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UNIT NO. 6

GLUCOCORTICOID-INDUCED OSTEOPOROSIS (GIOP)

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ABSTRACT

Glucocorticoid-induced osteoporosis (GIOP) is a form of secondary osteoporosis caused by the intake of glucocorticoid medication. It is characterised by rapid bone loss and takes place soon after glucocorticoid therapy is initiated (three to six months). This results in increased fracture risk. The increased risk is observed in patients taking 5 mg/day prednisolone (or equivalent) for 3 months. Therefore, clinicians should use the lowest dose of glucocorticoid for the shortest duration of time to control or treat the disease and consider steroid-sparing agent when appropriate. Patients who appear cushingoid should be evaluated to exclude excess endogenous or exogenous source of glucocorticoid. They should be evaluated for complications of glucocorticoid, including GIOP. BMD Testing using DXA is recommended for assessment of fracture risk in patients who will be started on glucocorticoid for three months at 5 mg/day prednisolone or equivalent. Patients who are at moderate to high risk of fractures or rapid bone loss should be treated with bisphosphonate, denosumab or teriparatide therapy to reduce the risk of fractures.

Keywords: Glucocorticoid; Osteoporosis; Fracture

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INTRODUCTION

Glucocorticoid-induced osteoporosis is a form of secondary osteoporosis caused by the intake of glucocorticoid medication. It is characterised by rapid bone loss (increased bone resorption, decreased bone formation)[1] of as much as ten percent of the Bone Mineral Density (BMD) within a year. The effect takes place soon after glucocorticoid therapy is initiated (three to six months).[2,3] This results in increased fracture risk. The average daily and cumulative glucocorticoid dose is correlated to the extent of bone loss and degree of increased fracture risk. The increased risk is observed in patients taking 5 mg/day prednisolone (or equivalent) for three months (Table 1).[3,4] Therefore, clinicians should use the lowest dose of glucocorticoid for the shortest duration of time to control or treat the disease and consider steroid-sparing agent when appropriate.

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Table 1: Average Adjustment of 10-Year Probabilities of a Hip Fracture or a Major Osteoporotic Fracture in Postmenopausal Women and Men ≥ 40 Years of Age According to Glucocorticoid Dose[5]

Dose Categorisation	Prednisolone Equivalent (mg/dL)	Average FRAX Adjustment Factor
Hip Fracture		
Low	<2.5	0.65
Medium	2.5 – 7.5	No adjustment
High	≥7.5	
Major Osteoporotic Fracture		
Low	<2.5	0.80
Medium	2.5 – 7.5	No adjustment
High	≥7.5	1.15

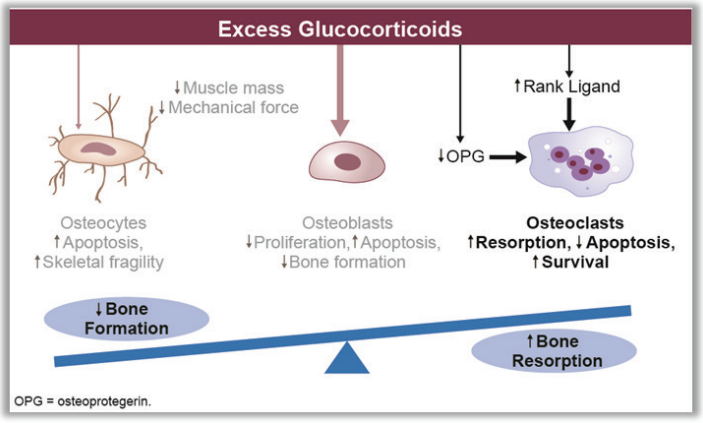
Glucocorticoid Medication

Glucocorticoids are naturally occurring or manufactured substance that has anti-inflammatory properties. They are prescribed for a variety of conditions6, including inflammatory rheumatic disorders (e.g. rheumatoid arthritis, systemic lupus erythematosus), lung disorders (e.g. asthma), etc. The types of glucocorticoids[7] include Hydrocortisone, Prednisone, Prednisolone, Dexamethasone and Methylprednisolone.

