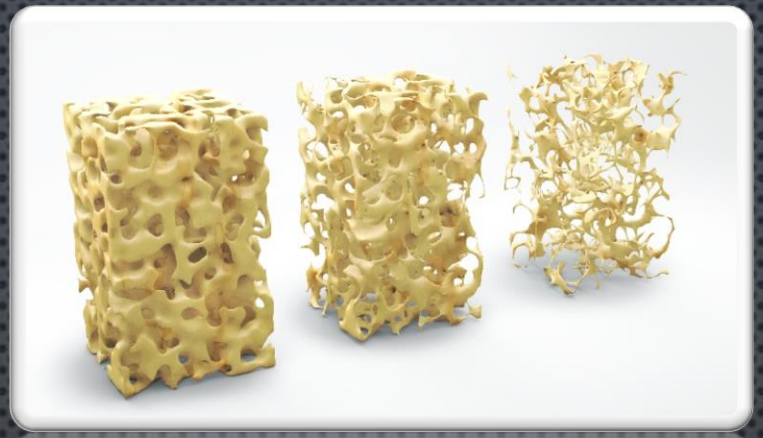


COMMON OSTEOPOROSIS QUERIES

(THOSE PRESENTED AT MEETING)

DR ALEXANDER COMNINOS

BSC (HONS) MBBS MRCP PHD

CONSULTANT ENDOCRINOLOGIST & FRACTURE LIAISON SERVICE CLINICAL LEAD | IMPERIAL COLLEGE HEALTHCARE NHS TRUST

HONORARY SENIOR LECTURER | IMPERIAL COLLEGE LONDON

What are the main secondary causes of low bone density?

Why important to consider?

- Not enough to just say that patient has osteoporosis
- Why do they have osteoporosis?
- Is there an underlying factor that has not been diagnosed or could be addressed before launching into osteoporosis treatment?

Women: ~30% secondary cause

Men: ~50-80% secondary cause

MESSAGE:
Consider secondary causes particularly in men and younger patients

Baillie SP et al. Age Ageing 1992;21:139–41.
Caplan GA et al. J R Soc Med 1994;87:200–2.
Fitzpatrick LA et al. Mayo Clin Proc 2002;77:453-68.

HISTORY (RISK FACTORS/SECONDARY CAUSES)

Over lifetime	DH
Previous fragility fracture	Current/previous drugs (steroids, aromatase inhibitors, progesterone, GnRH agonists, heparin, anticonvulsants, anti-retrovirals, Calcineurin inhibitors, PPIs, high dose statins)
Severe illness during lifetime & immobility	Dietary calcium (use online calculator)
Late menarche/irregular menses/early menopause (?HRT protection)	Vitamin D deficiency
History of low BMI (<18.5)	**FH**
PMH	Family history (especially if parental hip #)
Malabsorption (Coeliac/IBD/Bariatric surgery)	**SH**
Rheumatoid arthritis or other inflammatory disorder	Smoker/ex-smoker
Diabetes or other endocrine disorder (hyperthyroid, hyperparathyroid, GH deficiency, Cushings, hypogonadism)	EtOH ≥2u/day (women) or ≥3u/day (men)
Other (MS, myeloma, MGUS, mastocytosis, sarcoid, collagen disorder, OI, hypercalciuria, hypophosphatasia)	History of falls

EXAMINATION

BMI (normal 18.5-24.9)
General examination
Any other pathologies? (Cushings etc.)
Vertebral examination and distal neurology
Falls risk assessment including balance (Romberg)

INVESTIGATIONS

EACH CLINIC APPOINTMENT:

eGFR
PTH (not in primary care unless ca >2.5)
Adjusted calcium
Phosphate
Vitamin D
ALP
Bone formation marker: **ALP, P1NP**
Bone resorption marker: **urine NTx**, serum CTx

} ENDO BONE CLINIC

IMAGING:

DEXA (every 2-5 years)
Thoracic/Lumbar XRs (>4cm height loss or pain)

ADDITIONAL NEW PATIENT BLOODS (do the ones above as well):

FBC, ESR, LFTs, sex steroids (+/- LH, FSH, SHBG), prolactin, TFTs, protein electrophoresis & coeliac screen

CONSIDER FOLLOWING ADDITIONAL TESTS (if unexplained osteoporosis/suspicion of other 2ary cause):

24h urine calcium excretion	(hypercalciuria)
24h urine citrate excretion	(RTA)
Overnight Dex Test	(subclinical Cushings)
Serum tryptase	(mastocytosis)
ACE	(sarcoidosis)

} ENDO BONE CLINIC

MESSAGE:
If secondary cause suspected and/or identified

Referral to appropriate clinic (eg gastro, haematology)

Consider referral to Endocrine Bone Clinic (especially if young), unless confident to manage

How do I interpret a DEXA scan? – The Basics

Represents approximately 40-50% of fracture risk

Use:

T scores if **postmenopausal woman** or **man > 50y** or if **fragility #**

Normal	T score > -1
Osteopaenia	T score between -1 and -2.5
Osteoporosis	T score ≤ -2.5
Severe osteoporosis	T score ≤ -2.5 + fragility #

Z scores otherwise

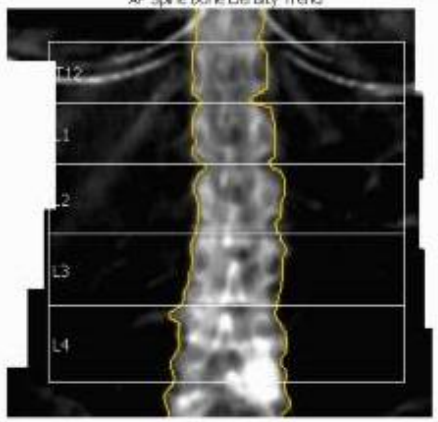
Normal	Z score between -2 and +2
Low BMD for chronological age	Z score ≤ -2

