The bone clinic

Corticosteroid induced osteoporosis

Guidelines for treatment

BACKGROUND Last year, *Australian Family Physician* published 'Guidelines for Management of Postmenopausal Osteoporosis', which were developed by Osteoporosis Australia. Recently, significant advances in our understanding of the treatment of corticosteroid osteoporosis have occurred.
OBJECTIVE The following guidelines, also developed by Osteoporosis Australia, and supported by the National Asthma Campaign, are to help general practitioners identify those patients at risk of this problem and to provide information about current treatment strategies.
DISCUSSION Corticosteroids are widely used and effective agents for the control of many inflammatory diseases. Corticosteroid osteoporosis is a common problem associated with the long term high dose use of these medications.

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Is there a difference between corticosteroid and postmenopausal osteoporosis?

Clinically, osteoporosis is synonymous with low bone density and predisposes to fractures during normal life.

The majority of osteoporotic fractures occur in people with bone mineral densities (BMDs) that are more than 2.5 standard deviation units below the young normal mean (T score <–2.5). However, bone loss due to corticosteroids can occur rapidly and fractures may occur at lower reductions in T scores, so preventive measures should be considered before that level, especially if patients are receiving long term corticosteroids. The risk of fracture with corticosteroids appears greatest in postmenopausal women and older men. Data regarding the risk of fracture in corticosteroid treated premenopausal women appears less striking. The following intervention guidelines have been developed from this data *(Figure 1)*.

- Strongly consider preventive therapy in patients with bone mineral density values lower than 1.5 standard deviations below the young normal mean (T score <–1.5) who are starting or receiving high doses (more than 7.5 mg prednisone/day or equivalent) of long term (three months or longer) corticosteroids.
- Strongly recommend treatment in patients who are receiving long term corticosteroids with BMD values lower than 2.5 standard deviations below the young normal mean (T score <–2.5) and in patients with osteoporotic fractures.

A Medicare rebate is available for densitometry in patients receiving greater than 7.5 mg oral prednisone (or equivalent) per day or greater than 800 μg of inhaled beclomethasone or budesonide/day for more than four months. A BMD measurement is recommended in all patients starting corticosteroids who meet these criteria.

Prevention of corticosteroid osteoporosis

Patients treated with corticosteroids should:

- have a diet with adequate calcium content and attempt regular weight bearing exercise where practical
- have good general nutrition with adequate intake of vitamin D, especially in elderly patients
- avoid tobacco use.

The risk of developing fractures with corticosteroid use appears to be increased by certain factors (*Figure 1*).

Although lifestyle prevention measures are important, pharmaceutical agents will frequently be necessary. These agents are discussed in more detail and are ranked according to levels of evidence (See *Table 1*, Guidelines for treatment of male osteoporosis, page 788).

Treatment of corticosteroid osteoporosis

Calcium

Calcium is weakly antiresorptive and supplementation may reduce negative calcium balance, especially in old age. Controlled trials[1-3] suggest calcium alone is probably insufficient to prevent rapid bone loss in patients starting high dose corticosteroids (E2).

Since most controlled trials of agents, described below have used concomitant calcium and vitamin D (ergocalciferol not calcitriol), it is appropriate to add a calcium supplement to most therapies, except calcitriol. In patients using bisphosphonates, calcium must not be taken at the same time of day as the bisphosphonate or the calcium will impair absorption of the drug.

Vitamin D and its metabolites

Vitamin D undergoes metabolism in the liver and kidney. Simple vitamin D is mainly available in Australia as ergocalciferol (Ostelin 1000 IU per capsule), or cod liver oil tablets (approximately 400 IU). Some calcium supplements also contain vitamin D but in low dose, eg. Caltrate + D (contains 200 IU). One study in patients with rheumatoid arthritis receiving chronic