Pathophysiology

Exogenous glucocorticoid therapy creates an excess of glucocorticoids[8] in the body. This causes the rates of bone formation and resorption to be uncoupled, resulting in bone loss. The excess glucocorticoid will stimulate osteocyte apoptosis[8], reduce proliferation and stimulate apoptosis of osteoblasts[4,9], and RANK Ligand expression and inhibited osteoprotegerin (OPG) expression.[6,10] (Figure 1)

Fig. 1: Effects of Exogenous Glucocorticoids on Bone[1]



The excess glucocorticoids also lead to other physiological responses that will also contribute to osteoporosis. For example, it increases the urinary calcium secretion[6], and reduces calcium absorption in the gut, resulting in lower serum calcium level which in turn lead to secondary hyperparathyroidism.[6] There is also increased risk of falls due to glucocorticoid-induced

myopathy[2] and loss of muscle mass.[1] The excess glucocorticoid can also lead to hypogonadism.[6]

Epidemiology

GIOP is the most common form of secondary osteoporosis6 and also the most common cause of osteoporosis in people younger than 50 years of age.[6] Thirty to fifty percent of patients on long term corticosteroid therapy will experience fractures[11,12], with an increased risk of hip fracture by 2-fold in women and 2.6-fold in men.[2]

In Singapore, one study shows that 47.6 percent of patients (post-menopausal women and men 50 years of age) had one or more secondary contributors of osteoporosis, of which 8.43 percent was attributed to glucocorticoid use (n=332).[13]

Risk Factors for GIOP

BMD does not necessarily correlate to fracture risk as glucocorticoid use results in an alteration of bone quality.[6] Other risk factors that increase fracture risk in patients treated with glucocorticoids[6] include: increasing age, previous fracture, female gender, history of falls, low body-mass index (BMI), duration of menopause and cigarette smoking.

Diagnosis

The diagnosis of patients with GIOP will include a good medical history to ascertain the use of glucocorticoid medication, including the possibility of alternative medicine being adulterated with glucocorticoid. Ask for a history of previous fractures as this is a significant risk factor for future fractures. Measure the patient's height to detect height loss (more than 2.5 cm in recent one year or more than 5 cm when compared to the maximum height when young) as this may indicate previous vertebra fractures.

The physical examination will detect the presence of cushingoid features (thin limbs with truncal obesity, inter-scapular and supraclavicular fat deposit, skin striae, proximal muscle weakness, etc.). During the evaluation, look out for glucocorticoid-induced cataract, hypertension, hyperlipidemia and diabetes mellitus.

Table 2 below suggests possible investigations to consider when indicated to exclude other secondary causes of osteoporosis.[5]

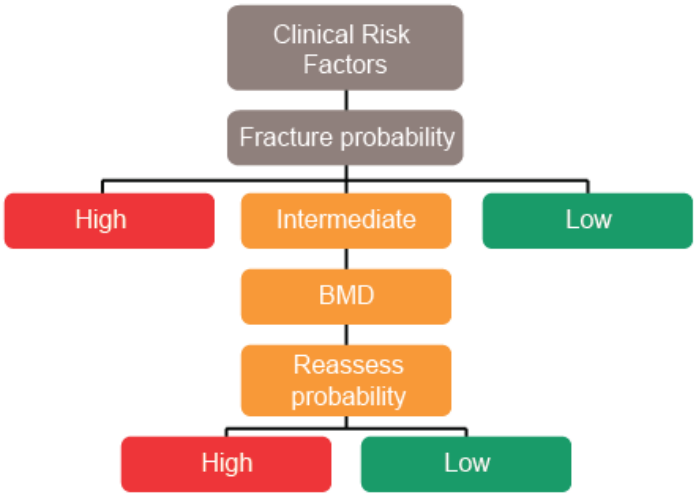
Table 2: Laboratory Tests to Exclude Other Causes of Secondary Osteoporosis

