Nottinghamshire Osteoporosis Guidelines

Produced in consultation with Nottinghamshire Osteoporosis Guidelines Development Group
Approved by APC: July 2019 Review Date: July 2022

Primary Prevention / no previous fragility fracture

For women receiving adjuvant aromatase inhibitors for breast cancer see here
For people with anorexia nervosa see NICE guidance

Age ≥ 50 with 2 or more risk factors (see appendix 4)

Calculate 10 year probability of fracture using FRAX® tool http://www.shef.ac.uk/FRAX
(Consider investigation if concerns about Malabsorption or Family history of early onset osteoporosis)

Age < 50 with major risk factors (see appendix 4) (e.g. current or recent use of oral or systemic glucocorticoids (see appendix 5), or untreated premature menopause)

Use FRAX® and measure BMD and consider referral if necessary. Refer to secondary care osteoporosis service.

High risk
(or patient unable or unwilling to go for scan)

Intermediate risk
(or have concerns re: Malabsorption / Family History / concordance / need for future monitoring by a DXA scan)

Low risk

Above NOGG treatment threshold*
Consider primary prevention
Consider referral if T-score below -4.5 or concerns regarding severity of disease. Refer to primary care nurse specialist (where available) or secondary care osteoporosis service.

DXA scan and Recalculate FRAX®

Below NOGG treatment threshold*
Consider Lifestyle advice (see pg 5)
Review if patient presents with new risk factors / fragility fracture

*** National Osteoporosis Guideline Group (NOGG) treatment threshold - See NOGG website**

- Exclude secondary causes - see routine investigations (appendix 3)
- Check baseline fasting CTx , U&Es, Ca^{2+}, Vit D
- Replace Ca2+ and/or Vit D if required (see pg 5)

Calculate Creatinine Clearance (see calculator here or use calculator embedded in GP clinical system)

Consider referral to primary care nurse specialist (where available) or secondary care osteoporosis service:
E.g. if oral bisphosphonates contraindicated, patient unable to take, or inadequate response.

Creatinine Clearance ≥ 30ml/min

1st line unless contraindicated
Alendronic acid PO 70mg weekly +/- Ca^{2+} and/or Vit D
2nd line if alendronic acid not tolerated or CrCl 30-35ml/min
Risedronate PO 35mg weekly +/- Ca^{2+} and/or Vit D
Consider referral to primary care nurse specialist (where available) or secondary care osteoporosis service for patients unlikely to comply with oral treatment for consideration of IV zoledronic acid.

Creatinine Clearance < 30ml/min

Review at 4 months:
Repeat fasting CTx + U&Es and review concordance / side-effects, (counsel patient and repeat in 3/12 if poor concordance or inappropriate administration detected)

- **Inadequate response**
  <30% reduction in fasting CTx despite appropriate administration and good concordance
- **or new fragility fracture**
- **or CrCL <30ml/min**
- **or intolerance**

Adequate response (> 30% reduction in fasting CTx and no new fractures)
and tolerated (renal function stable / no intolerable side-effects)

Continue therapy and review:
- When patient has a fracture OR
- 5 years or earlier as indicated by DXA report , if no fractures.

See bisphosphate treatment review (pg 4)

Secondary Prevention / Previous fragility fracture

Age ≥ 75 years

Age 50-74 years

Age <50 years

Hip fracture

Limb or vertebral fracture

Refer to secondary care osteoporosis service.

FRAX® tool and DXA scan (optional for baseline)

T-score below -2.5 confirmed by DXA scanning

Severe osteoporosis (T-score below -4.0) or multiple vertebral fractures
Or T-score below -3.5 and fracture

- Exclude secondary causes
  - see routine investigations (appendix 3)
- Check baseline fasting CTx, U&Es, Ca2+, Vit D

Consider referral to primary care nurse specialist (where available) or secondary care osteoporosis service:
E.g. if oral bisphosphonates contraindicated, patient unable to take, or severe osteoporosis

Replace Ca^{2+} and/or Vit D if required (see pg 5)

Calculate Creatinine Clearance (see calculator here or use calculator embedded in GP clinical system)

