INTRODUCTION
As we have gone into the depth of understanding of disease process of so many diseases, we have
got a long life span. And with the blessings of increased longevity, our disease patterns have been
changed. One of such is osteoporosis. Osteoporosis, the most common metabolic bone disease can
be defined as a disease characterized by low bone mass and micro architectural deterioration of bone
tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. In India, It is
assumed that more than 25 million people are having this problem in some form. Our life style and
skin complexion are responsible for such poor bone micro architecture. Indians have low vitamin
D levels due to inadequate sun exposure, skin pigmentation, vitamin D and calcium deficient diet.
Problem of this poor bone health is compounded by co-morbidities and their management. Drugs are
the leading causes of secondary osteoporosis and steroids are the leader among them.
Steroids may also come from endogenous source as in case of Cushing’s syndrome. In that situation
also patient may present with osteoporosis. But this is not a big issue compared to exogenous steroids,
because, problem of Cushing’s syndrome is not that common. Furthermore, osteoporosis is more
common in case of exogenous source of steroids.
Role of inflammatory process is better appreciated in more and more diseases. This understanding
leads to much more application of steroids in different diseases. It is mention worthy that up to 1%
of general population in western countries is treated with glucocorticoids. Because of inflammatory
process they are already potential candidates for developing osteoporosis. Steroids can accelerate
this process.
EFFECTS OF GLUCOCORTICOIDS ON MUSCLE AND BONES
Glucocorticoids can induce catabolic changes in muscles. Muscles protein synthesis is reduced leading
to muscles atrophy (no muscles necrosis) and weakness, particularly proximal groups. It is well
known that muscle strength is a determining factor of bone mass. So, increasing muscle weakness
can increase the scope of osteoporosis.
Steroids can decrease calcium absorption from intestine. At the same time, renal calcium excretion
is increased. So, final effect is negative calcium balance leading to secondary hyperparathyroidism.
In bone, glucocorticoids can increase apoptosis of osteoblasts and may prevent apoptosis of
osteoclasts.
PATHOGENESIS
Bone mass is the resultant of bone formation and resorption. Following steroid intake this balance is
lost because of reduced bone formation and increased bone resorption. Reduced bone formation is
due to direct inhibition of osteoblasts along with increased apoptosis due to steroid. Ultimately, this
steroid effect is translated into osteoporosis.
Bone mineral density (BMD) is correlated with fracture risk. But, it had been seen that in a given bone
mineral density the incidence of vertebral fractures is higher in patients receiving glucocorticoids than
Steroid Induced Osteoporosis

Glucocorticoids can inhibit LH/FSH release. Thus, gonadal hormone production is inhibited. Gonadal hormone is an important determinant of bone mass. Men on prednisolone (20 mg or more) were found to have low serum testosterone level.

Glucocorticoids can inhibit hypothalamic-pituitary-adrenal axis. So, adrenal androgen production is inhibited. Adrenal androgen is the major source of estrogen in post menopausal female.

CLINICAL FEATURES

Steroid induced osteoporosis is more prevalent in post menopausal female. It appears on the top of the already existing primary osteoporosis. Increased risk of fracture becomes clinically significant within few weeks of starting therapy. It may happen in any patient and with any dose of steroids. Bone loss is related to cumulative dose of steroids.

It is more rapid during early weeks, peaks at six months, followed by a slower, steady loss with continued use. Fracture risk is increased within first three months of starting therapy.

It can happen with any route of administration. However, this process may reverse following withdrawal.

Trabecular bone is initially affected. It can be documented by assessing spine and radius. This is just like primary osteoporosis. However, prolonged use can lead to involvement of the cortical bone such as femoral neck or humeral head. This can be manifested as aseptic necrosis of femoral neck or humeral head. This is not common with primary osteoporosis.

American College of Rheumatology has identified high risk category for Steroid Induced Osteoporosis. This has been shown in Table 1.

ROLE OF BMD ASSESSMENT BEFORE STARTING THERAPY

BMD measurement is not essential in all patients before starting steroids. However, there are certain situations where it should be done beforehand.

DIFFERENT METHODS TO MEASURE BMD

Dual Energy X-Ray Absorptiometry (DXA)

It is the most commonly used method for BMD assessment. BMD measurement at hip and lumbar spine using DXA is currently recommended for assessment of fracture risk and monitoring treatment response in individuals on steroids. DXA can give accurate values of bone mineral content (BMC). Bone mineral density (BMD) can be calculated by dividing bone mineral content (gm) by area of bone scanned (cm²).

