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GLUCOCORTICOID -INDUCED OSTEROPOROSIS

Osteoporosis is a common disease in Australia with 1.2 million people estimated to have osteoporosis and further 6.3 million with low bone density. Glucocorticoids, commonly used for asthma, rheumatoid arthritis and other inflammatory conditions, and after organ transplantation, increase the risk of osteoporosis. Up to 50% of people treated with glucocorticoids experience asymptomatic fractures after 3 months of therapy. The risk of fracture increases with age and with the dose and duration of glucocorticoid use. Vertebral fractures are the most common fractures associated with glucocorticoids.

Osteoporosis

Osteoporosis is a state of low bone mass, which predisposes people to fragility fractures. Osteoporosis is more common in women than men. About 50% of women can expect to sustain fragility fractures in their lifetime. The proportion of women with osteoporosis dramatically increases with age, affecting around 26% of women aged 80 and over. Post-menopausal women are more susceptible to osteoporosis. In Australia in 2015-6, the most common fracture sites were the hip (32%), the forearm (13%) and lumbar spine and pelvis (13%). Fractures in the spine (vertebral fractures) are common in older people, leading to height loss or changes in posture. Hip fracture is a serious and debilitating outcome of osteoporosis, usually requiring hospitalisation and surgery. Fractures may be a source of ongoing chronic pain and disability.

Mechanism

Glucocorticoids act mainly by slowing down the cells that form new bone. Approximately 30% less bone tissue is produced in people taking glucocorticoids compared to normal conditions. As a result, the bones may gradually lose some of their strength and become more prone to fracture after a minor bump or fall. Bone formation decreases early in glucocorticoid treatment. Glucocorticoids also interfere with the absorption of calcium in the intestine, and the way that the kidneys manage calcium.

They may also reduce the levels of hormones and other factors that are important for maintaining bone health, such as vitamin D. Steroid-induced myopathy may also increase the risk of fractures. Muscle weakness of the lower limbs can lead to falls, increasing the risk of fractures in all places. The risk of vertebral fractures increases within 3 months after initiation of treatment and peaks at about 12 months. There can be 10% bone loss of bone mineral density (BMD) in the first use of use, slowing down to an annual rate of 2-5%. The relative risk of clinically diagnosed vertebral fractures doubles in people who receive 2.5 to 7.5mg of prednisolone daily. The risk of hip fractures increases by about 50%.

Dose-dependent risk

Fracture risk with glucocorticoids is dose-dependent. People prescribed glucocorticoids at higher doses (7.5mg or more per day prednisolone or equivalent) for at least three months are at higher risk of osteoporosis and fracture. Lower doses (2.5mg-7.5mg daily) may increase the risk of fracture in some people. Intermittent use for less than three months of high dose oral prednisone/prednisolone also increases the risk of osteoporosis. Cumulative doses over 1g increase the risk of fractures. Cumulative doses above 5g increase the risk of vertebral fracture by a factor of 14 and the risk of hip fracture 3 times. The risk of fracture decreases rapidly when glucocorticoids are ceased.

Inhaled corticosteroids

High doses of inhaled corticosteroids used in the management of asthma and COPD for long durations also increase the risk of fracture. Fluticasone propionate (or equivalent) in doses of 1000 microgram or higher for more than 4 years increase the risk of fracture by 10%.

Fluticasone propionate 1000 microgram is approximately equivalent to:

- Beclomethasone dipropionate 800 microgram
- Budesonide 1600 microgram

continued over

- Ciclesonide 640 microgram
- Fluticasone furoate 400 microgram

Management
It is recommended that people over the age of 50 on glucocorticoid therapy (oral or inhaled) of 7.5mg per day for at least three months and with a T-score of -1.5 or less should receive drug therapy to prevent osteoporosis. This should be continued for the duration of the glucocorticoid therapy.

Residents who receive glucocorticoids should have adequate calcium, vitamin D, weight bearing exercise (as appropriate), avoidance of smoking and excessive alcohol intake. Calcium intake from diet and/or supplements should be 1000mg calcium per day. All residents in aged care should receive 600 to 800IU vitamin D3 (colecalciferol) daily due to inadequate sun exposure, and age-related changes in metabolism. Calcium alone is not effective in preventing rapid bone loss in residents starting corticosteroids.
Repeated efforts to reduce the dose of corticosteroids should be made when appropriate. Taking corticosteroids on alternate days does not prevent bone loss.

Bisphosphonates
Bisphosphonates increase BMD in people on glucocorticoids. Bisphosphonates inhibit bone resorption, preventing further bone loss. Studies have shown that bisphosphonates reduce the risk of new vertebral fractures by 43% compared to people taking calcium, vitamin D or both. Bisphosphonates are indicated and are available on the PBS to prevent fractures in those undergoing long-term corticosteroid therapy.
They are available as daily, weekly or monthly tablets (alendronate, risedronate), or as an annual infusion (zoledronic acid). Alendronate (Fosamax) and risedronate (Actonel) are also available in combination packs on the PBS with vitamin D and calcium carbonate.

Denosumab
Denosumab (Prolia), a monoclonal antibody against RANK-ligand, inhibits resorptive activity by a different mechanism to that of the bisphosphonates. It is administered as a 6-monthly subcutaneous injection Denosumab is registered in Australia to increase bone mass in patients with increased fracture risk due to long-term systemic glucocorticoid therapy; however, it is not available on the PBS for this indication.

Other agents
Other medicines used in the prevention and treatment of osteoporosis including teriparatide (Forteo) and raloxifene (Evista) are not approved on the PBS for the treatment of glucocorticoid-induced osteoporosis.

Summary
Osteoporosis is a condition that causes bones to become thin, weak and fragile. Fractures due to osteoporosis can result in chronic pain, disability, loss of independence and premature death. Glucocorticoid therapy is associated with an appreciable risk of bone loss, which is most pronounced in the first few months of use. Fracture risk increases with daily prednisone/prednisolone dose greater than 2.5mg daily. Both the daily dose and duration, as well as cumulative dose, impact on fracture risk. Bisphosphonates, in combination with calcium and vitamin D supplements, are the drugs of choice for prevention of glucocorticoid-induced osteoporosis. Bone strength improves after glucocorticoid discontinuation.

References
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