AUCKLAND Bonedensity

Managing Bone Health

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PRIMARY HYPERPARATHYROIDISM
A secondary cause of reduced bone density

Dr I Holdaway

When bone density is unexpectedly low for age (usually defined as a Z-score of -2 or lower) it is usual to suggest screening for secondary causes of reduced bone density. One of the disorders usually included in this recommendation is primary hyperparathyroidism (PHT). This condition is usually due to an adenoma in one parathyroid gland which over-produces parathyroid hormone (multiple adenomas, parathyroid hyperplasia and parathyroid carcinoma are all much rarer causes). The disorder may come to light when a raised serum calcium is detected on a random blood sample or when investigating those with osteoporosis, kidney stones, fractures or other complications of the disorder. In general, PHT is a relatively uncommon cause of reduced bone density, although the incidence of vertebral fracture in the disorder may be increased up to 2.7 fold.

The question arises "how often do those with mild HPT (serum calcium 2.6-3mmol/l) develop bone density problems and/or fractures?" What are the risks in leaving mild PTH untreated? For the first time these issues have been addressed in a randomised trial in Norway[1] where 191 individuals with serum calcium 2.6-2.8mmol/l due to PHT were randomised to surgical cure or observation without intervention over an average period of 10 years follow-up. Bone density was measured in the first 5 years of the study and was only 2-4& lower in the control group compared with the operated patients (p = not significant), and there was no increase in vertebral or non-vertebral fractures over 10 years (18% in controls and 16% in the operated group). Interestingly, other possible complications of untreated HPT were also not significantly different between the groups, including the frequency of renal stones, cardiovascular and cerebrovascular events, cancer, or overall mortality. Only 2% of the control group needed parathyroid surgery during follow-up because of falling bone density. These findings suggest that uncomplicated biochemically mild PHT can be safely kept under observation without surgical intervention. Indications for surgery during follow-up might include those aged <50 (who may have a more aggressive course), serum calcium rising above 3mmol/l, rapid bone loss on bone density scanning, or development of kidney stones. Notably, such patients are only a small minority of those with biochemically mild PHT at diagnosis. If surgery is needed this should be performed by a high-volume unit with experienced parathyroid surgeons.

An editorial co-authored by one of the ABD Directors, Associate Professor Andrew Grey[2], emphasised that this study for the first time provides useful guidelines for management of mild primary hyperparathyroidism derived from a randomised trial.

1. *Pretorius M et al, Ann Int Med 2022;175: 812*
2. *Bolland M & Grey A, Ann Int Med 2022; 175: 899*

Update on Use of Zoledronate for Fracture Prevention

Dr A Grey

Intravenous zoledronate therapy is effective in reducing fracture risk in older adults: relative risk reductions overall are 33-37%. Thus, treatment of a person with a baseline absolute 10-year fracture risk of 20% will reduce that risk to 13%, and about 14 such individuals need to be treated to prevent a fracture. Here are replies to some of the frequently asked questions about zoledronate.

How frequently should zoledronate be administered?
Clinical trial data demonstrate that fracture prevention is as good with 18-monthly infusions as 12-monthly. Indeed, 36-monthly infusions are as effective as 12-monthly. Bone density is maintained at hip and spine for 8-10 years after a single 5mg dose in older women. Thus, administration need not be more frequent than every 18 months and for many patients, administration up to 3 yearly may be reasonable.

How long can treatment continue?
There is no need for treatment to be time-limited. Annual administration of 5mg zoledronate for 9 years is not associated with adverse events. Thus, for patients with high fracture risk, ongoing treatment is both reasonable and sensible.

What are the possible side-effects?
(a)About 1 in 6 people experience fever or musculoskeletal pain as part of the 'acute phase' reaction with their first dose. It is sensible to warn patients about this. Symptoms typically occur within a day of infusion, last about 3 days and are mild-moderate in severity. Symptoms are similar to those experienced in viral infections and are caused by activation of T lymphocytes leading to cytokine release. Fewer than 1 in 10 people experience any symptoms of an acute phase reaction after a second dose and fewer than 1 in 30 after a third dose. Management includes analgesics and anti-pyretics as required.
(b) About 1 in 200 people experience ocular inflammation after the first dose. Ocular inflammation should prompt medical review.
(c) Osteonecrosis of the jaw is extremely uncommon in patients receiving intravenous zoledronate for osteoporosis, between 1 in 10,000 and 1 in 100,000 recipients. We are aware that some dental practitioners make extremely cautious recommendations but these risks are so low that there is no need to adjust treatment in a context of upcoming dental procedures.
(d) With oral bisphosphonates, it is standard practice to interrupt treatment for 1-3 years after about 5 years of use, to mitigate the low risk (5-10/10,000) of atypical femoral fractures during prolonged continuous use. For zoledronate, the risk of atypical femoral fractures is lower than with oral bisphosphonates, particularly if dosing intervals are greater than 1 year.

What level of renal function precludes use? This is uncertain, but Medsafe recommends against use of zoledronate in patients with creatinine clearance <35ml/min. We recommend measuring eGFR within 3 months of an infusion, or closer to the time if medical events have recently occurred. Referral for specialist advice should be considered if uncertainty exists. The Endocrinology Advisory Committee has requested that Pharmac fund denosumab for patients with high fracture risk and severe renal impairment who cannot receive zoledronate, but no decision has yet been communicated.

Why does zoledronate still require a Special Authority? We don't know! If administered at 18 month intervals, the drug costs the same as alendronate and less than risedronate. Pharmac is aware of this, but has not removed the restriction. The costs of administering zoledronate (staffing and intravenous lines) can reduce access to the medication for some patients in some parts of the country. We encourage practitioners in both primary and secondary care to consider strategies that permit administration of the drug at low cost to recipients, such as configuring clinics where several patients share the cost of staffing.