Creatinine Clearance ≥30ml/min

Creatinine Clearance <30ml/min

1st line if eGFR >35mL/min – Alendronic acid 70mg weekly **OR Zoledronic Acid IV infusion annually (check BNF for contraindications)** +/- Calcium and/or Vitamin D supplements
2nd line if alendronate / zoledronic acid contraindicated or not tolerated or Creatinine Clearance 30-35ml/min
Risedronate 35mg weekly +/- Calcium and/or Vitamin D supplements

Repeat fasting CTx, renal function and concordance / side-effect review at 3 months (if poor concordance or inappropriate administration detected, counsel patient and recheck again in 3/12) - only applicable for patients on oral alendronate or risedronate

- **Adequate response** (> 30% reduction in fasting CTx and no new fractures)
- **and tolerated** (renal function stable / no intolerable side-effects)

Continue therapy
Review at 5 years or earlier as indicated by DXA report (see bisphosphate treatment review – pg 4)

- **Inadequate response** (< 30% reduction in fasting CTx despite appropriate administration and good concordance or new fragility fracture) – re-investigate and exclude secondary causes.
- **or CrCL <30ml/min**
- **or intolerant of oral bisphosphonates**

Consider referral to primary care nurse specialist (where available) or secondary care osteoporosis service.
For ESRD (eGFR <15mL/min) refer to secondary care

Bisphosphonate treatment review

Timing of review:
after 5 years treatment with alendronate, risedronate or ibandronate
Or after 3 doses of zoledronic acid
Or post fracture

Investigations: DXA* scan and FRAX® recalculation
Repeat U+E's, Ca2+ and Vit D, and fasting CTx
* DXA may not be appropriate for some frail elderly patients or for patients who are unable to lie still on their back – contact specialist for advice if unsure.

Consider referral to primary care nurse specialist (where available) or secondary care osteoporosis service **if:**

a. Patient has recurrent fracture(s) or prevalent vertebral fracture(s)
b. BMD has deteriorated despite patient concordance with treatment
c. Creatinine Clearance has decreased to < 30mL/min
d. Patient has been on treatment for ≥ 10yrs
e. Patient reports thigh, hip or groin pain or dental pain, dental mobility or dental swelling which may indicate an atypical femoral fracture or osteonecrosis of the jaw

Patient has sustained one or more low trauma fractures despite adequate concordance (≥80% concordance for ≥2 years)

Exclude secondary causes (see routine investigations – appendix 3)

OR

Patient is **above** NOGG treatment threshold
OR
Hip BMD T-score below -2.5

Reasons for ineffectiveness identified? e.g.:
- Poor concordance to treatment (i.e. if <80%)
- Check Ca2+ and Vit D and replace if required (see pg 5)

Patient is **below** NOGG treatment threshold
OR
Hip BMD T-score above -2.5

Is patient still high risk? due to:
- Taking continuous oral steroids (≥7.5mg/ day prednisolone)
- Age > 75
- Previous hip or vertebral fracture

YES / **NO**

YES / **NO**

Consider referral to primary care nurse specialist (where available) or secondary care osteoporosis service

Consider second line therapy
E.g. change bisphosphonate or refer to secondary care for assessment of non-bisphosphonate therapy

Consider continuing existing therapy (with measures to correct ineffectiveness as required)
Consider specialist opinion at 10 years continuous therapy if no fracture **

Consider Drug holiday
Discontinue bisphosphonate for:
- 1 year - risedronate, ibandronic acid - limited information
- 2 to 3 years alendronic acid
- 3 years zoledronic acid

Continue $Ca2^{+}$ and Vit D supplements

*** Advise patient to report any side effects including thigh, hip, groin or dental pain, dental mobility or dental swelling*

Drug Holiday Reassessment (at indicated interval OR if new fracture):
Repeat DXA scan, fasting CTx and redo FRAX®
Consider restarting treatment if any of:
- Indication of deterioration on DXA scan
- Annual fasting CTx >0.3 micrograms/L
- New fragility fracture or new clinical risk factor(s)
- Above NOGG treatment threshold **If no conditions met reassess annually**

Lifestyle Advice

Advice for all patients;

- Smokers should be encouraged to stop smoking.
- Avoid excessive alcohol consumption (men and women ≤ 2 units per day).
- Undertake weight bearing exercise (within limits imposed by underlying disease).
- Ensure adequate calcium and vitamin D intake [RDI for calcium 700mg/day with 400 units daily of vitamin D for over 65s]. See ROS leaflet for calcium content of a wide variety of foods or Calcium calculator For housebound / nursing home elderly patients consider 800 units daily of vitamin D (See Vitamin D guideline).
- Maintain good nutrition and normal body weight (where possible).