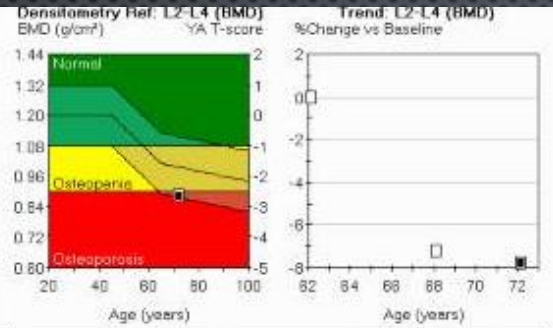
WHO 1996
NOGG 2017

How do I interpret a DEXA scan? – The Basics

72y old female

Spine





Region	BMD [1,6] (g/cm²)	Young-Adult [2] T-score	Age-Matched [3] Z-score
L1	0.643	-4.1	-2.4
L2	0.724	-4.0	-2.3
L3	0.887	-2.6	-0.9
L4	0.989	-1.8	-0.1
L2-L4	0.882	-2.6	-0.9

Trend: L2-L4

Measured Date	Age (years)	BMD [1,6] (g/cm²)	Change vs Previous (%)	Change vs Baseline (%)
01/08/2019	72.1	0.882	-0.7	-7.8
28/07/2015	68.1	0.888	-7.2	-7.2
04/08/2009	62.1	0.957	-	baseline

COMMENTS:

Image not for diagnosis

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Filename: nwyvpbnz.dfs
Scan Mode: Standard 37.0 µGy

1 - Statistically 68% of repeat scans fall within 1SD (± 0.010 g/cm² for AP Spine L2-L4)
2 - UK (ages 20-40) AP Spine Reference Population (v113)
3 - Matched for Age, Ethnic
6 - Standardized BMD for L2-L4 is 840 mg/cm².
11 - World Health Organization - Definition of Osteoporosis and Osteopenia for Caucasian Women: Normal = T-score at or above -1.0 SD; Osteopenia = T-score between -1.0 and -2.5 SD; Osteoporosis = T-score at or below -2.5 SD; (WHO definitions only apply when a young healthy Caucasian Women reference database is used to determine T-scores.)

GE Healthcare

Lunar Prodigy
DF+15083

Hip

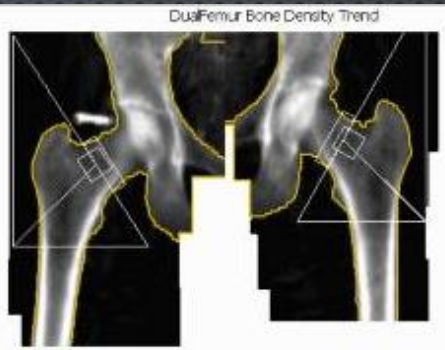
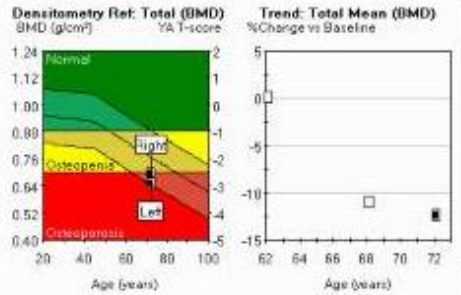


Image not for diagnosis



Region	BMD [1,6] (g/cm²)	Young-Adult [2,7] T-score	Age-Matched [3] Z-score
Neck			
Left	0.681	-2.5	-0.3
Right	0.669	-2.6	-0.4
Mean	0.675	-2.5	-0.4
Difference	0.011	-0.1	-0.1
Total			
Left	0.651	-2.9	-1.0
Right	0.693	-2.6	-0.6
Mean	0.672	-2.7	-0.8
Difference	0.042	0.4	0.4

Trend: Total Mean

Measured Date	Age (years)	BMD [1,6] (g/cm²)	Change vs Previous (%)	Change vs Baseline (%)
01/08/2019	72.1	0.672	-1.6	-12.5
28/07/2015	68.1	0.683	-11.1	-11.1
04/08/2009	62.1	0.768	-	baseline

COMMENTS:

1 - Statistically 68% of repeat scans fall within 1SD (± 0.010 g/cm² for DualFemur Total)
2 - UK (ages 20-40) Femur Reference Population (v113)
3 - Matched for Age, Weight (females 25-100 kg), Ethnic
6 - Standardized BMD for Total Right is 648 mg/cm², Total Left is 606 mg/cm².
7 - DualFemur Total T-score difference is 0.4. Asymmetry is None.
11 - World Health Organization - Definition of Osteoporosis and Osteopenia for Caucasian Women: Normal = T-score at or above -1.0 SD; Osteopenia = T-score between -1.0 and -2.5 SD; Osteoporosis = T-score at or below -2.5 SD; (WHO definitions only apply when a young healthy Caucasian Women reference database is used to determine T-scores.)

