RATIONAL TESTING

Testing for secondary causes of osteoporosis

Melissa O Premaor, 1 Juliet E Compston 2

This article summarises what tests should be offered to patients with low bone mineral density to exclude secondary causes of osteoporosis.

A 62 year old woman consulted her general practitioner about low back pain that had started while gardening. She was otherwise healthy, had no notable medical history, and took no medications. Menopause had occurred when she was 51 years old. Clinical examination was normal apart from tenderness over the lower thoracic and upper lumbar spine. A lateral spine radiograph showed vertebral crush fractures at the T12 and L1 vertebrae.

What is the next investigation?

Although back pain in itself is not an indication for bone densitometry, bone density should be measured if vertebral fractures are present. Bone mineral density of the lumbar spine and hip should be measured by dual energy x ray absorptiometry. Osteoporosis is diagnosed if the bone mineral density T score (number of standard deviations above or below normal peak bone mass) is less than or equal to −2.5 at either site. 1 However, fragility fractures often occur in individuals with osteopenia (T score −1 to −2.5). 2 Other causes of fracture such as malignancy (including myeloma) and trauma should be excluded, particularly if the bone mineral density is normal or high. All vertebral fractures should be investigated, regardless of whether they are symptomatic or an incidental x ray finding, as secondary causes of osteoporosis are present in about 30% of women and 55% of men with vertebral fractures. 1 4

LEARNING POINTS

Bone densitometry using dual energy x ray absorptiometry should be performed in patients with vertebral fractures to establish whether low bone mineral density is present.

Secondary causes of osteoporosis are present in about 30% of women and 55% of men with vertebral crush fractures.

Tests to exclude secondary causes include full blood count and erythrocyte sedimentation rate, bone biochemistry (serum calcium, phosphate, and alkaline phosphatase concentrations), liver and kidney function tests, serum thyroid stimulating hormone, and coeliac serology. In patients with vertebral fractures myeloma should be excluded using serum protein immunoelectrophoresis.

Full blood count and erythrocyte sedimentation rate

Anaemia is often present in coeliac disease, myeloma, and chronic inflammatory diseases. Leucopenia and thrombocytopenia may also be present in patients with myeloma. Erythrocyte sedimentation rate (or plasma viscosity) is usually substantially raised in myeloma and may also be increased in inflammatory disorders—for example, inflammatory bowel disease or rheumatoid arthritis.

Risk factors for fractures included in the FRAX algorithm

Age
Female sex
Low bone mineral density
Low body mass index
Previous fragility fracture
Parental history of hip fracture
Current smoking
Alcohol intake ≥3 units daily
Current glucocorticoid treatment
Rheumatoid arthritis
Secondary causes of osteoporosis (including diabetes (insulin dependent), osteogenesis imperfecta in adults, untreated longstanding hyperthyroidism, premature menopause or hypogonadism in men, chronic malnutrition or malabsorption, chronic liver disease, drugs such as aromatase inhibitors and androgen deprivation therapy)

A history should be taken to establish whether clinical risk factors for osteoporosis are present (box). The FRAX algorithm (developed by the World Health Organization) uses selected risk factors (box) with or without bone mineral density to estimate the 10 year fracture probability and is available at www.sheffield.ac.uk/FRAX. 6

Other investigations should be performed to exclude underlying conditions that increase the risk of osteoporosis (box). The likelihood of secondary osteoporosis is even greater if multiple vertebral fractures are present. 6 It is therefore essential to exclude underlying conditions that may contribute to low bone mineral density and fracture. Initial investigations in all patients should include full blood count and erythrocyte sedimentation rate, bone biochemistry, and renal and liver function tests. Further tests should be done if indicated by abnormalities in the initial blood tests or by clinical history and examination.
Bone biochemistry
Increased serum calcium concentration with a normal or low serum phosphate concentration may indicate primary hyperparathyroidism. Hypercalcaemia may also be present in subjects with myeloma or metastatic bone disease.

Serum parathyroid hormone concentrations should be measured if hypercalcaemia is present. In the presence of hypercalcaemia, a normal or raised serum parathyroid hormone suggests primary hyperparathyroidism, whereas most other causes of hypercalcaemia are associated with a low serum parathyroid hormone.

Serum 25-hydroxyvitamin D concentration should be measured if vitamin D insufficiency is suspected. Low serum 25-hydroxyvitamin D concentrations may also be associated with raised serum parathyroid hormone concentrations as a result of secondary hyperparathyroidism. Hypocalcaemia, hypophosphataemia, and a raised serum alkaline phosphatase suggest a diagnosis of osteomalacia. In most cases of osteomalacia the serum 25-hydroxyvitamin D concentration is low and the serum parathyroid hormone concentration is increased.

Renal and liver function tests
Chronic liver disease and chronic renal disease are associated with an increased risk of osteoporosis. A urine dipstick test should be done and serum creatinine and urea concentrations measured to screen for renal disease. Some impairment of renal function is common in patients with myeloma. Liver function tests should be requested to determine if liver disease is present.

Serology tests for coeliac disease
Patients with coeliac disease are at increased risk of osteoporosis. The presence of IgA endomysial antibody and IgA anti-tissue transglutaminase antibody in blood has high sensitivity and specificity as a diagnostic test. In patients with IgA deficiency these tests may be negative in the presence of coeliac disease, and IgG antibodies against transglutaminases should be assessed. In a few cases of coeliac disease antibody tests are normal, and if coeliac disease is strongly suspected, a jejunal biopsy, obtained during upper gastrointestinal endoscopy, should be performed.

Endocrine tests
Hyperthyroidism is associated with accelerated bone loss and increased risk of fracture. Low serum thyroid stimulating hormone concentrations indicate the presence of hyperthyroidism, and serum free thyroxine should then be assessed to confirm the diagnosis. If the serum free thyroxine concentration is normal, free tri-iodothyronine should be measured to identify cases of T3 thyrotoxicosis.

In men with vertebral fractures, serum testosterone should be measured to exclude hypogonadism.

Serum protein electrophoresis
Myeloma, a condition in which abnormal plasma cells in the bone marrow produce paraproteins, must be excluded in patients with vertebral fractures as about 1.0% of such cases may turn out to have myeloma. Serum protein immunoelectrophoresis should be performed to establish whether paraproteins are present. The presence of a paraprotein may indicate myeloma and the patient should be referred for specialist advice. Occasionally immunoglobulins may be suppressed, and in such cases urine should be tested for Bence-Jones proteins (light chains). “Monoclonal gamopathy of unknown significance” is diagnosed when paraproteins are present at low concentrations and no clinical or other biochemical abnormalities are present. Although currently monoclonal gamopathy of unknown significance is not actively treated, a recent study has shown an increased risk of fractures in patients with this condition.10

Outcome
Bone densitometry showed osteopenia with a T score of −1.6 in the spine and −1.7 in the total hip. Serum calcium, phosphorus, and alkaline phosphatase concentrations were normal. Serum 25-hydroxyvitamin D and parathyroid hormone, renal and liver function tests, coeliac serology tests, and serum thyroid stimulating hormone were also normal. Screening for paraproteins was positive, indicating a diagnosis of myeloma. She was referred to a consultant haematologist for further investigation and treatment.

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Patient consent not required (patient anonymised, dead, or hypothetical).

Some medicines need to be given at high initial doses (loading doses) at the start of treatment, before being reduced to a lower, maintenance dose. Reasons vary for the need for loading doses. In some patients the therapeutic level is needed very quickly—for example, phenytoin to stabilise a patient after a seizure. Loading doses are also needed for medicines that would otherwise take a long time to reach the desired therapeutic levels—for example, without a loading dose, it might take a month for a patient with heart failure to benefit from amiodarone.

Loading doses are complex to prescribe, as they require multistep calculations using information about the patient (such as weight) and the medicine (such as estimated volume of distribution or half-life). Staff may mistakenly continue loading doses instead of lowering to maintenance doses, particularly when patients move between settings (for example, from emergency departments to general wards or from hospital back to the community). Little evidence exists in the formal literature on frequency of error or harm, except for isolated case reports.1

From January 2005 to April 2010, staff in England and Wales reported 1165 patient safety incidents relating to loading dose errors. These included two deaths, four cases of severe harm, and 102 of moderate harm. A further death was reported by a coroner.

A typical incident report reads: “Patient prescribed loading dose of 1 g phenytoin [on ward name] then maintenance dose of 1 g BD [twice daily] (usual maintenance dose is around 300 mg OD [once daily]) on Friday … Five 1 g doses were administered over the weekend. Screened by a pharmacist on the Sunday and incorrect dose not picked up and queried with the medical team. Patient not seen by any medical team on Monday. I noticed wrong dose on Tuesday morning and crossed off prescription and discussed with medical team. Patient died Wednesday . . .”

Problems identified by the National Patient Safety Agency

Most serious incidents (all deaths and half of cases of serious harm) reported to the agency relate to four high risk medicines—warfarin, amiodarone, digoxin, and phenytoin. However, over 80 types of medicines were named in one or more incidents, showing that errors with loading doses apply to a large number of medicines, some of which are used rarely.

Analysis of incidents suggested gaps in knowledge and awareness of staff (especially junior doctors and nurses) of differences between loading and maintenance doses and potential for harm. Types of error included:

- Problems in making complex calculations at time of loading dose
- Delay or failing to give loading dose, resulting in patient deterioration
- Loading dose repeated in error or maintenance dose not prescribed, including information not transferred with patients on discharge
- Infusion rate not changed when maintenance dose administered.

What can we do?

The rapid response report recommended system changes to reduce errors. The first action was for organisations to identify a list of the critical medicines (including the “top four”: warfarin, amiodarone, digoxin, and phenytoin) for which the loading dose errors can cause substantive harm. This may contain subsections for particular clinical specialties, such as neonatal units administering loading doses of caffeine and metronidazole. Organisations were also asked to use tools such as loading dose worksheets, prescription charts (with preprinted stickers), handover protocols, and discharge summaries to ensure good communication on transfer, and to introduce documented checking processes by medical, nursing, and pharmacy staff. Some of these tools are available online (at www.patientsafetyfirst.nhs.uk/forums/Default.aspx?TopicId=463).

For individual clinicians

- Ask yourself: “Is a loading dose essential to improve the outcome for this patient?” For example, some services have adopted protocols to start patients safely on warfarin for atrial fibrillation without using loading doses.2 Or could you use an alternative drug, one that does not require a loading dose, for this patient instead?
- Ensure you have the information you need to calculate the loading dose and subsequent maintenance doses, including the patient’s weight and the medicine’s half life.
- Get your loading dose independently checked by colleagues before the drug is given.
- Write up loading doses on the drug chart as “once only” doses in a separate section from maintenance doses.
- For infusion doses, specify the length of infusion time when prescribing a loading dose on the drug chart, and draw up only the required amount. This should ensure that even if the infusion time is
prolonged, no more will be given as the syringe will be empty and the pump will sound an alarm. The maintenance doses should be drawn up and given in a separate syringe.

- General practitioners and community pharmacists who are continuing treatment for patients that was started in secondary care should be quick to challenge doses that seem abnormally high. For example:
  - Doses of digoxin greater than 250 µg daily in adults (greater than 125 µg in those aged over 70 years) should rarely be seen
  - Amiodarone doses higher than 200 mg daily should be queried (the maximum licensed dose for maintenance is 200 mg)
  - Phenytoin doses greater than 500 mg daily should be rarely seen, although there may be wide variability among patients in phenytoin serum levels with equivalent dosage, so a wide range of doses is used
  - Warfarin doses may vary considerably among patients. Any newly started treatment at doses greater than 5 mg should be considered abnormal in the community.

What else do we need to know?
Reported incidents showed a range of loading dose regimens used in hospitals. Evidence based loading regimens and detailed protocols for key high risk medicines need to be developed nationally. Further evidence is also needed on safe alternatives to loading doses for different indications, where they exist.

When developing guidance, the National Patient Safety Agency considered removal of critical loading dose medicines from general clinical areas, a strategy used for other high risk medicines, such as potassium chloride or midazolam. However, healthcare providers did not find this acceptable, given the range of drugs affected and the risk of delay for critical medicines. But the agency did ask organisations to review stock locations and consider whether removal was appropriate for some high risk medicines.

Longer term solutions are needed to minimise errors. Solutions include design of inpatient medicine charts and electronic equivalents that force distinctions between loading and maintenance doses, as well as software in infusion pumps that can specify the type of dose and limit the dose.

How will we know when practice has become safer?
All NHS organisations were given until November 2011 to complete the actions outlined in the rapid response report. To measure improvement, local organisations could do simple baseline reviews by analysing loading dose incidents for key high risk medicines (such as phenytoin or amiodarone) and repeat this over time. Local audits of process would include review of drug charts and worksheets and other tools available for staff.

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