Falls risk assessment and advice should be performed in those at increased risk of falling (see *NICE guidelines 2013*)

Patient information leaflets:
NOGG leaflet on osteoporosis available here
ROS leaflet for all about osteoporosis available here and facts about food available here

Calcium and Vitamin D replacement

- When co-prescribing vitamin D supplements with an **oral** anti-resorptive agent (alendronate, risedronate etc), maintenance therapy may be started without the use of loading doses.
- For patients about to start a **parenteral** anti-resorptive agent (i.e. zoledronic acid or denosumab), rapid correction of vitamin D deficiency may be required. Consider prescribing a treatment loading regimen if the vitamin D level is below 50nmol/L, followed by regular maintenance doses. (See Vitamin D guidelines for dosing information).
- See Nottinghamshire Vitamin D guidelines for further advice on vitamin D replacement and supplements,
- Calcium supplements only necessary if calcium intake from diet is ≤700mg per day. Use calcium calculator to estimate average daily calcium intake.
- For patients with severe hypocalcaemia consider specialist advice regarding replacement and/or investigation.

CTx (see appendix 7 for more detail)

- **Fasting** CTx (i.e. only water pre test) is currently the preferred test in Nottinghamshire and is a marker of bone resorption. It can be used to monitor concordance and effectiveness of oral bisphosphonate treatment .
- A **30%** reduction from baseline of CTx is considered to indicate a significant reduction in bone turnover .
- Samples should be collected in EDTA (Purple top tubes). Stability of sample has been demonstrated for up to 24 hours in EDTA. Collection in other sample tubes not advisable for stability reasons.

References

- NICE (2008) Raloxifene for the primary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal guidance 160. Last updated Feb 2018
- NICE (2017) Bisphosphonates for treating osteoporosis. NICE technology appraisal guidance 464. Last updated Feb 2018
- NICE (2017) Osteoporosis. NICE Quality Standard 149
- NICE (2008) Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women NICE technology appraisal guidance 161. Last updated Feb 2018
- Denosumab for the prevention of osteoporotic fractures in postmenopausal women. NICE technology appraisal guidance 204 (2010)
- NICE Clinical Knowledge Summaries: Osteoporosis - prevention of fragility fractures last revised Dec 2016
- NICE (2012) Osteoporosis: assessing the risk of fragility fracture (NICE clinical guideline 146. Last updated Feb 2017
- National Osteoporosis Guidelines Group (NOGG) 2017: Clinical Guideline for prevention and treatment of osteoporosis. Last updated July 2018
- WHO FRAX Tool available at: http://www.shef.ac.uk/FRAX/
- Nottinghamshire Area Prescribing Committee Guidelines on Vitamin D deficiency available at: http://www.nottsapc.nhs.uk
- UKMI Q&A: Do gastric adverse events influence the choice of bisphosphonate for the treatment of osteoporosis?
- NUH (2015) Adjuvant Use of Aromatase Inhibitors for Early Breast Cancer, NUH Breast Services Guideline
- NICE (2017) Eating disorders : recognition and treatment. Nice guideline 69.