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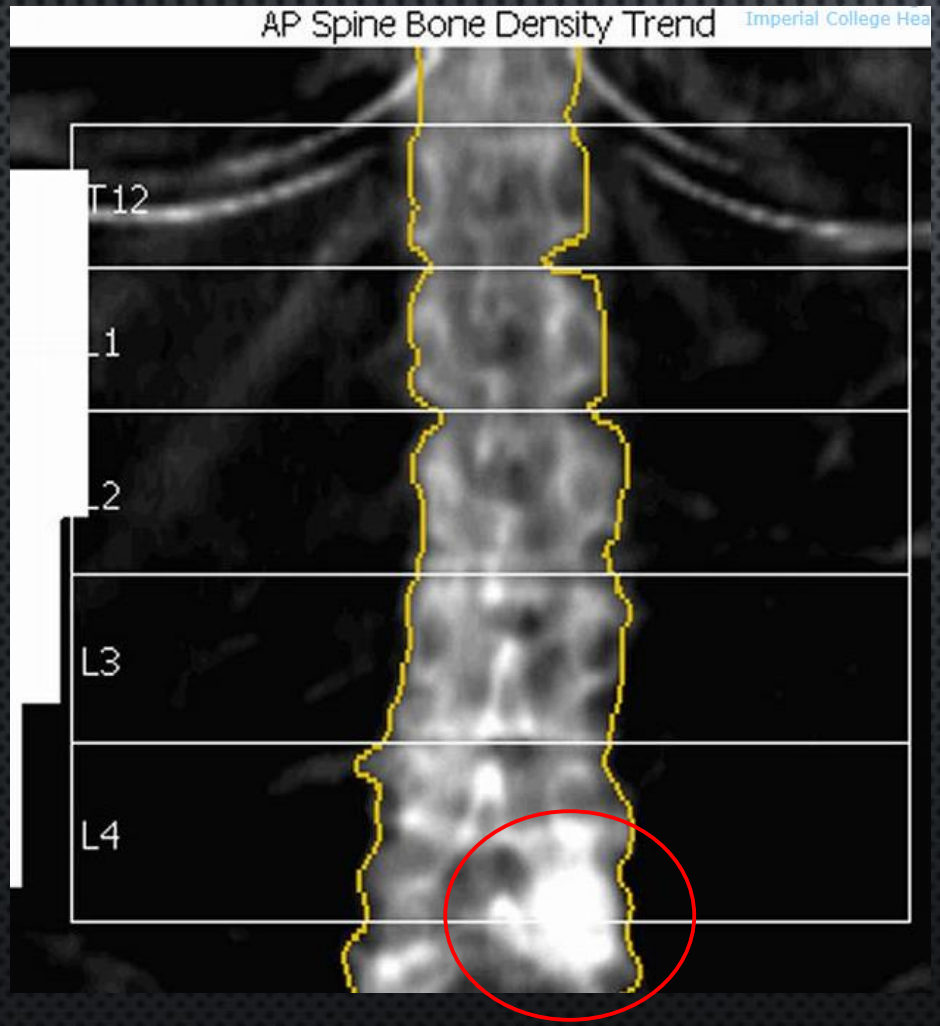
GE Healthcare

Lunar Prodigy
DF+15083

How do I interpret a DEXA scan? – The Basics

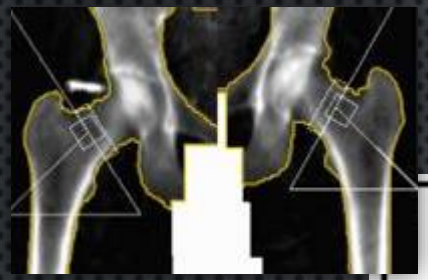
Spine



ANCILLARY RESULTS: AP Spine

Region	BMD[1,6] (g/cm²)	Young-Adult[2] (%)	Young-Adult[2] T-score	Age-Matched[3] (%)	Age-Matched[3] Z-score	BMC (g)	Area (cm²)	Width (cm)	Height (cm)
T12	0.639	-	-	-	-	4.7	7.4	2.9	2.55
L1	0.643	57	-4.1	69	-2.4	5.5	8.5	3.2	2.64
L2	0.724	60	-4.0	73	-2.3	7.4	10.2	3.5	2.95
L3	0.887	74	-2.6	89	-0.9	10.5	11.8	3.9	3.05
L4	0.989	82	-1.8	99	-0.1	14.5	14.6	4.5	3.26
L1-L2	0.687	59	-4.0	72	-2.3	12.9	18.7	3.3	5.59
L1-L3	0.764	65	-3.4	79	-1.7	23.3	30.5	3.5	8.64
L1-L4	0.837	71	-2.9	86	-1.2	37.8	45.1	3.8	11.89
L2-L3	0.811	68	-3.2	81	-1.5	17.9	22.0	3.7	6.00
L2-L4	0.882	74	-2.6	89	-0.9	32.3	36.6	3.9	9.25
L3-L4	0.944	79	-2.1	95	-0.4	24.9	26.4	4.2	6.30

Message
-Beware false elevations due to degenerative change
-Choose vertebrae appropriately



How do I interpret a DEXA scan? – The Basics

For FRAX use Fem Neck Mean

Region	BMD[1,6] (g/cm²)	Young-Adult[2,7] T-score	Age-Matched[3] Z-score
Neck			
Left	0.681	-2.5	-0.3
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Trend: Total Mean

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28/07/2015	68.1	0.683	-11.1	-11.1
04/08/2009	62.1	0.768	-	baseline

How do I decide if patient needs treatment?

FRAX online tool

- www.shef.ac.uk/FRAX
- 10 year probability of major osteoporotic or hip fracture

- Validated in independent cohorts (Kanis et al. 2007)
- Major osteoporotic = clinical spine, hip, forearm, humerus #
- Assumes patient has not had treatment yet

Downsides
-number & type of fractures
-falls risk
-dose effects of risk factors

Alternative is Qfracture
-gives 1-10y risk
-no BMD input
-covers additional risk factors (FH, diabetes, falls, dementia, nursing/care home, systemic disease, antidepressants, E2 therapy etc.)

Example 3

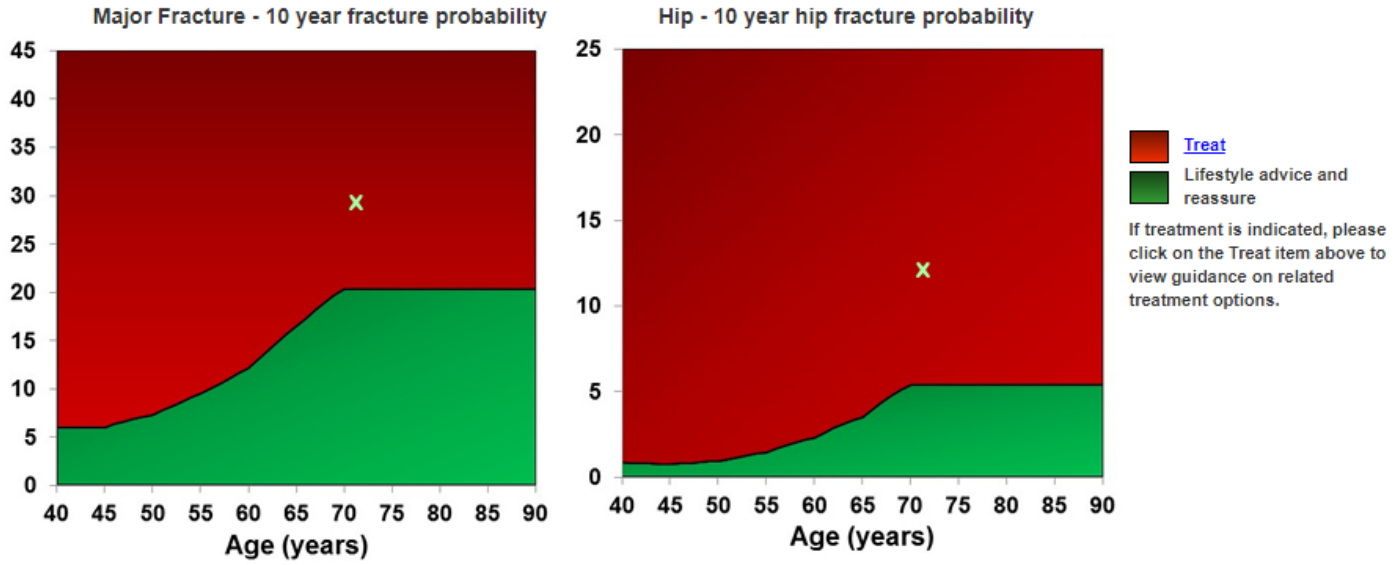
How do I decide if patient needs treatment?

