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Leaders

Prevention of glucocorticoid induced osteoporosis

Most physicians are well aware that osteoporosis is one of the major complications of glucocorticoid treatment. Only a limited number of physicians, however, simultaneously prescribe medication to prevent the occurrence of glucocorticoid induced osteoporosis. Daily practice (in Europe) was recently evaluated in the area of Nottinghamshire in the United Kingdom.[1] A community survey was carried out to determine the prevalence of continuous use of oral corticosteroids and simultaneous treatment to prevent osteoporosis. This survey covered a population of over 65 000 inhabitants; 303 patients, representing 0.5% of the population, had been taking oral corticosteroids for at least three months. The mean dose was 8 mg prednisolone daily, the medium duration of treatment was three years. In the course of four years only 41 of these 303 patients (14%) had received medication to prevent osteoporosis. In a large teaching hospital in the UK calcium supplementation was prescribed for only 6% of the patients treated with corticosteroids.[2] These data clearly illustrate that measures to prevent glucocorticoid induced osteoporosis are not common in daily practice.

In clear contrast with this daily practice are the recent recommendations published by the American College of Rheumatology Task Force on Osteoporosis Guidelines.[3] These guidelines are quite clear. For patients starting long term glucocorticoid treatment, bone mineral density (BMD) measurements should be performed. The BMD of a patient may be expressed as a T score (the difference in standard deviation (SD) with respect to the peak bone mass in a young adult of the same race and sex) or a Z score (the difference in SD with respect to that found for healthy age matched controls of the same race and sex). Patients with a BMD 1 SD or more below the peak bone mass (that is, T score <-1) are considered to have a low BMD, while those with a T score <-2.5 SD are considered to have osteoporosis.[4] This BMD measurement determines the patient's risk for osteoporotic fractures. The patient should be educated about glucocorticoid induced bone loss, various lifestyle modifications—mainly smoking, alcohol, and exercise—should be discussed, and calcium and vitamin D supplementation should be started. Further treatment depends on the BMD. When a woman's T score is <-1 SD, hormone replacement therapy (HRT) should be started. If there are contraindications for HRT a bisphosphonate or calcitonin should be prescribed. If the BMD is normal, HRT should be suggested for postmenopausal women. It is advised to repeat BMD measurements six or 12 months after the start of glucocorticoid treatment to determine the efficacy of the therapeutic intervention. If the BMD decreases by more than 5% from baseline, anti-osteoporotic medication should be changed or added.

These recommendations are more strict than those of a UK consensus group on glucocorticoid induced osteoporosis,[5] in which there was less emphasis on calcium and vitamin D. HRT or bisphosphonates, or both, were suggested for patients with the highest risk, in this consensus defined as a Z score <-1 or a T score <-2.5 or as regimens of higher (>15 mg/day) doses of corticosteroids.

Both consensus groups emphasise the need for preventive treatment of patients receiving glucocorticoid treatment (7.5 mg prednisone or more daily) for a prolonged period (six months or more) of time. Why is it so difficult for us to implement these guidelines in daily practice? I have heard various physicians express the following doubts:

(1) What is the clinically relevant dimension of the problem?
(2) Do indeed all patients become osteoporotic, or are there subgroups at greater risk?
(3) How convincing are the data that show that preventive measures indeed forestall fractures?

What is the clinically relevant dimension of the problem?

Crude estimates are that the prevalence of osteoporotic fractures in chronic corticosteroid treated patients varies from 30% to 50%.[6] The American consensus group estimated this prevalence to be 25%.[3] Most available data were not collected at the general population level but at the hospital level and relates to specific patient groups. A study of patients with rheumatoid arthritis showed that patients taking corticosteroids were subject to approximately twice the risk of hip fractures as those who were not taking corticosteroids.[7] Although this is indeed a clinically relevant increase in fracture risk, the total number of hip fractures is fortunately still rather low and therefore is not considered a clinically relevant problem in daily practice. The incidence of vertebral deformities in patients treated with corticosteroids is much higher. For patients with rheumatoid arthritis receiving corticosteroids, it was found that the number of vertebral deformities, as given by the Kleerekoper score, was nearly five times as high as in the control RA group.[8] When these osteoporotic patients were asked about their complaints, only one in three remembered an episode of sudden pain in the back. Thus the incidence of clinically symptomatic vertebral fractures is much lower than the incidence of vertebral deformities. Though many people experience some backache now and then, quite often the occurrence of a vertebral deformity is

not noted by the patient. It is therefore quite probable that many physicians also do not recognise the high incidence of these side effects of glucocorticoids.

Do indeed all patients become osteoporotic, or are there subgroups at greater risk?

There is no doubt that everybody who is treated for a prolonged period of time with glucocorticoids will lose some bone. However not everybody will experience a fracture. The following potential risk factors might be relevant:

(1) Low bone mineral density before the glucocorticoid treatment is started. When patients already have a low bone mass, such as postmenopausal women or male patients with hypogonadism, the risk of osteoporosis is increased.
(2) Higher dose of glucocorticoids: it has become clear that skeletal wasting is most rapid during the first six months of treatment and that the skeletal effects of glucocorticoids are both dose and duration dependent, while the cumulative dose also affects the severity of bone loss.[9] There is no consensus regarding a so called safe dose. Some studies suggest that doses of 7.5 mg or less prednisone a day are relatively safe.[10] However, in most observational studies many confounders, such as age, underlying disease, duration of treatment and so on, preclude reliable conclusions.
(3) The underlying disease: for two selected groups, rheumatic patients [11] and patients with asthma [12] a fracture incidence of 50% and 'only' 11% respectively has been reported. Most of these fractures were vertebral deformities and probably only a small proportion was noted by the patients themselves. It has become clear that in an inflammatory disease such as rheumatoid arthritis bone turnover is increased, positively correlated with disease activity.[13] Though it has been attractive to suggest that the positive effect of glucocorticoids on disease activity may counterbalance the negative effect of these drugs on bone[14]; this has not been proved.
(4) The risk of falling: patients who are more prone to fall have an increased risk for fractures. The risk for fractures can be explained for only 40% by the value of BMD; the other 60% will be explained by other factors; one of the most important factors will be the risk of falling.

Though we are well aware of these risk factors at the group level, it is still quite difficult to predict bone loss at the individual level. Measurement of BMD, perhaps followed by a second measurement after six months of treatment, could be indicative in this respect.

Therefore, if we were to look at the available data cynically: we aim to prevent clinically relevant bone loss in less than 25% of the patients but are unable to single out the individual patient most at risk.

How convincing are the data that show that preventive measures indeed forestall fractures?

Since the beginning of the 1980s we have become more and more aware of the negative effects of corticosteroids on bone. It is therefore remarkable that only a limited number of randomised, double blind, placebo controlled trials has been carried out to investigate the preventive effect of bone active agents on BMD or the fracture incidence among glucocorticoid treated patients. In view of the magnitude of the problem more data are urgently needed. We have to realise that most of the data used in clinical decision making come from studies on postmenopausal osteoporosis or on treatment of glucocorticoid induced fractures.

It is relevant to discuss the major mechanism by which glucocorticoid induced bone loss occurs: inhibition of bone formation by direct action on osteoblasts. Reduced intestinal absorption of calcium and decreased renal tubular reabsorption of calcium, leading to hypocalcaemia and secondary hyperparathyroidism, and an indirect effect on the ovaries and testes also contribute.[15] To prevent the hypocalcaemia and secondary hyperparathyroidism, calcium and vitamin D have been given for some time now.[16] Recently two randomised double blind placebo controlled trials confirmed earlier, methodologically less sound, trials showing that calcium and vitamin D supplementation indeed prevent bone loss in patients treated with low dose corticosteroids. Treatment with 1,25-dihydroxy vitamin D (calcitriol) and calcium stabilised BMD in the lumbar spine in patients just starting with moderate to high doses of glucocorticoids.[17] Calcitriol is an expensive and potent vitamin D analogue, however, that can cause hypercalcaemia and hypercalciuria. When patients who were already receiving glucocorticoids for some time, were treated with the parent vitamin D component (and calcium) even some bone gain was found.[18]

Only two limited studies form the basis for the statement in the American guidelines that all postmenopausal women taking glucocorticoids should receive HRT if there are no contraindications.[19 20] Evidence for the use of bisphosphonates is stronger[21–24]: the number of patients evaluated in the different studies was much larger and the effect, expressed as an increase in BMD, is more convincing. However, more definitive studies are in progress.

In the American consensus[3] the use of bisphosphonates is, in my opinion, underrated; the UK consensus has a more balanced view in this respect.[5] There are of course also other drugs that can be used to treat glucocorticoid induced osteoporosis.[25] Limited studies have also been performed with calcitonin, androgens, and fluoride; none of these studies are in my opinion decisive.

So, what should we do in daily practice for patients receiving glucocorticoids?

We should at least implement the following basic measures:

(1) Prescribe glucocorticoids in the lowest possible dose and discontinue as soon as possible.
(2) Try to reduce the activity of the underlying disease.
(3) Stimulate physical activities and avoid immobilisation.
(4) Avoid factors that increase the risk of falling.
(5) Supply calcium to achieve a minimum calcium intake of at least 1000 mg per day.
(6) If hypovitaminosis is likely, such as in house bound patients, supply vitamin D, at least 400 IU/day.

If we are able to implement these basic measures on a large scale, involving all patients treated with glucocorticoids, we will take an important step forward.

And what about further measures? Should we give HRT or bisphosphonates to every patient treated with corticosteroids? Personally, I am still reluctant to say yes, and presently I use the following practical guidelines:

(1) In postmenopausal women treated with glucocorticoids who are clearly at high risk, I do not need a BMD measurement to recommend the use of HRT; when these women object to this treatment or there is a contraindication for this therapy, I would treat them with bisphosphonates. The only reason to measure BMD in these patients would be to monitor the efficacy of the installed treatment.
(2) In other patients I prefer to measure BMD. If a patient has a low BMD (T score <-1 SD) at the start, then I give additional treatment, such as HRT or bisphosphonates.

I remain reluctant to give additional treatment to the other patients, but I would like to reconsider my opinion as

soon as more reliable data are available. At present there is a need for studies elucidating which strategy should be used: should we be fairly conservative, only supplying calcium and vitamin D, or should we be aggressive and give everybody HRT or bisphosphonates, irrespective of additional risk factors, or should we use a more selective strategy, better defining risk factors at the start of treatment and for instance six months later?

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