calcium intake is also widespread in Indians. Adequate intake of calcium and vitamin D helps maintain bone mass, improve muscle strength and reduce fracture risk. Oral vitamin D reduces the risk of hip fracture only when calcium supplementation is added.<sup>12</sup> Similarly preservation of bone mineral density (BMD) was seen in elderly men and women with combined calcium and vitamin D, but the effect was not maintained with calcium alone.<sup>13</sup> Supplementation of calcium and vitamin D should be directed at individuals with known risk factors such as elderly age, glucocorticoid treatment, co-morbidities like rheumatoid arthritis (RA).<sup>14</sup> Compliance is essential for efficacy of the supplementation for long-term.<sup>15</sup> Optimum intake of calcium and vitamin D are essential to achieve maximum benefit from pharmacological intervention such as bisphosphonates. It is recommended to take calcium (1000 mg or more per day) and vit D (800 IU or more) regularly in a subject with osteoporosis.<sup>16</sup> In the Indian setting it is suggested that 2000 IU/day of vitamin D be supplemented as lower doses are usually unable to achieve optimum 25(OH)D levels (> 30 ng/mL).

Commonly used calcium supplements include calcium carbonate and calcium citrate. Calcium carbonate is best absorbed in an acidic environment and is taken with food. Calcium citrate does not require an acidic pH. Calcium supplements are better given in two divided doses for better absorption. The risk for renal stones does not increase in patients taking physiological doses of calcium.<sup>17</sup> The fear of calcium supplement (without co-administered vitamin D)

associated with an increased risk of cardiac events<sup>18</sup> is not tenable in our population with low calcium and vitamin D.

Cholecalciferol (vit D3) is produced by skin exposed to UV light and is a form of vitamin D present in fish. Vit D3 and ergocalciferol can be synthesized and are used as vitamin supplements to fortify the foods. Alfacalcidol is superior to vitamin D in the treatment of established GIOP in some studies.<sup>19</sup> Active form of vitamin D, calcitriol or 1,25-dihydroxy vitamin D (formed by hydroxylation in the liver and then in the kidney) 0.5–1.0 µg/day should be given if there is evidence of malabsorption, renal insufficiency or low urine calcium.<sup>20</sup> Cholecalciferol (vit D3) is given 1000–2000 units/day in GIOP. Sun exposure to the body is recommended in the mornings for 10–30 minutes a day at least 3 times a week. At recommended doses vitamin D toxicity does not occur. Vitamin D prevents cardiovascular disease, modulates innate and adaptive immune functions, prevents autoimmunity,<sup>21</sup> retards infections and corrects metabolic bone disease.

Some examples of the dietary foods rich in calcium are tabulated below:

Food item	Portion	Calcium (mg)
Skimmed milk	1 cup (250 mL)	300
Plain low fat yogurt	1 cup	415
Cheese	25 g	150
Orange juice (added Ca)	1 cup	300
Spinach (boiled)	1 cup	245
Canned salmon	90 mL	180
Cheese pizza	1 slice	110
Almonds	28 g/24 nuts	70

### Bisphosphonates

Bisphosphonates are the cornerstone of treatment of GIOP; however, there is no consensus on what is the best time to initiate treatment with bisphosphonates. This is mainly related to absence of conclusive data on efficacy of primary prevention in pre-menopausal women and in patients on low dose prednisolone. Further the data on fracture risk reduction is less. American college of Rheumatology guidelines are more liberal whereas British guidelines are more conservative.

Bisphosphonates reduce bone resorption by inducing osteoclast apoptosis as well as have minor effect on osteoblasts. Among the different bisphosphonates, cyclic Etidronate, alendronate, Risedronate, Ibandronate, Pamidronate as well as Zoledronic acid have shown efficacy in GIOP.<sup>22–24</sup> In current practice Alendronate and Risedronate are most

widely used. They lead to about 3–4% increase in BMD over placebo when given along with calcium and vitamin D for a period of 1 year. The data on fracture risk reduction is sparse.

#### *When should they be used?*

Primary prevention. Bisphosphonates should be used in all patients initiating GC (Prednisolone > 7.5 mg/day) for more than 3 months if they fulfill any of the following conditions:

1. Post-menopausal women.
2. Men > 65 years.
3. Baseline BMD T-score < -1.5.
4. Previous fragility fracture.

In pre-menopausal women one needs to be cautious as bisphosphonates stay in body for long time, data on their efficacy is limited and potential teratogenic risk.

#### *What are the options?*

1. Alendronate 35–70 mg/week or daily dose of 5–10 mg/day (oral).
2. Risedronate 35 mg/week or 5 mg/day (oral).
3. Ibandronate 150 mg/month (oral) or 3 mg IV once in 3 months.
4. Zoledronic acid 5 mg given as IV infusion once a year.

Yearly Zoledronic acid is a good alternative in patients where compliance and cost are a major problem.

#### *What are the precautions?*

It should be avoided in patients with significant renal disease, hypocalcemia or esophageal disease.

### **Calcitonin**

Calcitonin is used as a second line treatment for established GIOP after bisphosphonate failure. It has remarkable effect on pain because of osteoporotic fracture. Calcitonin prevents bone loss at the lumbar spine by about 3% compared to placebo, but has no effect on femoral neck BMD or on fracture risk.<sup>25</sup> It is given as 100–200 units/day as nasal spray. Subcutaneous calcitonin is no longer used. With the availability of teriperatide, calcitonin is rarely used.

### **Parathormone analogues (Teriperatide)**

It is the most physiological treatment for GIOP as it results in normal bone formation. Eighteen months treatment with daily SC injection led to a 6% increase in spinal BMD over alendronate and an absolute increase of nearly 8% in spinal BMD at the end of the study. Radiographic detected fractures

were also reduced in the teriperatide group. There was no difference in the toxicity profile. In this study nearly 70% patients were post-menopausal women, had T-score < -2.5 and in 30% had previous vertebral fracture.<sup>26</sup>

Thus teriperatide may be useful in these high risk patients. In further follow-up of this study the effect was maintained till 36 months. Problems include need for daily injections and the high cost.

### **Hormone therapy**

Men on long-term GC should be evaluated for possible hypogonadism and if testosterone level is < 300 ng/mL should be started on androgens as this leads to 4–5% increase in lumbar spine BMD after 12 months.<sup>27</sup> Various testosterone esters like 30 mg of proprionate, 60 mg of phenylprionate, 60 mg of isocaproate, and 100 mg of decanoate/day or 250-mg/month intramuscular depot injection can be used. However, carcinoma prostate should be excluded according to age specific screening guidelines before start of treatment. Even though HRT increases BMD in postmenopausal women there is no data of its use in GIOP.

### **Other treatments**

Therapies like strontium, fluorides and vitamin K have either not been studied or have not shown benefit in GIOP.

The American College of Rheumatology has come out with guidelines for GIOP based on FRAX tool.<sup>29</sup> We Indians can follow the FRAX tool applied for Singapore Asian Indians.

Thus in adults the therapies given below have the following grades of recommendation.

<i>Drug</i>	<i>Effect on spinal and femur BMD</i>	<i>Effect on vertebral fracture</i>
Etidronate	A	Limited data
Risedronate	A	Limited data
Alendronate	A	Limited data
Ibandronate	A	No data
Zoledronic acid	A	Limited data
Calcitonin		No data
HRT	A	No data
Testosterone	A (but no effect on femoral BMD)	No data
PTH analogue	A	Limited data

Data on non-vertebral fracture risk is not available.

**Children**

Glucocorticoids are widely used in treatment of systemic onset JIA, juvenile dermatomyositis, nephrotic syndrome etc. In a small study of 22 patients weekly alendronate (1–2 mg/kg/week) led to increase in volumetric BMD, decrease in markers of bone turnover and had no adverse effect on bone growth. Alendronate was also found to be safe in children.<sup>28</sup> Since there is no data on its role as primary prevention or reduction of fracture risk in children it should be used in children who are receiving chronic glucocorticoids >0.125 mg/kg and have low BMD for their age.