Appendix 1: Specialist Initiation Treatment Options

Table1: Drug	Route of admin.	Restrictions / Contraindications	Licensed Dose	Monitoring and Side-Effects
Ibandronic Acid *Amber 2 - specialist recommendation*	**ORAL**	3rd line oral option where alendronate and risedronate have not been tolerated. No data available for hip fracture reduction. Not recommended if Creatinine Clearance ≤30ml/min	150mg PO **monthly**	As per other oral bisphosphonates
Raloxifene *Amber 2 - specialist recommendation*	**ORAL**	NICE recommended for secondary prevention only in postmenopausal women when alendronate/ risedronate can't be used. Contraindicated in women with child-bearing potential, a history of venous thromboembolism, unexplained uterine bleeding, Hepatic impairment and severe renal impairment (although <6% of dose excreted in urine) Caution in women with a history of stroke or with risk factors for stroke	60mg PO daily	Side-effects include leg cramps, oedema, flu syndrome and hot flushes. Increased risk of VTE
Zoledronic acid *Amber 2 / Red (see notes)*	**IV**	Available for initiation only by osteoporosis specialists as an alternative to alendronic acid. Continuation of prescribing in primary care only possible in areas where CCG pathway for primary care administration exists.	5mg IV yearly	See algorithm notes regarding drug holidays. Please note date received by patient on GP systems to prevent inappropriate use of oral bisphosphonates
Ibandronic Acid (Bonviva®) *Red - specialist prescribing only*	**IV**	For initiation by osteoporosis specialists only in patients with an unsatisfactory response, intolerant, contraindicated or physically unable to comply with oral bisphosphonates or yearly IV zoledronic acid.	3mg IV injection every 3 months	See algorithm notes regarding drug holidays. Please note date received by patient on GP systems to prevent inappropriate use of oral bisphosphonates
Denosumab (Prolia®) *Red - specialist prescribing only*	**SC**	For initiation by osteoporosis specialists **for post menopausal women** as per NICE TA for patients in whom IV bisphosphonates aren't suitable. Also for men under the community Fracture Liaison Service. Continuation of prescribing in primary care only by the community fracture liaison service as per Denosumab SOP for HCOP patients. Correct hypocalcaemia and vitamin D deficiency before starting. Consider dental check-up and carry out invasive procedures before initiating treatment (risk of osteonecrosis of the jaw).	60mg subcutaneous injection every 6 months +/- oral Ca^{2+} and/or Vit D.	Side-effects include skin infection, predominantly cellulitis, and hypocalcaemia . See MHRA safety updates on Osteonecrosis of the Jaw and Hypocalcaemia (Aug 2014) , Hypocalcaemia (Oct 12) Atypical femoral fractures Feb 13
Teriparatide (Forsteo®) *Red - specialist prescribing only* Supplied via homecare	**SC**	For **initiation by osteoporosis specialists only** in men* and post-menopausal women as per NICE TA in patients unable to take or have had an unsatisfactory response to oral bisphosphonates AND meet NICE criteria regarding age and T-scores. Caution in moderate renal impairment; avoid if severe. Maximum duration of treatment limited to 24 months in both men and women. *NHSE Interim Clinical Commissioning Policy Statement: Teriparatide for Osteoporosis in Men (adults)	20 micrograms subcutaneous injection daily **for maximum 24 months** +/- oral Ca^{2+} and/or Vit D.	Side effects include headache, nausea, dizziness and postural hypotension.

Appendix 2: Fracture prevention efficacy table

Table 2: Anti-fracture efficacy of approved treatments for postmenopausal women with osteoporosis when given with calcium and vitamin D (traffic lighted according to Nottinghamshire Joint Formulary classification) . Adapted from NOGG guidelines 2013. Colours reflect the traffic light classifications for the medicines in Nottinghamshire

Drug	Vertebral Fracture	Non-vertebral fracture	Hip fracture
Alendronate (Green)	A	A	A
Risedronate (Green)	A	A	A
Raloxifene (Amber 2)	A	Not adequately evaluated	Not adequately evaluated
Zoledronic acid (Red)	A	A	A
Ibandronate (Red)	A	A#	Not adequately evaluated
Denosumab (Red)	A	A	A
Teriparatide (Red)	A	A	Not adequately evaluated

Evidence grading: A based on meta-analysis or at least one randomised controlled trial

\# in subsets of patients only (post-hoc analysis)

Appendix 3: Recommended routine investigations

Recommended routine investigations to exclude non-osteoporotic causes of fragility fractures and undiagnosed secondary causes of osteoporosis include:

- ❑ X-ray of the fracture. Arrange lateral X-rays of the lumbar and thoracic spine when there is spinal pain, loss of height, or kyphosis.

- **Blood tests: -**
  - ❑ Full blood count
  - ❑ ESR or C-reactive protein
  - ❑ liver function tests
  - ❑ renal function tests
  - ❑ bone profile
  - ❑ thyroid function tests

- **For people with a fragility fracture**, **exclude non-osteoporotic causes** and arrange investigations as appropriate if there are features of:
  - ❑ Metastatic bone cancer
  - ❑ Multiple myeloma
  - ❑ Osteomalacia
  - ❑ Paget's disease

- **Consider undiagnosed secondary causes for osteoporosis** and arrange investigations as appropriate, especially in people with a fragility fracture who are at low risk for the condition (including men of any age, pre-menopausal women, and women in early menopause). Consider:
  - ❑ Endocrine conditions such as untreated premature menopause in women, hypogonadism in men, diabetes, and hyperthyroidism.
  - ❑ Rheumatological conditions such as rheumatoid arthritis, and other inflammatory arthropathies.
  - ❑ Chronic gastrointestinal diseases that cause malabsorption such as Crohn's disease, ulcerative colitis, and coeliac disease.
  - ❑ Chronic liver disease.
  - ❑ Chronic obstructive pulmonary disease.

Appendix 4: Risk Factors

Clinical risk factors used for the assessment of fracture probability

(from NOGG guideline)

- ❑ Age
- ❑ Sex
- ❑ Low body mass index (≤19kg/m^2)
- ❑ Previous fragility fracture, particularly of the hip, wrist and spine including morphometric vertebral fracture
- ❑ Parental history of hip fracture
- ❑ Current glucocorticoid treatment (any dose, by mouth for 3 months or more). **Local** consensus on bone protection for those on intermittent courses of steroids in appendix 5 below.
- ❑ Current smoking
- ❑ Alcohol intake of 3 or more units daily
- ❑ **Secondary causes of osteoporosis** including: -
  - ❑ Rheumatoid arthritis
  - ❑ Untreated hypogonadism in men and women
  - ❑ Prolonged immobility
  - ❑ Organ transplantation
  - ❑ Chronic obstructive pulmonary disease
  - ❑ Type I diabetes
  - ❑ Hyperthyroidism
  - ❑ Gastrointestinal disease that causes malabsorption e.g. Crohn's, UC or coeliac
  - ❑ Chronic liver disease
  - ❑ Falls *

* Falls are not presently accommodated in the FRAX algorithm

Major risk factors (relating to primary prevention in the <50year olds)

- ❑ current or recent use of high-dose oral corticosteroids of more than or equivalent to 7.5mg prednisolone daily for more than 3 months.
- ❑ **Local** consensus on bone protection for those on intermittent courses of steroids in appendix 5 below.
- ❑ Untreated premature menopause

Appendix 5: Preventing glucocorticoid induced osteoporosis

Local consensus (from osteoporosis specialists) – Three or more high dose oral steroid courses in a year is a trigger to consider the need for bone protection. However, note that some patients who have had fewer than three courses a year may also be at risk if other risk factors are present.

Further guidance on the prevention of glucocorticoid induced osteoporosis is available from the Royal College of Physicians (2002) and the American College of Rheumatology (2017).

Please follow the links below for advice on management beyond the scope of these guidelines:

Royal College of Physicians: https://cdn.shopify.com/s/files/1/0924/4392/files/glucocorticoid-induced-osteoporosis-guideline.pdf

American College of Rheumatology: https://www.rheumatology.org/Portals/0/Files/Guideline-for-the-Prevention-and-Treatment-of-GIOP.pdf

Appendix 6: Counselling for patients on bisphosphonates

All patients must be informed of the following information before starting on a bisphosphonate.

General advice on bisphosphonates;

- To keep taking their bisphosphonate as it is a long term therapy to prevent fragility fracture. That they will also be prescribed calcium and vitamin D supplementation if their dietary calcium intake and vitamin status have been assessed and are inadequate
- If on oral treatment, advise the patient to stop taking the bisphosphonate and seek medical advice if they experience any signs or symptoms of possible oesophageal reaction, e.g. dysphagia, pain on swallowing, retrosternal pain, or new/worsened heartburn
- Advise the person to have regular dental check-ups, before starting oral bisphosphonate treatment if they have poor dental status, and to tell their dentist that they are taking a bisphosphonate, particularly if they are going to undertake invasive dental procedures (due to a very rare risk of osteonecrosis of the jaw). Advise patients to inform of any dental mobility, pain or swelling.
- Advise the patient to stop taking the bisphosphonate and seek medical advice if they experience inner thigh pain – usually only occurs after approx. 3 years of treatment. This could be a sign of an atypical fracture.

Patient concordance;

- Patient concordance with bisphosphonates is poor due to side effects (e.g. oesophageal reaction as listed above, musculoskeletal pain, joint swelling, headache, dizziness, tiredness. See patient information leaflet for full list). To ensure the benefits are realised it is suggested patients are assessed a month after starting treatment by the GP, practice nurse or pharmacist to check how things are going and assess concordance.
- Advise the patient that If oral doses are frequently missed they should speak to their GP about different treatment options (also see note below about missed doses).

