Osteoporosis and Vitamin D

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Disclosures

Unrestricted educational grants

- Lilly
- Servier
- Amgen

Unrestricted research grant

- P&G (now WC)

Consultancy work

- Servier

- What is osteoporosis
- What is the role of vitamin D
- Current concepts of fracture risk reduction
- Example of patient pathway
- Drug treatment regimes
  - To reduce fracture risk
  - To replace/supplement vitamin D
- Case studies

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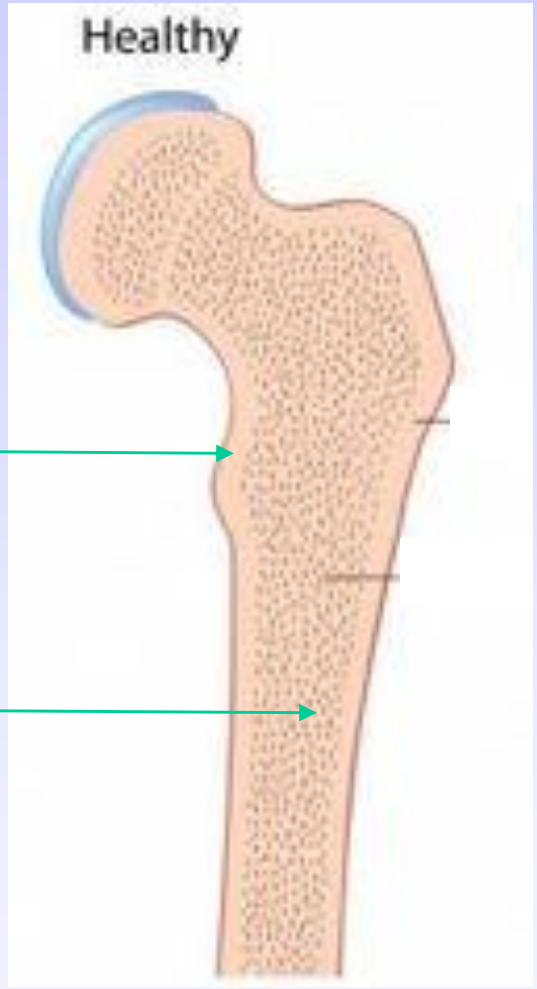
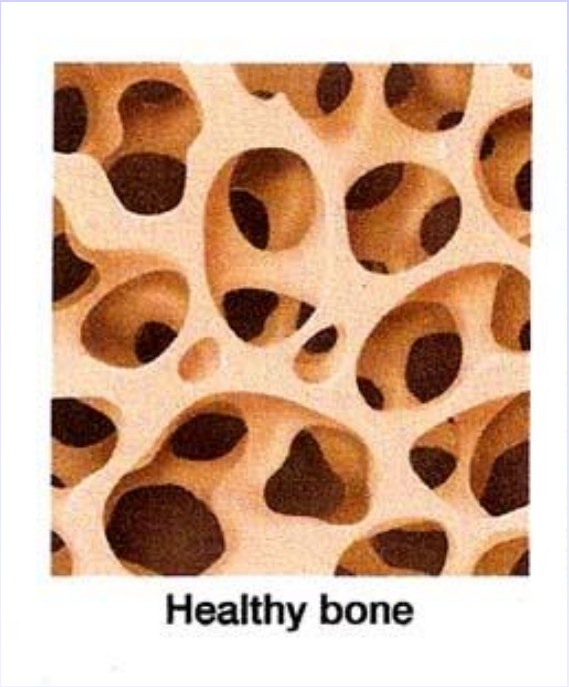
Normal bone structure