www.shef.ac.uk/FRAX

Osteopaenia + Previous # + Parental hip

Welcome to the NOGG 2017 Guideline Update. These new thresholds ensure equality of access to treatment for older patients with and without fracture (for full details, see the Guideline document)

Intervention Threshold



TREAT

How do I decide if patient needs treatment?

MESSAGE

- Use fracture risk algorithm to decide on treatment especially in osteopaenia
- Simple to use and evidence-based
- Good for 'convincing' patients that treatment needed
- Thresholds for treatment vary by country (eg threshold in US >20% major # & >3% hip #)

www.shef.ac.uk/FRAX

What should I do if the patient does not tolerate alendronate?

Alendronate –> Risedronate -> Binosto -> IV Zoledronate/SC Denosumab

Primary Care	Referral to Endocrine Bone Clinic

Binosto = Buffered effervescent alendronate solution, weekly (£22.80/month on NWL Formulary)

Interactive Case 2

- 74y old woman referred to endocrine clinic
- On alendronate for 5 years following diagnosis of lumbar osteoporosis and was above FRAX threshold
- No secondary cause identified
- No steroid use
- No history of fragility fractures
- FRAX currently below treatment threshold
- DEXA last week shows:
  - Lumbar T score -1.2 (+5% improvement from 5y before)
  - Total Mean Hip T score -2.5 (+3% improvement from 5y before)

Should you continue or stop the alendronate?

A Stop Alendronate and start annual IV Zoledronate

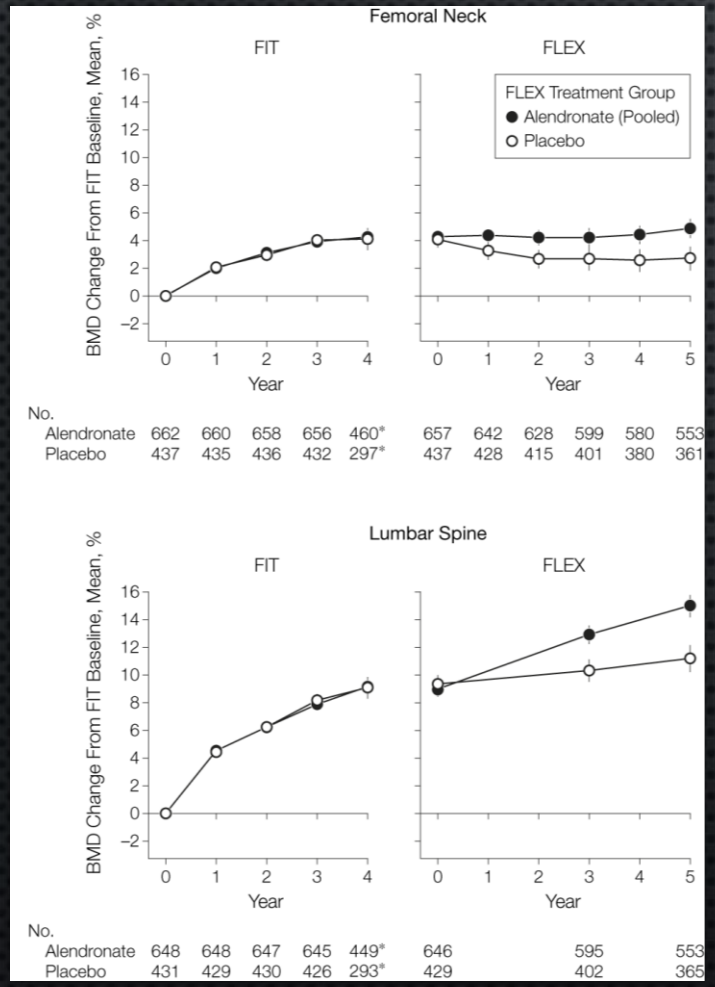
B Continue Alendronate and add annual IV Zoledronate alongside

C Stop Alendronate and re-assess in 2 years ('Bisphophonate holiday')

D Stop Alendronate and re-assess in 5 years ('Bisphophonate holiday')

E Continue Alendronate for further 5 years

What do I do after 5 years of oral bisphosphonate?