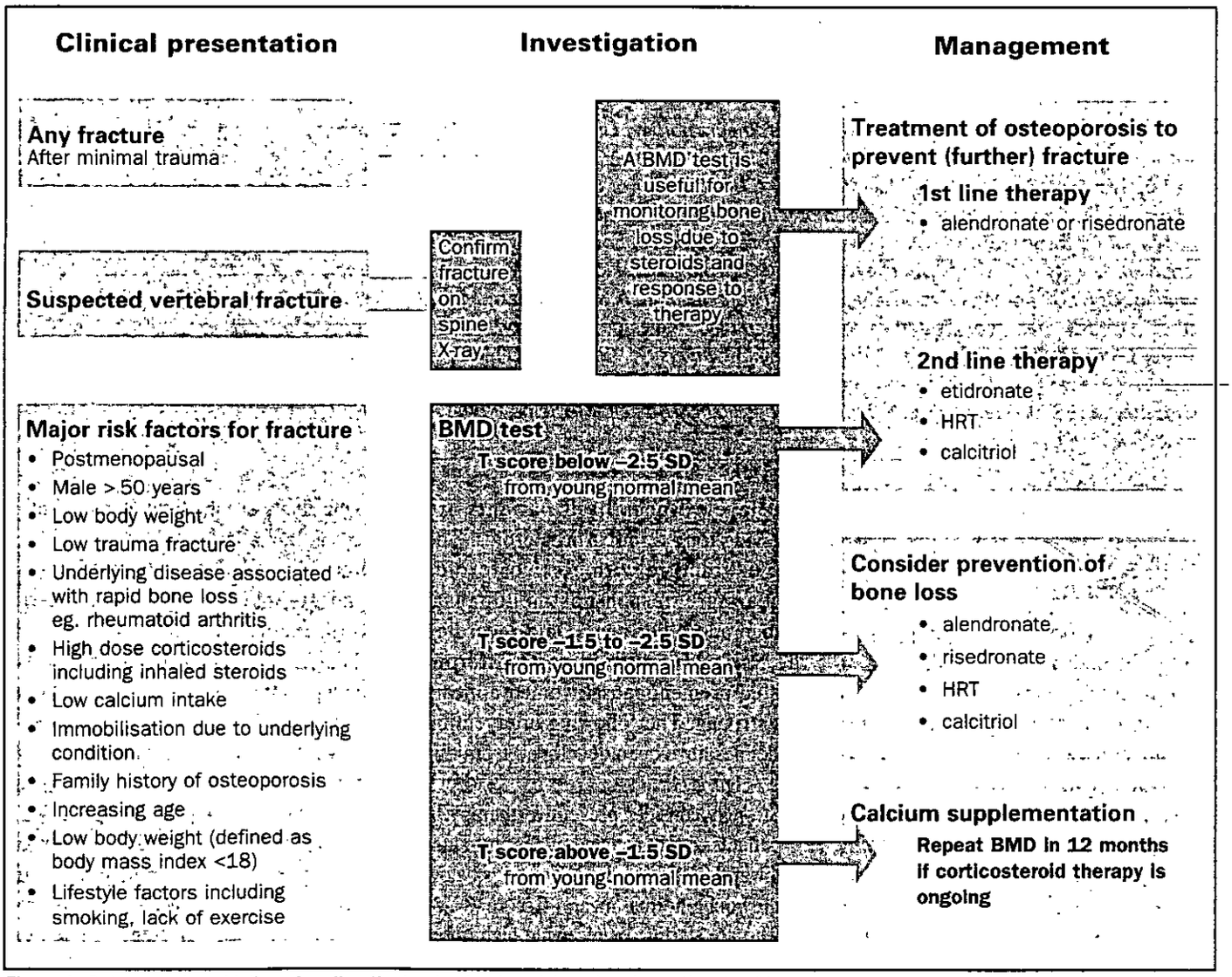

Figure 1. Osteoporosis guidelines for all patients starting/receiving chronic corticosteroids.

low dose corticosteroids for rheumatoid arthritis[4] observed a small gain in bone density in patients treated with calcium plus 500 IU/day vitamin D3 (E2).

Calcitriol is the active hormonal form of vitamin D. Its primary action results from increased calcium absorption. Several trials[2,5,6] have shown active vitamin D metabolites (such as calcitriol) can prevent spinal bone loss in patients starting corticosteroids (E1) although no effect was demonstrated at the hip. Hypercalcaemia and hypercalciuria may occur but are uncommon in patients treated with calcitriol in a dose of 0.5 μg daily, but may occur in patients who have a high calcium intake or who have co-existing renal impairment. Hence calcium supplements must be avoided in these patients, since hypercalcaemia may worsen the renal failure.

Hormone replacement therapy

Long term oestrogen therapy remains the gold standard for prevention of bone loss in postmenopausal women but there is little data in corticosteroid osteoporosis. One randomised controlled trial in patients with rheumatoid arthritis who were receiving chronic low dose corticosteroids[7] showed a benefit of oestrogen on bone density (E2).

In men, there has been one small trial in asthmatic men receiving chronic corticosteroids comparing testosterone, 250 mg/month with calcium, 1000 mg.[8] After 12 months, testosterone increased lumbar BMD by 5%, which was significant compared to calcium (E2).

Although these data do not provide strong evidence, hormone replacement therapy should be considered if hypogonadism is present.

Selective oestrogen receptor modulators

Selective oestrogen receptor modulators like raloxifene act to decrease bone resorption, like oestrogen, while not stimulating the breast or uterus. One recent controlled clinical trial suggests that raloxifene may inhibit spinal bone loss related to corticosteroid induced osteoporosis.[9] Raloxifene is available on the PBS (Authority required) for established postmenopausal osteoporosis in patients with fracture due to minimal trauma and could be used in women taking corticosteroids as an alternative to oestrogen.

Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption. Currently three bisphosphonates, etidronate (Didrocal and Didronel), alendronate (Fosamax) and risedronate (Actonel), are approved in Australia on the PBS (Authority required) for the treatment of established osteoporosis in postmenopausal women with fracture due to minimal trauma. Etidronate and alendronate are also approved on the PBS (Authority required) for the treatment of established osteoporosis in men with fracture due to minimal trauma.

