CLINICAL PRACTICE

Boning up on osteoporosis – current thinking on management

***Dr David Kendler**, Assistant Professor of Medicine at the University of British Columbia, Vancouver, and President-Elect of the International Society for Clinical Densitometry, was in South Africa recently. **Emma Buchanan** spoke to him.*

***EB:** I'm particularly interested in new directions in osteoporosis treatment, and problem areas in treatment and diagnosis. For starters, who to screen and treat?*

DK: The World Health Organization drew up the T-score categorisation in 1993. It's now being redesigned, going beyond the T-score to incorporate other important risks, the most important being age and prior fractures. It will level the playing field, shifting treatment from low-risk younger women to elderly patients at graver 10-year risk of fracture. However, risk factors are not sufficiently sensitive to detect all those at risk. Moreover, if we wait until patients have already sustained a fracture, we miss out on early intervention and fracture prevention. Conversely, dual-energy X-ray absorptiometry (DEXA) increases cost!

Age is a potent risk factor. In the US it is considered that bone density studies should be done in women *and men* over 65, though in South Africa and the UK and Europe age alone is not used as an indication to scan. Then there is race – in the US black skin has been found to be protective, white skin implies highest risk, Chinese and Hispanics are in between. (This may not hold true for South African blacks, and certainly not for Asians and those of mixed ancestry.) We look at prior fractures, such as vertebral and Colles' fractures, and don't forget to ask about a family history of fractures. On the WHO hit list are smoking and alcohol consumption (though moderate use of alcohol may not be harmful – the WHO will define the limit as the equivalent of 2 glasses of wine a day, for both men and women). Another risk factor is long-term steroid therapy, and the WHO is also going to include rheumatoid arthritis.

Very thin women seem to be at higher risk?

Yes, the theory is that adipose tissue helps you convert testosterone to oestrogen, even after the menopause.

Right, on to treatment!

No! Treatment shouldn't just be a knee-jerk reaction – treating the number, not the patient! It's vital to consider secondary causes in all patients with low bone mass. Take a basic history and do a physical and a panel of chemistries. Causes of low bone mass other than osteoporosis are osteomalacia and primary hyperparathyroidism (which is commonly missed). Causes of secondary osteoporosis include gastrointestinal abnormality, endocrine diseases and malignancies.

Consider factors outside low bone mass that may elevate the patient's risk, such as prior fracture and risk of falls.

Er – do you mean dangerous sports, hazardous occupations?

Not at that age! No, you ask – 'do you fall?'. Falling has a huge social impact; these patients can become afraid to go out. There's a lot that can be done to prevent falls – gait and balance training, and exercise (walking type), not just to improve bone health but to strengthen muscles. Look at the patient's shoes, even her spectacles. A walking aid will be helpful. And good placebo-controlled trials have shown that vitamin D might reduce body sway and reduce the risk of falls.

I have read that recent research by the Women's Health Initiative shows that calcium supplements don't necessarily have a beneficial effect on the bones after all?

The media pick out things with news value and capitalise on them! The WHI researchers considered it unethical to take calcium supplements away from the healthy study population, so control subjects taking calcium continued to do so. They were getting about 1 200 mg per day, which is sufficient. Going beyond that isn't going to do any further good and the body can't absorb it anyway. So what they found is entirely to be expected – that the 2 000 mg/d the study group were getting was of no more benefit than 1 200, and even had some adverse effects – renal calculi due to excretion of the excess calcium.

And the vitamin D helps the body absorb the calcium from the gut – you need to take both?

Yes. And the WHI subjects were only getting 400 IU/d – vitamin D has no effect at doses lower than 700 - 800 IU/d.

Remember that in all the trials of osteoporosis drugs the control group weren't on *no* treatment – they were getting a placebo *plus calcium and vitamin D*.

Yet the medical aids here in South Africa won't pay for them!

It's the same in Canada, it's crazy.

Are we ready to reach for the prescription pad now?

As a general statement, therapy needs to be tailored to the patient and the perceived and potential risks and benefits in her individual case.

Antiresorptives

The oldest member of the antiresorptive group, oestrogen, has known antiresorptive effects but also other benefits – and risks. Menopausal symptoms remain the primary indication, with the bonus of protecting bone. And the known risks preclude the long-term therapy needed to protect bone life-long.