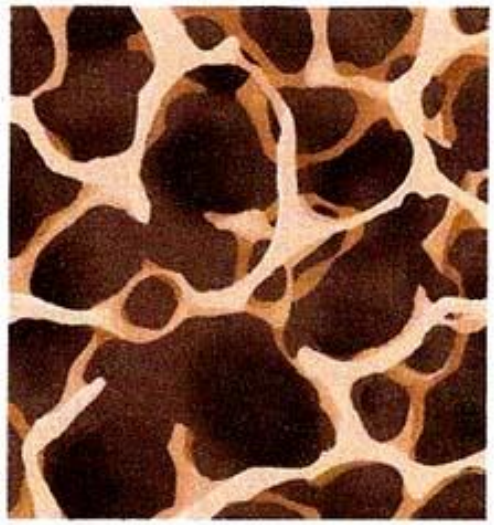


Cortical bone

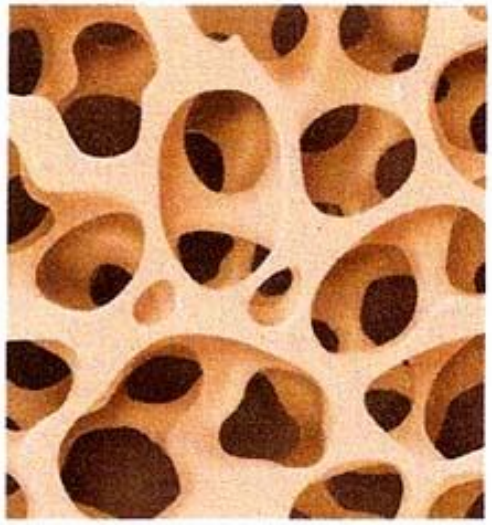
Trabecular bone



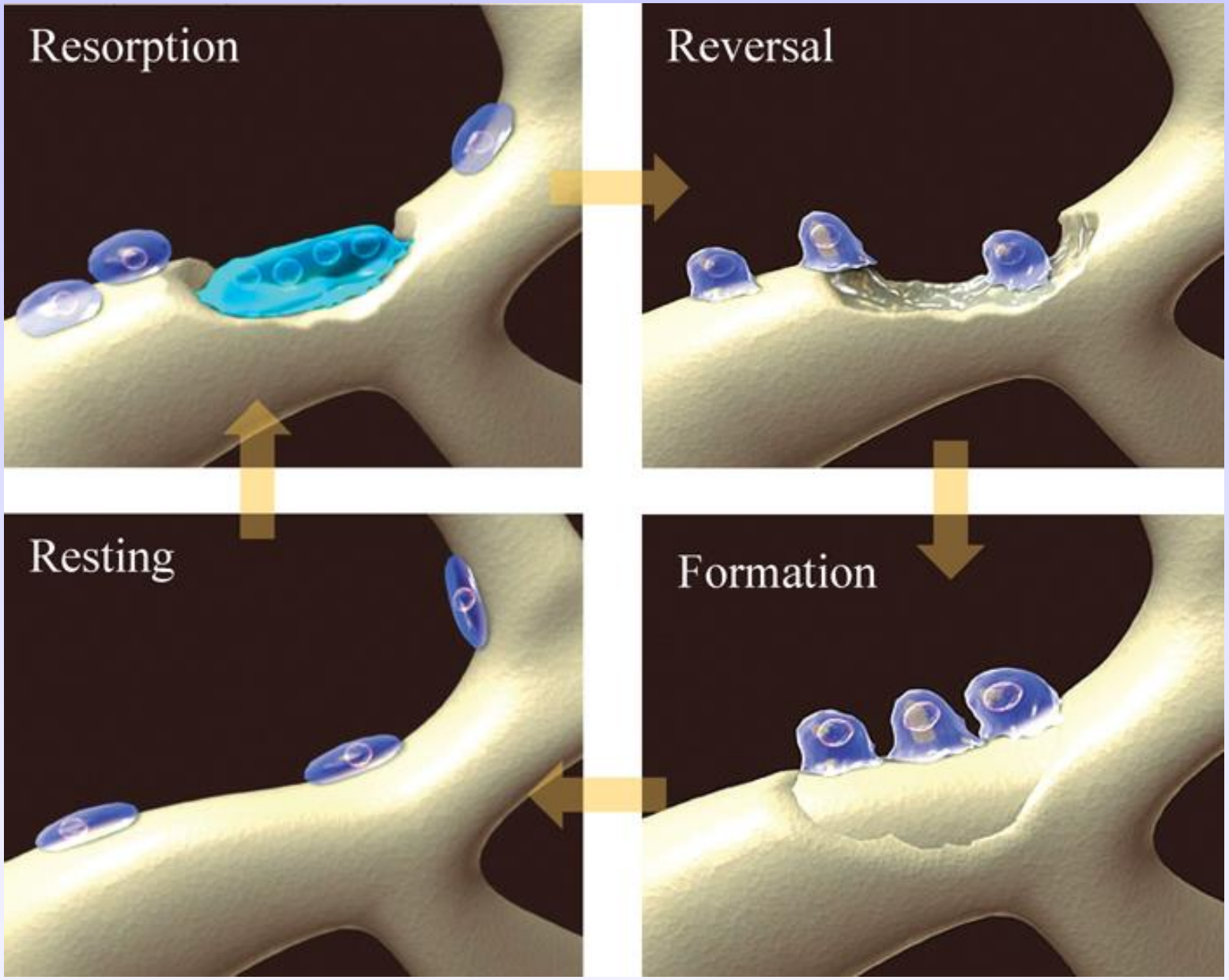
Osteoporosis



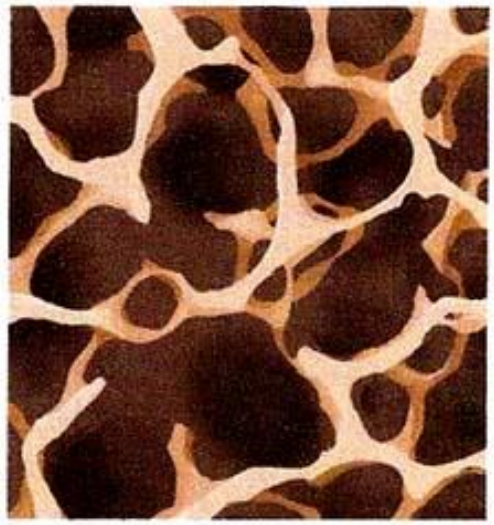
Osteoporotic bone



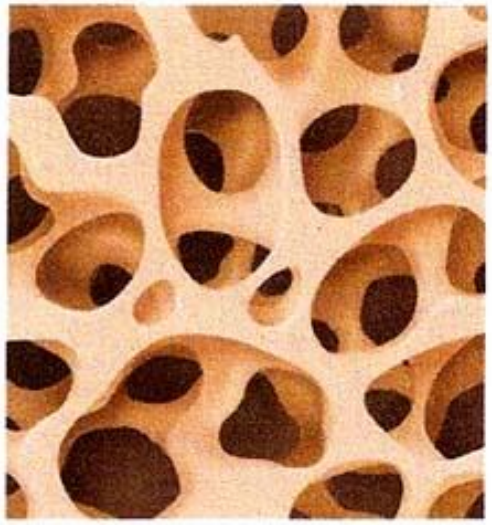
Healthy bone


Resorption
Reversal
Resting
Formation

Osteoporosis



Osteoporotic bone



Healthy bone

Consequence of osteoporosis