It takes very short time (5 to 20 minutes) to scan and radiation exposure is minimal (<10 mrem) with it. Same machine should be preferred each time for measuring BMD in a single patient to ensure consistency.

Quantitative CT (QCT)

It measures true BMD (gm/cm³) at axial and appendicular skeleton. It can measure trabecular BMD even in the presence of osteoarthritis. It has a role in assessment of BMD in ankylosing spondylitis. DXA may give a false high values in ankylosing spondylitis due to ligament calcification. The main disadvantage is high radiation exposure (100 to 300 mrem) compared to DXA.

Peripheral DXA

Phalanges, distal radius, calcaneum can be assessed. It cannot predict hip fracture risk as accurate as that of DXA. It should not be used for screening for GIOP or monitoring response to therapy.

Single Energy X-Ray Absorptiometry (SX-A)

It can assess BMD of peripheral skeleton like distal radius and calcaneum. The predictive capacity for hip and vertebral fracture is less than that of DXA. It should not be used for screening for GIOP or monitoring response to therapy.

Biochemical markers

They are not recommended for the diagnosis of osteoporosis. Bone resorption markers (N-telopeptide, C-telopeptide) can be used in addition to a BMD assessment to identify high risk patients for future fracture. They are also used for monitoring of response to treatment.

Table 1: High risk category for Steroid Induced Osteoporosis

<table>
<thead>
<tr>
<th>High risk category for steroid induced osteoporosis.</th>
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<tbody>
<tr>
<td>• Low BMI.</td>
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<tr>
<td>• Parental history of hip fracture.</td>
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<tr>
<td>• Current smoking.</td>
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<tr>
<td>• ≥3 alcoholic drinks daily.</td>
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<tr>
<td>• Higher daily glucocorticoid dose.</td>
</tr>
<tr>
<td>• Higher cumulative glucocorticoid dose.</td>
</tr>
<tr>
<td>• Intravenous pulse glucocorticoid</td>
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<tr>
<td>• Declining central BMD measurement.</td>
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• Age more than 65 years
• History of fragility fracture
• Premature menopause (< 45 years)
• Family history of fragility fracture
• BMI < 19 kg/m²
• Prolonged immobilization
MANAGEMENT OF STEROIDS INDUCED OSTEOPOROSIS

Life style modification

Physical activity has positive impact on BMD. Weight bearing exercises are more beneficial than non-weight bearing exercises. They improve the strength of muscles and bones of lower limbs and lower spine. Alcohol and smoking should be discouraged. Reduced muscle strength associated with poor balance is risk factor for falls. They can be improved by progressive resistance training. Gradual withdrawal of psychotropic drugs will help to prevent fall, home hazard should be assessed (floor, carpets, poor lighting, steps, etc.). Cataract surgery can be done to improve the sight. Walking aids and better foot wear can be advised.

Calcium and vitamin D

Most individuals in our country are vitamin D deficient suggesting inadequate sun exposure. Dark skin is also preventing adequate vitamin D synthesis. Low calcium intake is also very common in our community. Calcium and vitamin D should be supplemented to patients not having risk of bone loss and are on lower doses of steroids for short duration (5 mg or less for less than 3 months). Antiresorptive therapy should be considered in addition for patients who have associated risk factors, pre-existing bone loss and who are on higher doses of steroids for longer duration. In the Indian setting it is suggested that 2000 IU/day of vitamin D (cholecalciferol) should be supplemented as lower doses are usually unable to achieve optimum 25(OH)D levels (>30 ng/mL). Sunlight exposure is recommended in the mornings for 10–30 minutes a day at least three times a week.

Bisphosphonates

This is the cornerstone of treatment of Steroids induced osteoporosis. 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. Alendronate (35–70mg/week or of 5–10mg/day, oral), Risedronate (35mg/week or 5 mg/day, oral), Ibandronate (150 mg/month, oral or 3 mg IV once in 3 months), Zolendronic acid (5 mg IV infusion once a year) can be advised. Bisphosphonates should be used in all patients as primary prevention initiating Prednisolone > 7.5 mg/day for more than three months particularly in post-menopausal women and elderly men.