A second group of agents with 'bone plus' effects are the selective oestrogen receptor modulators (SERMS). Raloxifene has good data showing a reduced incidence of vertebral but not non-vertebral fractures.

Why the distinction?

Remember you are aiming to tailor therapy to the individual patient. A very important consideration when the risk of hip fracture is high (typically in the older patient) is to choose a product that has demonstrated activity at the hip site.

An extraskeletal benefit of raloxifene is that it may reduce the risk of invasive breast cancer by 70%. The downside is worsening of postmenopausal flushes, and an increased incidence of venous thrombosis.

Calcitonin is another product with both skeletal and extraskeletal effects, though it's not used much in South Africa (or North America). It is particularly useful in the patient with acute vertebral fracture, where it has a pain relieving effect.

Bisphosphonates

These are bone-only agents, with beneficial effects on the skeleton alone. Alendronate can reduce vertebral and non-vertebral fractures in postmenopausal women by approximately 50%. Data are also favourable in men and steroid-induced osteoporosis – it's useful in a wide profile of patients. Its side-effects of gastric intolerance, and the fact that it's a mission to take, have in part been overcome by weekly dosing. Risendronate has a similar fracture risk reduction (both vertebral and non-vertebral), the side-effect profile is similar, and dosing is also weekly. From a clinician's perspective, though, it produces lesser increases in bone mineral density than alendronate – and patients want to see an improvement!

With the bisphosphonates clinicians always want to hear about longer intervals between doses. Not registered yet (but approved for other indications) are ibandronate, with a once-monthly oral dose, and zoledronate, with an annual IV injection.

Bone anabolic therapies

Only teriparatide (PTH 1-34) has been approved. It's another product with just a single action – to stimulate a bone anabolic response – and it has been shown to be very effective in reducing the risk of both vertebral and non-vertebral fracture. It's given as daily subcutaneous injections, and therapy is limited to 18 months due to rat osteosarcoma concerns.

It's prohibitively expensive in South Africa?

Its use here is limited to patients with severe osteoporosis (i.e. a low bone mass plus two or more fractures) and/or those with failed antiresporptive therapy (i.e. who have fractures or markedly lose bone despite adequate antiresorptive therapy).

Dual-action bone agents

New on the scene and unique in a class is strontium ranelate (SR), with bone anabolic properties that stimulate new bone formation as well as antiresorptive effects, leading to significant increases in bone density with significant reduction in both vertebral and non-vertebral fracture risk. Its side-effects are limited to mild nausea and diarrhoea, usually resolving within 3 months.

The most attractive feature of SR is its dual mode of action. You are building up as well as protecting bone, and this agent offers the greatest potential rises in BMD.

There is a concern about venous thrombo-embolic events?

Yes, there was a small excess of VTE events in patients treated with SR. It's a low-frequency event – not a contraindication but a caution.

What happens when you discontinue treatment with SR?

Speculating on the basis of animal models, half the strontium leaves the skeleton in 10 weeks. We don't know how this will translate to the clinical situation, but a trial in progress will answer this question.

Combining therapies

What about combining therapies – seems to me like a good idea!

Combining antiresorptive agents is feasible but not always practical – costs rise sharply, and so does the potential for side-effects! Trials of combinations of bisphosphonates and oestrogen have shown an increase in bone density but not a corresponding reduced fracture risk. But I wouldn't necessarily hesitate to add on a second agent if indicated – or even substitute monotherapy with an agent that will be more effective in that particular case.

What about oestrogen in combination with SR?

There are no data, I would not be inclined to combine them. **Sequential therapy** is a fruitful area of research though.

There have been good trials looking at PTH alone, alendronate alone, and the two in combination. The best bone benefits were with PTH or alendronate! It is now well established that combination therapy with PTH and alendronate results in blunting of the anabolic effects of PTH, and it's therefore not recommended. But sequential therapy worked well – PTH first to build bone, then a switch to alendronate as antiresorptive. It cuts costs dramatically, and you 'step the patient up the ladder'.

Follow-up

Just a few words on follow-up?

A tough one. Most clinicians believe it's very important for patient perseverance – positive feedback will encourage her to continue treatment. But the time interval needs to be long enough to detect change. Many therapies result in stabilisation of bone mass, not a discernible increase. The patient needs confirmation that she is doing well, but at present our measuring tool is operating at the limits of its ability. Follow-up is vitally important, but problematic.