**Key points**

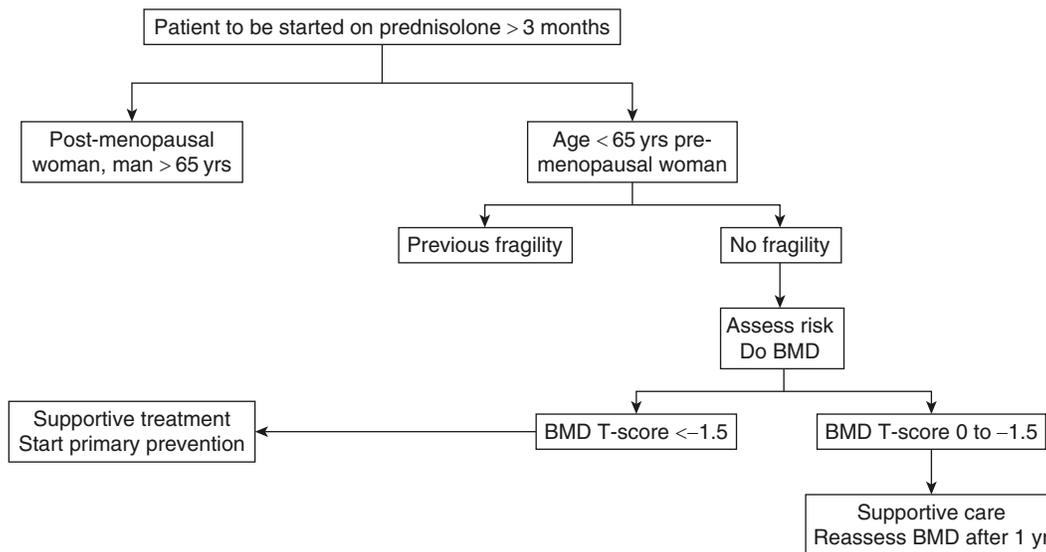
1. No dose or route of Glucocorticoid is without effect on bone.
2. Use minimum dose of oral glucocorticoids for shortest period of time.
3. Use steroid sparing immunosuppressive drugs like Methotrexate, Azathioprine whenever indicated.
4. Use inhalational route in patients with asthma and enema in ulcerative colitis.
5. Use supportive therapy like balanced nutrition, adequate calcium, regular exercise, avoidance of smoking and alcohol.
6. Assess fracture risk at initiation of therapy by using FRAX tool.

7. Start primary prevention in high risk group (post-menopausal women, men > 65 years and those with previous fragility fracture).
8. In those without high risk factors do a baseline BMD if T-score < -1.5 start primary prevention.
9. If baseline T-score > -1.5, follow-up and assess BMD after 1–2 years if therapy with glucocorticoids is being continued.
10. Assess fracture risk at initiation of therapy by using FRAX tool (FRAX tool for Singapore Indians is available and can be applied to our Country). (<http://www.sheffield.ac.uk/FRAX>).

**Disclosures:** Indian Rheumatology Association received an unrestricted grant from Ranbaxy Ortholands for making these guidelines but they did not have any representative in the expert committee which formulated these guidelines.

**Disclaimer:** Medicine is an ever changing science. New research and clinical experience may result in additions or alterations to the existing drug therapy. The authors have tried to provide information that is complete and in accordance with the standard of care at the time of publication. The readers are however advised to check the information contained herein with other appropriate sources such as product information sheet etc. to apprise themselves of any changes/amendments in drug dosages/treatment regimens.

The opinions expressed in this publication are those of the experts and do not necessarily represent the stated policies of Indian Rheumatology Association. Although great



Flow chart showing an approach to a patient while starting glucocorticoids.

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