Calcitonin

It can inhibit bone resorption particularly at high turnover situation. It has also some analgesic effect which is useful in recent painful vertebral fractures. Calcitonin is available as subcutaneous preparation as well as nasal spray. Subcutaneous preparation is more effective but less well tolerated. It can produce gastrointestinal side effects. Calcitonin can be given as 100–200 units/day as nasal spray.

Parathormone analogues (Teriparatide)

It is the best alternative in the management of steroids induced osteoporosis when patients are not improving or having new fractures despite ongoing bisphosphonate therapy. It can increase trabecular bone mass substantially and reduce the fracture risk. Main limitations are its cost and parenteral preparation. During therapy, monitoring should be done for both hypercalcemia and hypercalciuria. Prior or concomitant bisphosphonate therapy should be avoided because it can blunt its action.

Hormone therapy

Long-term glucocorticosteroid can induce hypogonadism. So, this possibility should be evaluated in male patients. If testosterone level is found less than 300ng/mL, it should be replaced as this leads to 4–5% increase in lumbar spine BMD after 12 months. On the other hand; it is well known that HRT increases BMD in postmenopausal women. But there is no strong evidence to support its use in Steroids induced osteoporosis.

MANAGEMENT PROTOCOL OF STEROIDS INDUCED OSTEOPOROSIS

American College of Rheumatology has recommended different policy for different population for the prevention and treatment of glucocorticoids-induced osteoporosis. Risk stratification has been done according to FRAX tool (WHO Fracture Risk Assessment Tool).

- Low Risk: FRAX <10% for 10-year major osteoporotic fracture.
- Medium Risk: FRAX 10 – 20% for 10-year major osteoporotic fracture.
- High Risk: FRAX >20% for 10-year major osteoporotic fracture.

1. Approach to postmenopausal women and men age >50 years initiating or receiving glucocorticoid

Low Risk Group: Preventive policy in this group is shown in Table 2.

Medium Risk Group: Preventive policy in this group is shown in Table 3.
Steroid Induced Osteoporosis

Table 3: Approach to postmenopausal women and men age >50 years initiating or receiving glucocorticoid medium risk group

<table>
<thead>
<tr>
<th>Glucocorticoid Dose</th>
<th>Recommendation</th>
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<tr>
<td>&lt;7.5 mg/day</td>
<td>Alendronate, Risedronate</td>
</tr>
<tr>
<td>&gt;7.5 mg/day</td>
<td>Alendronate, Risedronate, Zolendronic acid</td>
</tr>
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High Risk Group: Preventive policy in this group is shown in Table 4.

2. Approach to premenopausal women and men age <50 years initiating or receiving glucocorticoid

There is no recommendation for the population without any prevalent fragility fracture.

But in case of prevalent fragility fracture of women with childbearing potential if glucocorticoid (prednisolone ≥7.5 mg/day) is to be continued for more than three months alendronate, risedronate or teriparatide is recommended.

In case of prevalent fragility fracture of women without childbearing potential or men age more than 50 years if glucocorticoid is to be continued for more than three months alendronate, risedronate, Zolendronic acid or teriparatide is recommended.

If glucocorticoid is to be continued for less than three months in this population it can be managed only with Bisphosphonates without Teriparatide.

MONITORING FOR PATIENTS ON GLUCOCORTICOID THERAPY

American College of Rheumatology has recommended monitoring guidelines for patients who are on Glucocorticoid therapy for duration of more than three months.12

- Serial BMD
- Annual serum 25-hydroxyvitamin D measurement
- Annual height measurement
- Assessment of incident fragility fracture
- Assessment of osteoporosis medication compliance

CONCLUSION

Osteoporosis is one of the major limitations of steroid use. But, we neither ignore the anti-inflammatory role of Glucocorticoid nor avoid this divine drug in various diseases of different systems. As we will use this drug more and more, we have to pay for it in different forms particularly at the cost of our bone minerals. Best alternative is developing selective Glucocorticoid Receptor agonists. They are supposed to have the anti-inflammatory role of Glucocorticoid without having transactivating undesired effect. But until and unless dreams come true, only effective precautions can protect health of our bones. Indian Rheumatology Association guidelines9 endorsed by Endocrine Society of India and Indian Society for Bone & Mineral Research can be a working tool in Indian context for prevention and management of glucocorticoid-induced osteoporosis.

REFERENCES:

