

CURRENT MANAGEMENT OF CORTICOSTEROID INDUCED OSTEOPOROSIS (CIO)

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SKELETAL COMPLICATIONS

- Incidence and Prevalence of Skeletal Complications.

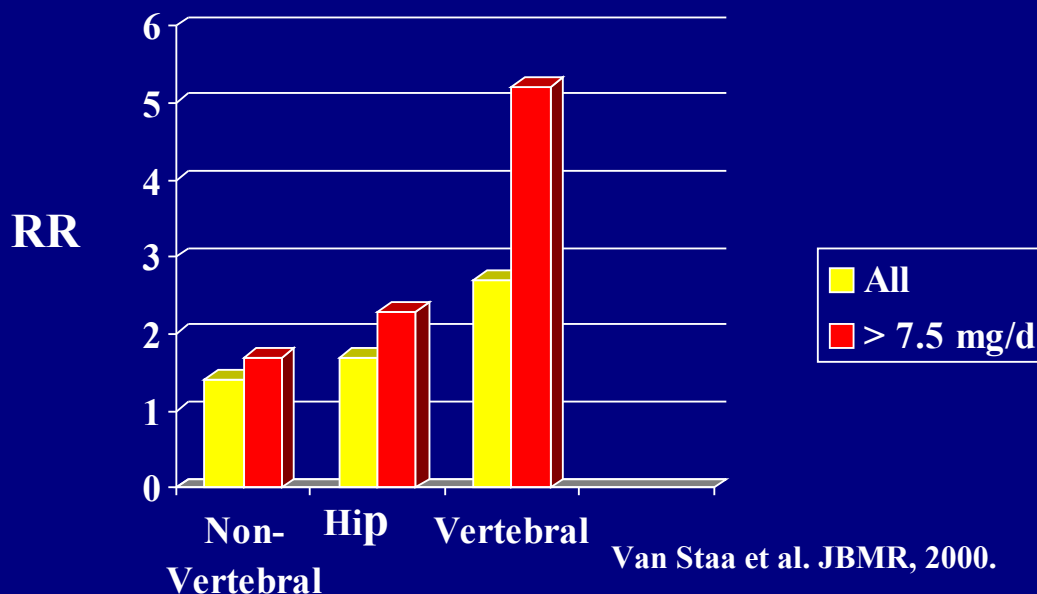
There is a high rate of skeletal fractures in patients commencing and continuing on oral corticosteroids (CS's). This occurs irrespective of the underlying condition for which the CS's are prescribed. However these diseases are also often associated with the premature development of osteoporosis and include rheumatoid arthritis, ulcerative colitis and Crohn's disease.

The large U.K. GP cohort study of Van Staa¹ demonstrated that at any onetime about 0.5% of this population are receiving oral CS's. This prevalence figure rises to 1.5% if we consider only those patients over the age of 55. In a general medical clinic hospital population this amounts to 1.0%². The Figure below summarises the relative risk (RR) of fractures at different skeletal sites in the total population and those receiving more than 7.5 mg or oral CS's daily.

- *Harvey Cushing stated that in patients with the disease that now bears his name and is due to excessive corticosteroid release³: "The greatly compressed bodies of the vertebrae ...were so soft they could easily be cut with a knife." - 1932.*

Risk of Fractures with Oral Glucocorticoids

UK General Practice Research Database – 244235 Users



- Skeletal complications of CS use are now much more commonly seen in patients exposed to iatrogenic CS's for the treatment of a variety of diseases – most commonly rheumatic and respiratory. Ultimately 50% of individuals receiving long-term oral CS's will suffer fractures.
- Axial skeleton - spine and ribs are common sites for fractures which however can occur at any skeletal site.
- Rapid initial phase of bone loss of up to 12% during the first few months followed by 2-5% per year.
- Doubling of the relative risk of hip, distal forearm and proximal humerus fractures in patients with rheumatoid arthritis (RA) receiving CS's⁴.
- Doubling of hip fracture risk⁵.
- Four to five fold increases in the prevalence of vertebral fracture in two studies^{6,7} but not in a third⁸.
- Osteonecrosis is a common accompaniment of corticosteroid use and is thought to be due to apoptosis of osteocytes and osteoblasts. This may occur in as many as 25% of patients⁹.
- Other drugs will contribute to bone loss (methotrexate, immunosuppressants (cyclosporin), anticonvulsants – particularly phenytoin, carbamazepine and sodium valproate and low dose heparin).

BONE DENSITOMETRY

- Fractures occur at a BMD 1.0 SD higher than in postmenopausal osteoporosis.
- In post-menopausal women with RA, treated with CS's, there is a 6.2 fold increase in the RR of vertebral fracture but a decrease of less than 1 SD in BMD¹⁰.
- Baseline BMD necessary for establishing risk of fracture and for guiding treatment.
- Lumbar spine and upper femur preferred sites.
- Follow-up at 12 months following commencement of treatment is suggested to establish whether bone loss is continuing particularly with preventative treatment (Medicare item number 12312).

NORMAL PATHOPHYSIOLOGICAL MECHANISMS OF BONE TURNOVER

- Tight control of bone turnover in the normal skeleton.
- Basic Multicellular unit (BMU) – is a complex structural and functional unit that incorporates osteoblasts and osteoclasts in a well-orchestrated spatial and temporal relationship.
- 3-4 million BMU's initiated each year, 1 million operating at any one time.
- Osteoclasts and osteoblasts are integrated via a local cytokine network and mechanical signals.
- Osteoclasts removed by apoptosis - life-span avg 2 weeks.
- Osteoblasts - 3 months.

PATHOGENETIC MECHANISMS OF CIO

- Impaired calcium and vitamin D metabolism?
- Secondary hyperparathyroidism and increased sensitivity to PTH?
- Hypercalciuria.
- There is variable increased osteoclastic activity.
- Impaired osteoblastogenesis and increased apoptosis of osteoblasts.
- There is aberrant control of the BMU with more rapid cycling through the unit and deeper bone resorption pits.

PREVENTION AND TREATMENT OF CIO

- Modification of Life-style factors – ceasing smoking, moderating alcohol intake.
- Alternative CS's.
- Deflazacort - Limited data. It was thought to be useful but has now been discarded
- Budesonide in IBD.
- Minimise dose of inhaled CS – newer inhaled treatments?
- **Calcium and Vitamin D** in combination can prevent ongoing bone loss in patients maintained on low dose CS's for more than 6 months¹¹. However in patient's who are osteopaenic or osteoporotic or are commencing CS's more effective treatment is advised. A daily calcium intake of 1200-1500 mg and Ergocalciferol (ostelin) 1000 units daily is recommended.
- Bone density increases at the spine in women who are receiving oral CS's and **HRT**. There is no evidence of an effect at the hip nor fracture data available^{12,13}.
- BMD of the spine increases when hypogonadal men receiving oral CS's are treated with testosterone for 1 year.
- A meta-regression analysis showed that **calcitonin** given with vitamin D was more effective than calcium alone but significantly less effective than bisphosphonates¹¹.
- **Sodium etidronate** (with calcium and vitamin D) has improved bone density at the spine¹⁴ and **pamidronate** given over 12 months has prevented bone loss in patients receiving prednisone¹⁵.
- Patients given **alendronate (Fosamax)** and **risedronate (Actonel)** within 4 months of commencing oral CS's have preservation of bone mass at the spine and hip as do patients on chronic GC therapy. Compression fractures of the spine were prevented by both of these bisphosphonates^{16,17}.

TREATMENT RECOMMENDATIONS

- Minimise dose of corticosteroids where possible – additional immunosuppressive treatment may be needed in some patients. Avoid continuous inhaled corticosteroids where possible. These treatment approaches are best undertaken in conjunction with the appropriate specialist.
- Obtain a base-line bone density assessment in patients commencing CS's and repeat at 12 monthly intervals in patients continuing CS's.
- Maintain an adequate intake of calcium and vitamin D as indicated above.
- Commence a bisphosphonate (**Alendronate, risedronate, sodium etidronate or pamidronate**) as prophylaxis against bone loss in patients who are osteopaenic

or osteoporotic at baseline or who will receive a dose of prednisolone of ≥ 7.5 mg daily for > 3 months.

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