Etidronate

This is used in a cyclical regimen for osteoporosis, usually for two weeks every three months. A number of controlled trials with etidronate show prevention of bone loss in patients starting corticosteroids and increases in bone density in patients on chronic corticosteroids.[3,10,11,12] A reduction in vertebral fracture rate was seen in postmenopausal women in one study.[3] Etidronate has been associated with lower, but not upper, gastrointestinal events. The risk of mineralisation defect with the cyclical regimen is very low.

Alendronate

This is an aminobisphosphonate. It is a more potent inhibitor of bone resorption than etidronate and does not affect mineralisation. Several controlled clinical trials have shown prevention of bone loss in patients starting corticosteroids and increases in bone density in patients on chronic corticosteroids. A reduction in vertebral fracture rate was seen in postmenopausal women.[13] The use of alendronate may be associated with an increased risk of upper gastrointestinal events in patients receiving corticosteroids. A once weekly 70 mg preparation may be more convenient than 10 mg daily.

Risedronate

This is also a more potent inhibitor of bone resorption than etidronate. Several controlled clinical trials[14,15] have shown prevention of bone loss in patients starting corticosteroids and increases in bone density in patients on chronic corticosteroids. A reduction in vertebral fracture rate was also seen in postmenopausal women.

The overall evidence for bisphosphonates in corticosteroid osteoporosis is such that it should be considered first line (E1). Calcium should not be taken at the same time of day as a bisphosphonate, since it interferes with absorption.

Anabolic steroids

Nandrolone is frequently used in general practice in Australia. Although long term corticosteroid therapy is an approved indication in Australia, there is little trial data[16] to support its use in corticosteroid osteoporosis (E3). There is a high incidence of virilisation with bone effective dosages and there are no long term safety data.

Monitoring therapy

After corticosteroid therapy has been initiated, it is important to monitor patients to ensure that bone loss is not excessive. Dexa bone scan (DXA) measurements are useful techniques for monitoring because of their excellent precision, and they can be performed rapidly and conveniently. It is worth noting that changes of less than 3% are within the precision error of most machines and therefore should not be regarded as representing significant change. Changes due to corticosteroids are generally in excess of this.

It is recommended that a repeat DXA be performed within a year of starting corticosteroids and/or treatment to prevent associated bone loss. Repeat measurements should be performed on the same machine for monitoring. It is important to remember that patients receiving long term corticosteroids may have 'silent' compression fractures, or if they are elderly may have co-existing degenerative changes which may pseudo-elevate their spinal BMD values and give a false 'sense of security'. All patients should have spinal radiography to supplement the information obtained with DXA scans. Femoral neck BMD values may prove to be of greater benefit in these patients. Ultrasound should not be used as an alternative to DXA for diagnosis or monitoring.

Conclusion

Postmenopausal women and older men receiving corticosteroids are probably at the greatest risk of rapid bone loss and consequent vertebral fracture and should be strongly considered for preventive measures. In younger individuals receiving corticosteroids, the decision to use osteoporosis prevention is less straightforward and will depend upon a number of factors including baseline BMD, anticipated dose and duration of corticosteroids and other risk factors. Based upon available evidence the rank order of choice for prophylaxis would be a bisphosphonate followed by an active vitamin D metabolite or HRT.

Although calcium alone appears unable to prevent rapid bone loss in patients starting corticosteroids, it should be considered in those patients with normal BMD values. If an active vitamin D metabolite is used, calcium supplementation should be avoided unless dietary calcium intake is low. The evidence for hormone replacement is limited, but HRT should be considered if hypogonadism is present. Addition of a bisphosphonate in postmenopausal patients already taking estrogen replacement therapy may enhance the bone density response. In patients receiving chronic low dose corticosteroids, treatment with calcium and vitamin D may help to prevent further bone loss.

Resources for patients and healthcare professionals

Osteoporosis Australia has a range of education materials available for patients and healthcare professionals, which cover different aspects of osteoporosis and its management (Free call number 1800 242 141). There are regular courses on osteoporosis and self management, which teach people how to maintain bone mass, how to avoid falls and fractures, and how to live more comfortably with osteoporosis.
Osteoporosis Australia website:
www.osteoporosis.org.au

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SUMMARY OF IMPORTANT POINTS

- Although primary prevention in patients commencing corticosteroids is essential, treatment of patients on chronic long term often low dose corticosteroids is equally important.
- The risk of osteoporotic fractures is greatest in postmenopausal women and older men.
- Patients receiving 7.5 mg or more oral prednisone or 800 μg or more of inhaled beclomethasone or budesonide/day or equivalent for three months or more should undergo bone densitometry.
- The most effective interventions include bisphosphonates, hormone replacement therapy and vitamin D and its metabolites.