Investigation	Cause Excluded
Full blood count and erythrocyte sedimentation rate (ESR)	Anaemia, monoclonal gammopathy
Calcium, urea, and estimated glomerular filtration rate (eGFR)	Chronic kidney disease (CKD)
Calcium, phosphate, alkaline phosphatase, and albumin	Primary hyperparathyroidism, malignancy, osteomalacia, Paget disease
Estrogen, testosterone and follicle-stimulating hormone (FSH)*	Hypogonadism
IgA anti-tissue transglutaminase antibodies or IgA endomysial antibody	Celiac disease
Immunoglobulins, Bence Jones proteins, and serum free light chains	Monoclonal gammopathy
Serum vitamin D	Vitamin D deficiency
Serum thyroid stimulating hormone (TSH)	Hyperthyroidism
* Not required in postmenopausal women.	

Ministry of Health (MOH) Recommendations[14]

- BMD Testing using DXA is recommended for assessment of fracture risk in patients who will be started on glucocorticoid for three months at 5 mg/day prednisolone or equivalent[15]
- Repeat bone mineral density should be done yearly while patients are on continuous glucocorticoid therapy
- BMD T-score of -1.5 SD (femoral neck and/or spine) for treatment of glucocorticoid-induced osteoporosis[16]

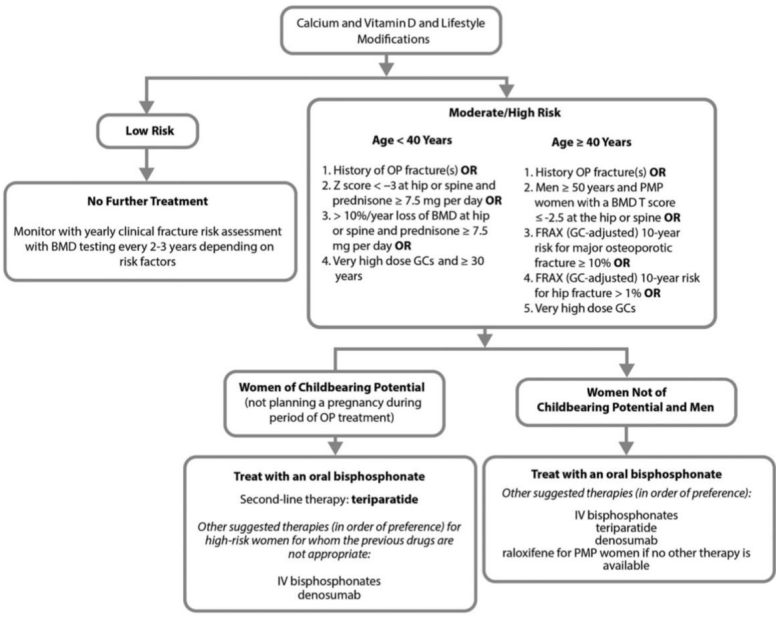
Fig. 2: Diagnostic approach to GIOP[5]



Treatment

Fractures due to steroid-induced osteoporosis can be prevented if appropriate measures are taken.[17] However, only 4 percent to 5.5 percent of patients receive bone-protective medication while taking glucocorticoids.[18] MOH Recommendations include the use of bisphosphonate, denosumab and teriparatide therapy to treat GIOP for patients who are at moderate to high risk of fractures or rapid bone loss.[14] The American College of Rheumatology has similar recommendations as well[19] (Figure 3).

Fig 3: Initial Pharmacological Treatment for Adult[19]



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LEARNING POINTS

- **The increased risk of GIOP is observed in patients taking 5 mg/day prednisolone (or equivalent) for 3 months. Therefore, clinicians should use the lowest dose of glucocorticoid for the shortest duration of time to control or treat the disease and consider steroid-sparing agent when appropriate.**
- **BMD Testing using DXA is recommended for assessment of fracture risk in patients who will be started on glucocorticoid for 3 months at 5 mg/day prednisolone or equivalent.**
- **Patients who are at moderate to high risk of fractures or rapid bone loss should be treated with bisphosphonate, denosumab or teriparatide therapy to reduce the risk of fractures.**