Administration advice for oral bisphosphonates;

- The tablet must be swallowed whole and taken with a glass of plain water (at least 200 ml); it must not be sucked or chewed because of a potential for oropharyngeal ulceration.
- It should be taken while in an upright position and they should not lie down for at least 30 minutes after taking the tablet.
- The tablet must not be taken at bedtime or before getting up in the morning.
- Once weekly preparations should be taken on the same day each week.
- **Alendronate** must be taken at least 30 minutes before the first food, other medicinal product, or drink (other than plain water) of the day.
- **Risedronate** should be taken at least 30 minutes before the first food, other medicinal product, or drink (other than plain water) of the day. Alternatively it may be taken between meals — should be taken at least 2 hours before or at least 2 hours after any food, other medicinal product, or drink (other than plain water).
- Do not take with **food, milk and dairy products, and medicinal products containing polyvalent cations** (such as calcium, magnesium, iron, and aluminium — for example antacids) as they interfere with absorption of the bisphosphonate. If taking calcium supplements, consider omitting morning dose of calcium supplement on the day that the bisphosphonate is taken.

Missed doses: For once-weekly oral preparations of alendronate or risedronate, advise the person:

- To take the missed tablet on the day that it is remembered.
- To continue taking one tablet once a week, on the day the tablet is normally taken.
- That two tablets should not be taken on the same day

Helpful information:

- **The Royal Osteoporosis Society** (www.theros.org.uk) provides support and information to people affected by osteoporosis, influences health and social care provision, and works to improve public understanding of osteoporosis.
- **The NHS website** has a health encyclopaedia which has an article on Osteoporosis at: http://www.nhs.uk/conditions/Osteoporosis/Pages/Introduction.aspx

Appendix 7: Monitoring osteoporosis treatment with oral bisphosphonates

Background
The decision to introduce osteoporosis treatment is based on fracture risk assessment, often including measurement of bone mineral density (BMD). BMD measurements are strongly predictive of fracture risk and are the basis for diagnosis of osteoporosis. BMD measurements are not, however, a good tool to assess response to most osteoporosis treatments.

Why monitor osteoporosis treatment?
First-line treatment for osteoporosis is usually with oral alendronic acid (70 mg weekly). The aim is for treatment to be taken correctly and regularly for a minimum of 5 years in the first instance and for the patient to remain calcium and vitamin D replete during this time. Treatment needs to be taken according to detailed instructions (see appendix 6).

Oral bisphosphonates are poorly absorbed with only approximately 1% of each dose being absorbed even with total compliance with these instructions.

Many patients fail to persist with osteoporosis treatment while many others experience a sub-optimal response due to unintentional poor compliance or impaired absorption. Monitoring treatment response identifies poor response enabling treatment to be modified to improve fracture risk reduction. It has also been shown that monitoring treatment response may improve compliance and persistence with osteoporosis treatment.

How is treatment monitored?
It is important to check with the patient that they are following the instructions and continuing to take treatment regularly. Conventionally, osteoporosis treatment has been monitored by making periodic measurements of BMD but this is not an effective method because:

- BMD changes with osteoporosis treatment are small and slow
- The magnitude of measurement error with BMD is similar to the change in response to treatment

In a typical patient it is not possible to measure a significant BMD response until they have taken treatment for over 18 months. In patients with unreliable BMD measurements it may take considerably longer. Serial BMD assessment is not, therefore, a useful technique to improve compliance with treatment as compliance problems generally arise early.

An alternative approach to monitoring is to measure biochemical markers of bone turnover (BTM). These show large and rapid changes in response to osteoporosis treatment allowing detection of a significant treatment response within a few months. It has also been shown that changes in BTM are a better predictor of reduced fracture risk than changes in BMD.

BTMs have been used in Sheffield and Nottingham to monitor osteoporosis treatment in the metabolic bone clinics for over 10 years. Until recently, experience in primary care has been limited locally and there has not been a viable automated test available. The introduction of CTx gives the opportunity to use biochemical monitoring in the community.

Continued…

What is CTx?
The carboxy terminal telopeptide of collagen type I of type I collagen (CTx) is a by-product of bone resorption (during Osteoclastic hydrolysis of collagen) which is released into the circulation and excreted in the urine. As a result it is specific for the bone resorption which should be inhibited by bisphosphonates.

It is dependent on time of day and food (must be collected after an overnight fast), but is stable in an EDTA sample tube for up to 24 hours post collection. Serum CTx is the international standard test for bone resorption. Within a few months of starting treatment it is usually possible to measure a significant decrease in CTx indicating treatment response.

How is treatment response defined?
The aim is to see a response to treatment indicated by a significant decrease in bone resorption. This decrease in bone resorption correlates with a decrease in fracture risk. A significant decrease in bone turnover will be expected from patients responding to oral bisphosphonates. The following would indicate a response to therapy:

- A reduction of the CTx concentration by more than 30% from baseline
- If no baseline CTx is available an empirical value of <0.30ug/L 3 months apart may indicate adherence / adequacy of treatment.

Age related reference ranges:

Males		Females	
30 - 50 years	<0.58 micrograms/L	Up to 45 years	<0.57 micrograms/L
51 – 70 years	<0.70 micrograms/L	>45 years	<1.01 micrograms/L
>70 years	<0.85 micrograms/L		

Is there any point in giving treatment if the baseline level of CTx is low?
In a patient with osteoporosis the bone turnover may not be increased but there may still be imbalance between the processes of resorption and formation leading to bone loss. It is therefore still helpful to initiate treatment with an anti-resorptive treatment such as alendronic acid to restore bone remodelling balance as treatment has been shown to reduce fracture risk regardless of the baseline level of bone turnover. If the baseline CTx level is undetectable it would be advisable to repeat the test ensuring that the patient is fasted overnight. If the CTx remains undetectable discuss with specialist prior to initiation of treatment to exclude possible causes for low bone turnover or adynamic bone disease i.e. hypoparathyroidism, post whole body irradiation and chemotherapy.

What is the significance of a very high level of CTx?
A very high CTx result indicates high bone turnover. This is usually associated with accelerated bone loss and may be an indication that there is an underlying cause of bone loss. Possible causes include secondary causes of osteoporosis, severe vitamin D deficiency / osteomalacia, malabsorption, thyrotoxicosis or, less commonly, the presence of other pathology (e.g. Paget's disease of bone, malignancy or myeloma).

Importantly, CTx increases following a fracture or orthopaedic surgery. The increase is maximal shortly after the insult but returns to baseline levels within 3-5 months. This may vary depending on the extent and nature of the fracture or surgery. Therefore it is important to exclude recent fractures, particularly once treatment has commenced. In the absence of recent fracture or orthopaedic surgery, a value greater than 1.5 to 2 times the upper limit of normal should alert the clinician to further investigation.

Continued…

Chronic kidney disease may lead to a falsely raised CTx and in patients with CKD 4 and 5 the CTx may be 4-6 times the upper reference limit. In these patients bisphosphonates are contra-indicated and this would therefore not create any problems.

What should be done if the 3 month measurement of CTx does not show a response to treatment?

1. Check compliance with treatment

- Both the bisphosphonate and any calcium and vitamin D supplements
- Ensure the dosing instructions are being followed correctly
    - If poor compliance is identified, re-educate, recheck compliance after 1-2 months and recheck CTx in 3 months' time
    - If compliance issues cannot be reliably addressed or are due to side effects consider change in treatment
        - If side-effects, consider weekly risedronate. If this is unsuitable or not tolerated or ineffective, consider referral
        - If difficulty with oral dosing, consider referral to specialist for parenteral preparation such as an annual infusion of zoledronic acid or 6-monthly denosumab

2. Check whether the patient has sustained any fractures since the baseline measurement

If so, ensure compliance is good and re-check CTx at 6 months.

3. If compliance is good and no fractures, undertake investigations to identify potential malabsorption or other underlying cause of poor response

- Bone profile, PTH, Vitamin D, TSH, coeliac antibodies, myeloma screen may be helpful
- Treat any reversible cause identified
    - Discuss with specialist or refer if appropriate

With thanks to Sheffield Teaching Hospital for allowing Nottinghamshire APC to adapt their document on which this appendix is based.

References

- UptoDate: Use of biochemical markers of bone turnover in osteoporosis. Rosen et al 2012
- Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster J-Y, Borgstrom F, Rizzoli R, on behalf of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) (2008) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 19:399–428
- Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards Osteoporos Int 2010

Appendix 8: List of contributors

With thanks to the following people for their contribution to the development of this guideline.

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