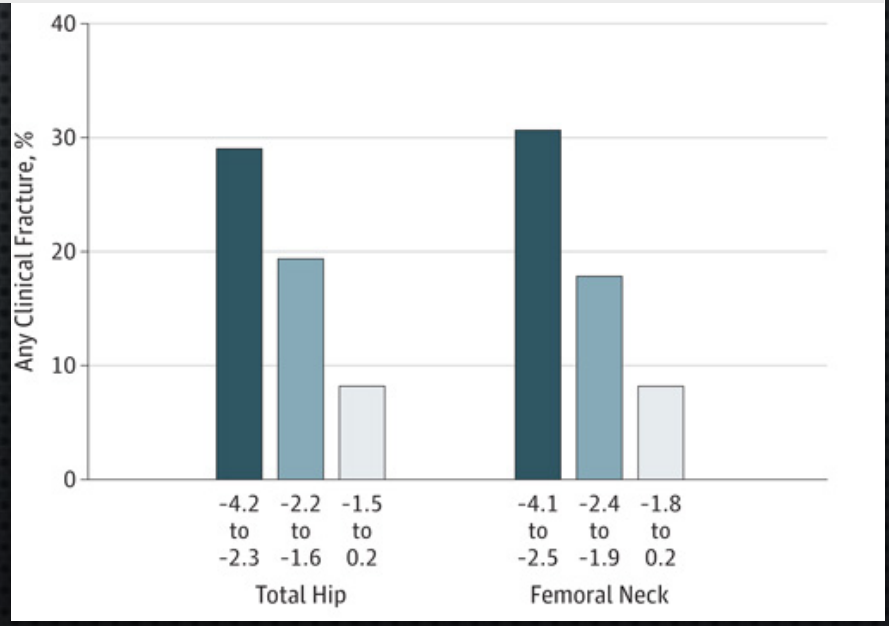


All on ALN (4y)	ALN or placebo (5y)

Black et al., *JAMA*. 2006;296(24):2927-2938

In first 2 years after stopping Alendronate:
-Minor losses at hip (but still above original baseline)
-Stable at spine

Risk of fracture on stopping alendronate by T score



On stopping fracture risk greatest if hip T score < -2.5

Bauer et al., *JAMA Intern Med. 2014 Jul; 174(7): 1126–1134*

What do I do after 5 years of oral bisphosphonate?

HIGH RISK PATIENTS

Reassess at 5 years and continue if:

- >75y
- Previous hip/vert # OR Occurrence of fragility # during treatment (having excluded poor compliance/secondary cause)
- ≥ 7.5mg prednisolone (or equivalent)
- Hip BMD T score ≤ -2.5
- Above NOGG intervention threshold

Otherwise stop and reassess in 1.5-3y or if #

NOGG 2017

What do I do after 5 years of oral bisphosphonate?

'Bisphosphonate holiday'

Not retirement

- Alendronate: ~2y
- Risedronate: ~1.5y
- IV Zoledronate: ~3y

Allows microarchitectural remodelling, thereby rapidly reducing cumulative risks of AFF/ONJ

Bones still protected due to longlasting action of bisphosphonates – tell patients

NOGG 2017

What do I do after 10 years of oral bisphosphonate?

Reassess in 1.5-3y or if #

Interactive Case 3

A 76 year old woman attends your clinic and is very anxious

She has just read in the Daily Mail that bisphosphonates cause necrosis of the jaw (ONJ) and she would like to stop them immediately.

Do you:

A Agree that high risk of ONJ and so should stop Alendronate immediately

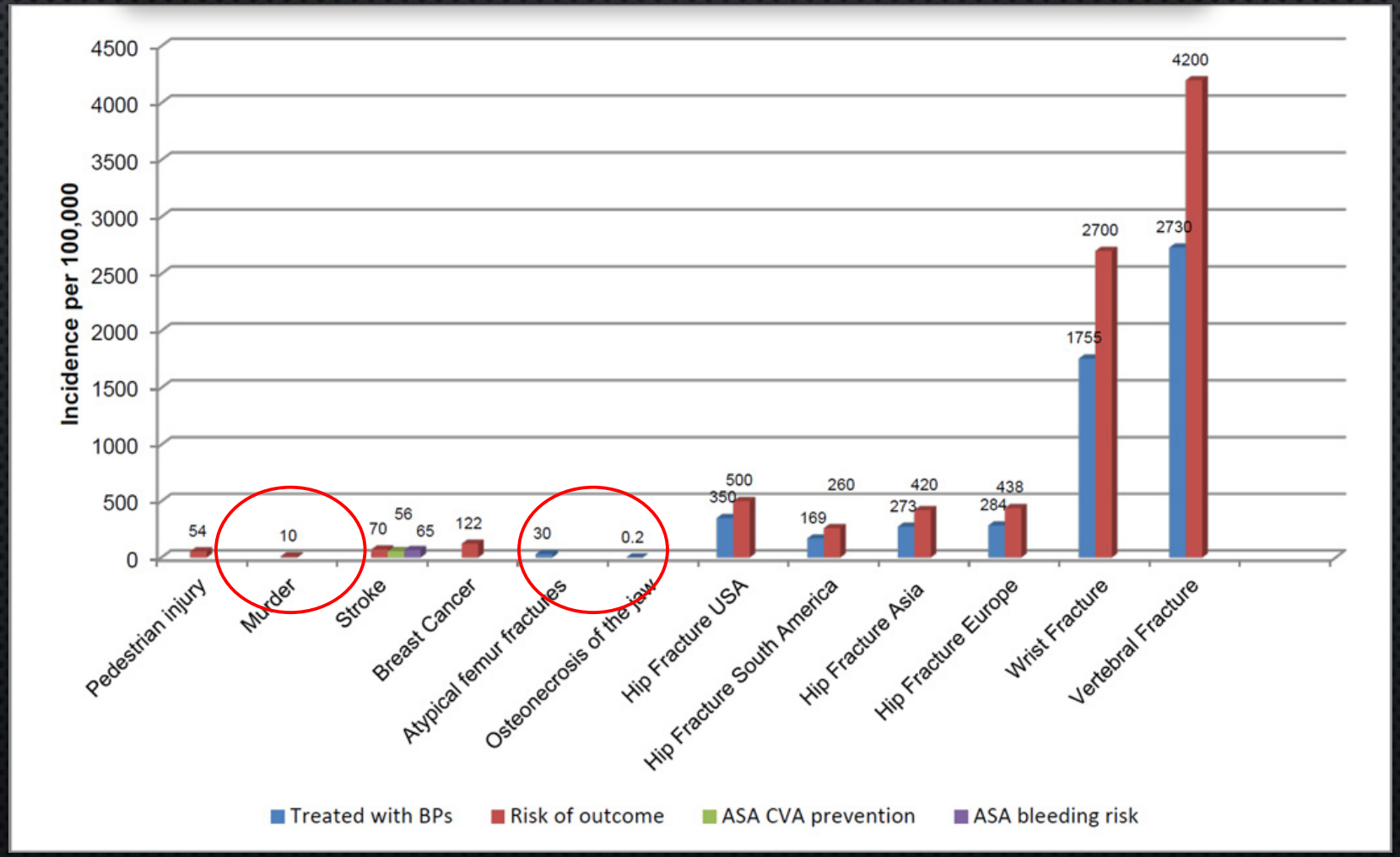
B Advise switching to Densoumab injections as do not cause ONJ

C Inform patient that more likely to get murdered than get ONJ

D Advise her that bisphosphonates do not cause ONJ

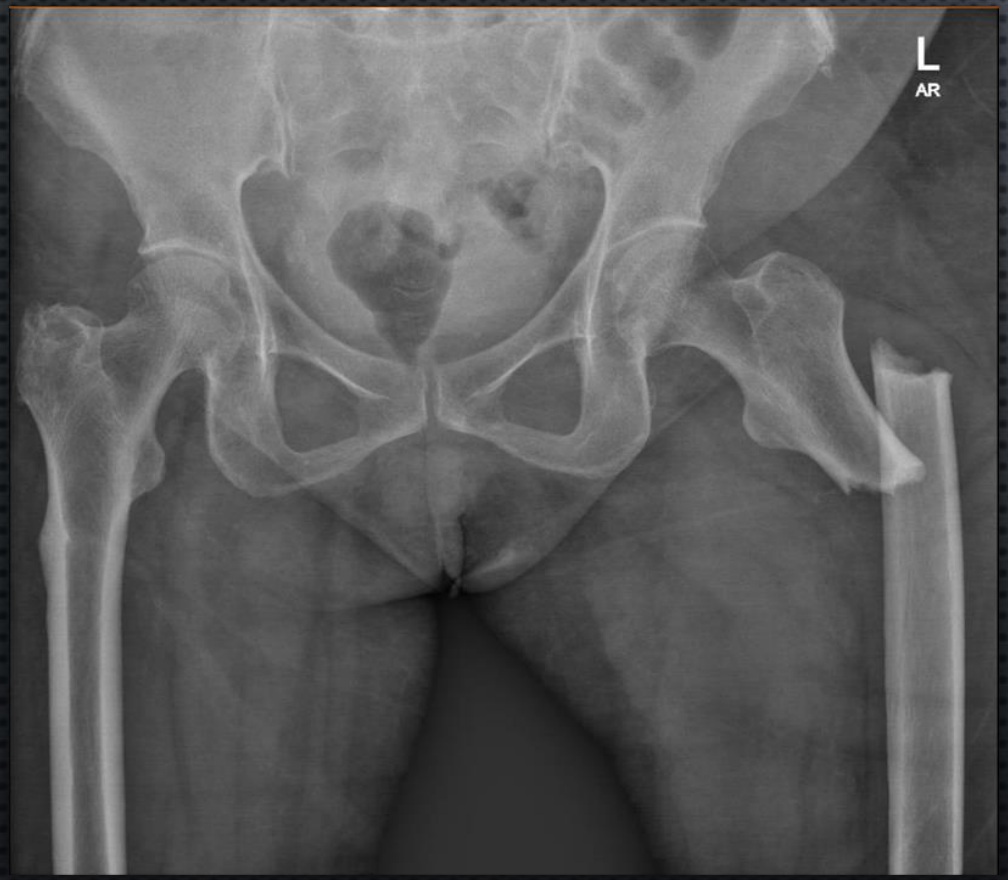
E Advise switching to Risedronate

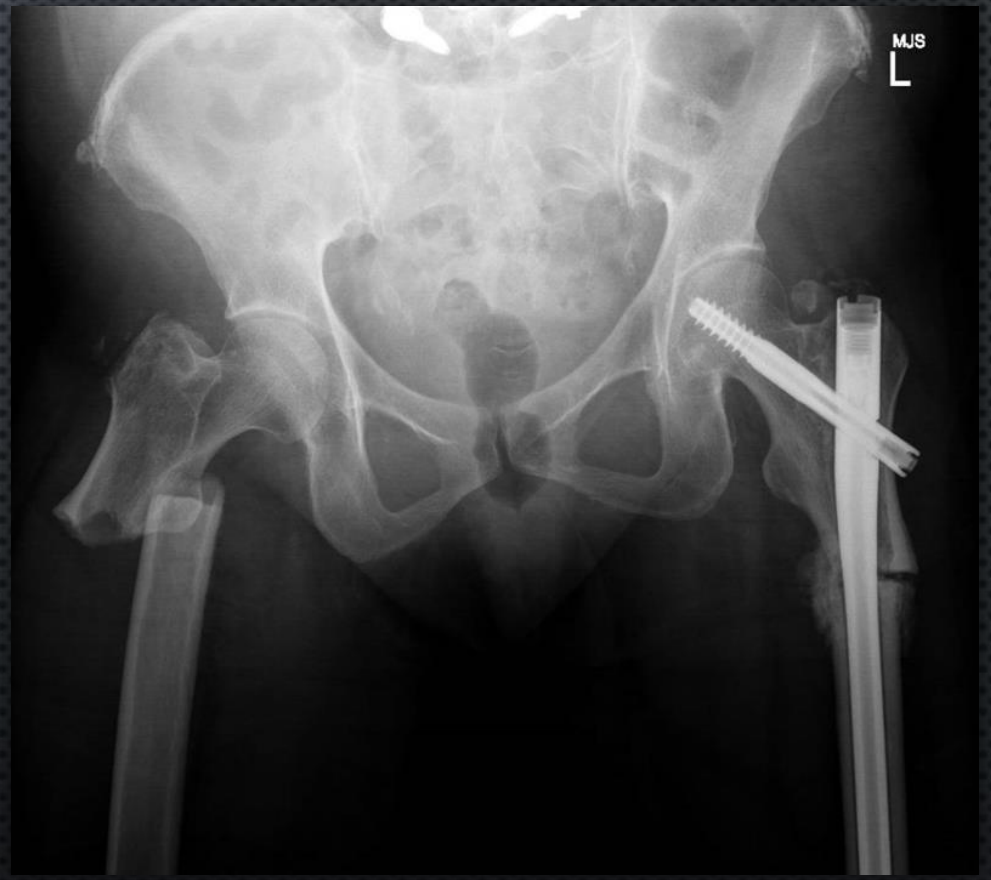
What are the risks of Atypical Femoral Fractures (AFF) and Osteonecrosis of the Jaw (ONJ) really?



Adler et al. J Bone Miner Res 2016;31:16-35.

What are the risks of Atypical Femoral Fractures (AFF) and Osteonecrosis of the Jaw (ONJ) really?





Usually prodromal pain

Patients advised to report any unexplained thigh, groin or hip pain while on BPs/Dmab -> XR

What are the risks of Atypical Femoral Fractures (AFF) and Osteonecrosis of the Jaw (ONJ) really?

MESSAGE

- AFF/ONJ risks are very small
- Delay starting treatment until dental work complete
- Risks generally outweighed by benefits of treatment
  (eg ~0.1% risk increase of ONJ and AFF, compared to 40% reduction in hip # on BP (8% -> 4.8%))

Interactive Case 4

The same 76 year old woman attends your clinic

She has now been on alendronate for 6 years but now needs a dental extraction urgently

She is very anxious about the 'high risk' of complications

She has no other risk factors for ONJ but her dentist has said that he will NOT perform the extraction unless the alendronate is stopped

Do you:

A Agree that high risk of ONJ and so should stop alendronate immediately

B Advise switching to densoumab injections

C Continue alendronate

D Do a hip Xray to check for incomplete atypical femoral fractures

E Advise switching to risedronate

What do I advise if the patient needs dental work and is on a bisphosphonate/denosumab?

NHS England

Dental Management of Patients Prescribed Bisphosphonates - Clinical Guidance

(Produced in conjunction with the Dental LPN for Shropshire and Staffordshire)

January 2015

Authored by – Dept. of Oral and Maxillofacial Surgery, University Hospitals of North Midlands NHS Trust (UHNM)

Contact - Tim Malins, Lead Clinician. Dept. of Oral and Maxillofacial Surgery, UHNM.

These guidelines are based on the best evidence that is currently available. New evidence and research will be constantly influencing these guidelines and consequently these should be treated as a fluid resource. As new research is carried out these guidelines are subject to change.

Steroids, smoking, alcohol, dental trauma, diabetes, infections, chemo/DXT, coagulopathy

What Are Bisphosphonates and How Do They Work?

Bisphosphonates are drugs that reduce bone resorption by hindering the formation, recruitment and function of osteoclasts. Bisphosphonates are used most commonly in the management of osteoporosis, but are also used in the management of many other non-malignant and malignant conditions. Bisphosphonates can have a significantly positive effect on the quality of life of patients by reducing or delaying onset of disease or treatment complications, such as bone fractures and bone pain. However, bisphosphonates accumulate at sites of high bone turnover, such as in the jaw. This may reduce bone turnover and bone blood supply and lead to death of the bone, termed osteonecrosis. The condition of particular concern for dentists is bisphosphonate–related osteonecrosis of the jaw.

What is Bisphosphonate-related Osteonecrosis of the Jaw (BRONJ)?

BRONJ is defined as exposed, necrotic bone in the maxilla or mandible that has persisted for more than eight weeks in patients taking bisphosphonates and where there has been no history of radiation therapy to the jaw. Symptoms include delayed healing following a dental extraction or other oral surgery, pain, soft tissue infection and swelling, numbness, paraesthesia or exposed bone.

It should be acknowledged that BRONJ is an extremely rare condition, and it is very important that patients are not discouraged from taking bisphosphonate drugs or from undergoing dental treatment.

Note: There is no supporting evidence that BONJ risk will be reduced if the patient temporarily, or even permanently, stops taking bisphosphonates prior to invasive dental procedures since the drugs may persist in the skeletal tissue for years. If a patient has taken bisphosphonates in the past but is no longer taking them for whatever reason (i.e. completed or discontinued the course, taking a drug holiday), allocate them to a risk group as if they are still taking them.

Reduce risk factors

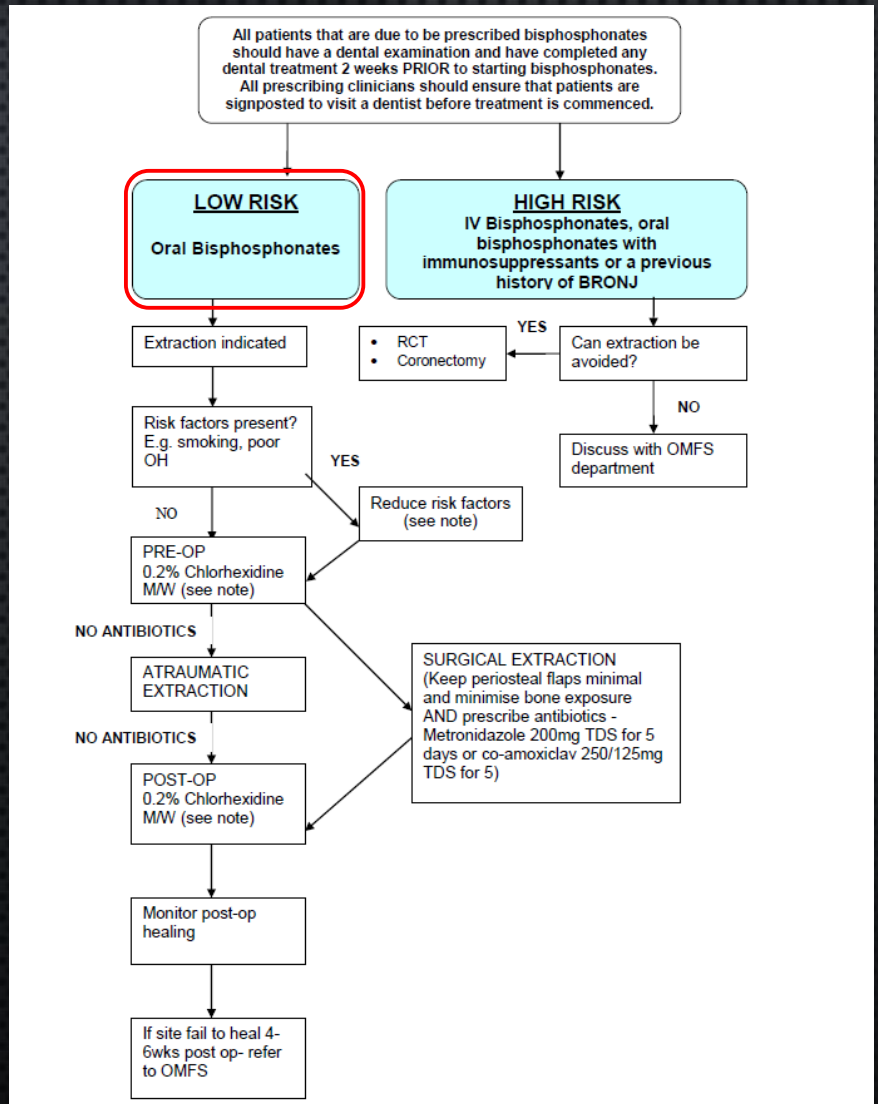
Whenever possible, patients should be encouraged and counselled to stop smoking. Oral hygiene and periodontal health should be improved prior to any surgical procedures. However, the unnecessary delay or avoidance of appropriate treatment cannot be supported and each case should be considered on its own merits.

Chlorhexidine mouthwash

All patients to rinse with Chlorhexidine mouthwash twice daily during the week before extractions are done. There is no evidence that pre- and post-operative antibiotics are effective in preventing BRONJ. Immediately before the extractions, the area should be irrigated/wiped with chlorhexidine. Use atraumatic technique, and avoid raising flaps. Primary soft tissue closure should be achieved wherever possible.
24 hours post-operatively patients should rinse with Chlorhexidine twice daily for 2 months, and should be reviewed regularly to monitor healing.

Children or infants on bisphosphonates

There is currently insufficient evidence to give any meaningful guidance on treating young children on bisphosphonates. In such cases it is advisable to seek specialist advice and refer to an OMFS dept. for assessment and treatment.



REFERENCES:
1. Dental extractions and bisphosphonates: the assessment, consent and management, a proposed algorithm. N. Malden et al. British Dental Journal. Vol 206 No.2, 2009
2. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate -Related Osteonecrosis of the Jaw- 2009 Update
3. Oral Health Management of Patients Prescribed Bisphosphonates- Summary Guidance. Scottish Dental Clinical Effectiveness Programme, April 2011
4. Bisphosphonates Fact File. British Dental Association, September 2008

Can I give Denosumab in the community and how?

Usually preferable for patient convenience

Generally we can give the first dose in clinic to save time (and review 12-18 monthly)

Then in Primary Care….

Continue every 6 months (no later than 7 months)

Check calcium, Vit D and renal function within 6 weeks prior to dose:

- Normal calcium
- Vit D >50 nmol/l
- eGFR >25 (if <25 will need bloods at day 7-10 to ensure no hypocalcaemia)
- Ensure adequate Calcium + Vit D intake (eg Accrete D3, 1 tablet BD)

Generally continue for at least 5y (many patients >10y)

Seek specialist advice before stopping (as gains lost in 12-18m and risk of multiple vert #)

What to do if the patient fractures on a bisphosphonate?

Don't Panic!

1. Check compliance
2. Consider secondary causes
3. THEN Consider if treatment failure

BPs reduce fracture risk by 40-45% but not completely

What constitutes treatment failure?

What to do if the patient fractures on a bisphosphonate?

TREATMENT FAILURE:

- ≥ 2 Fragility fractures on treatment

OR

- 1 Fragility fracture + Failure to suppress BTMs/Decreasing BMD

OR

- Failure to suppress BTMs + Decreasing BMD

NOTE
-# of hand, skull, feet, ankle are not considered fragility #
-Significant drop in BMD is 5% at spine and 4% at hip
-BTMs (Bone Turnover Markers NTx, CTx, P1NP) should drop >25% on treatment initiation (if no baseline then lower half acceptable)

Diez-Perez et al., Osteoporosis Int. 2012;23:2769-74

Who should I refer to the Endocrine Bone Clinic (HH/SMH)?

-Secondary osteoporosis (especially when young) where specialist opinion may help

-Multiple fragility fractures/T scores < -4

-Multiple bisphosphate intolerance / contraindications (hypocalcaemia, oesophageal disorders, delayed gastric emptying)

-Oral treatment failure as per previous slide (?IV Zol/SC Dmab)

-eGFR < 30 ml/min/1.73m^2 (Alendronate limit is 35, Risedronate limit is 30 (BNF)) ?denosumab

-Refer to orthopaedics if thigh/hip/groin pain on bisphosphonate/dmab

-Refer to dentist if dental pain/mobility/swelling

On an unrelated note: In general, avoid checking PTH unless patient has abnormal calcium level.

Measuring parathyroid hormone in primary care (NG132, May 2019)

1.1.5 Measure parathyroid hormone (PTH) for people whose albumin-adjusted serum calcium level is either:

- 2.6 mmol/litre or above on at least 2 separate occasions or
- 2.5 mmol/litre or above on at least 2 separate occasions and primary hyperparathyroidism is suspected.

1.1.6 When measuring PTH, use a random sample and do a concurrent measurement of the albumin-adjusted serum calcium level.

1.1.7 Do not routinely repeat PTH measurement in primary care.

1.1.8 Seek advice from a specialist with expertise in primary hyperparathyroidism if the person's PTH measurement is either:

- above the midpoint of the reference range and primary hyperparathyroidism is suspected or
- below the midpoint of the reference range with a concurrent albumin-adjusted serum calcium level of 2.6 mmol/litre or above.

1.1.9 Do not offer further investigations for primary hyperparathyroidism if:

- the person's PTH is within the reference range but below the midpoint of the reference range and
- their concurrent albumin-adjusted serum calcium level is below 2.6 mmol/litre.

1.1.10 Look for alternative diagnoses, including malignancy, if the person's PTH is below the lower limit of the reference range.

THANKYOU FOR LISTENING

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