- Increased risk of fracture (broken, chipped or cracked bone)
- Increases ‘low trauma’ fracture
- Typical osteoporotic fractures occur at the
  - Hip
  - Spine
  - Humerus
  - Forearm (Colles)
- No other symptoms (no pain!)

Risk factors for development of osteoporosis

- Low peak bone mass
- Accelerated bone loss

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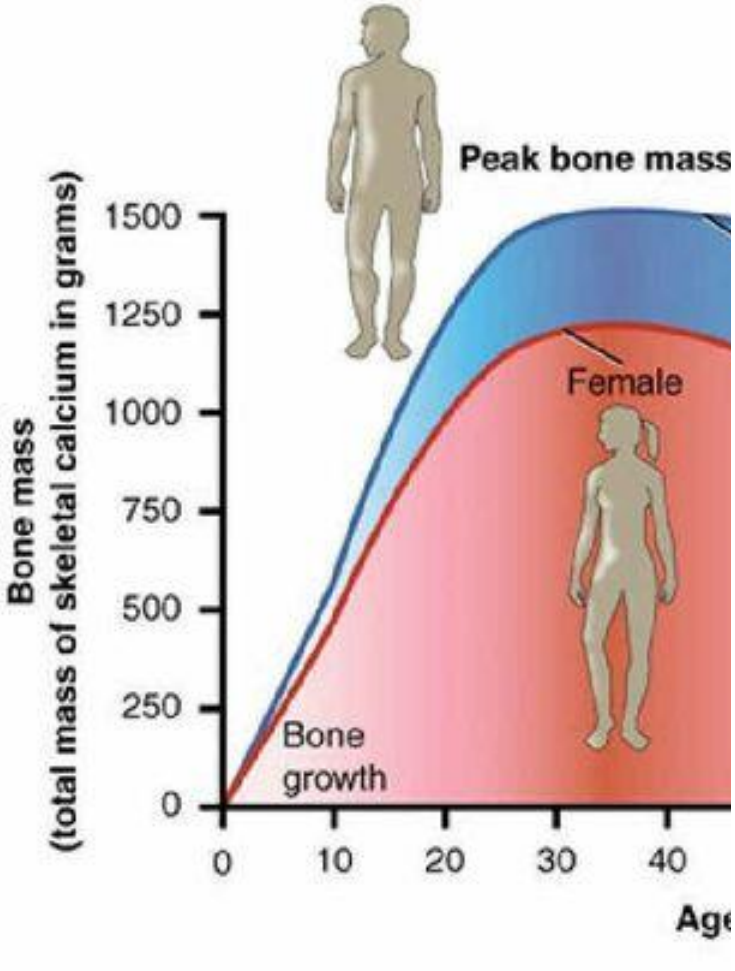
Low peak bone mass



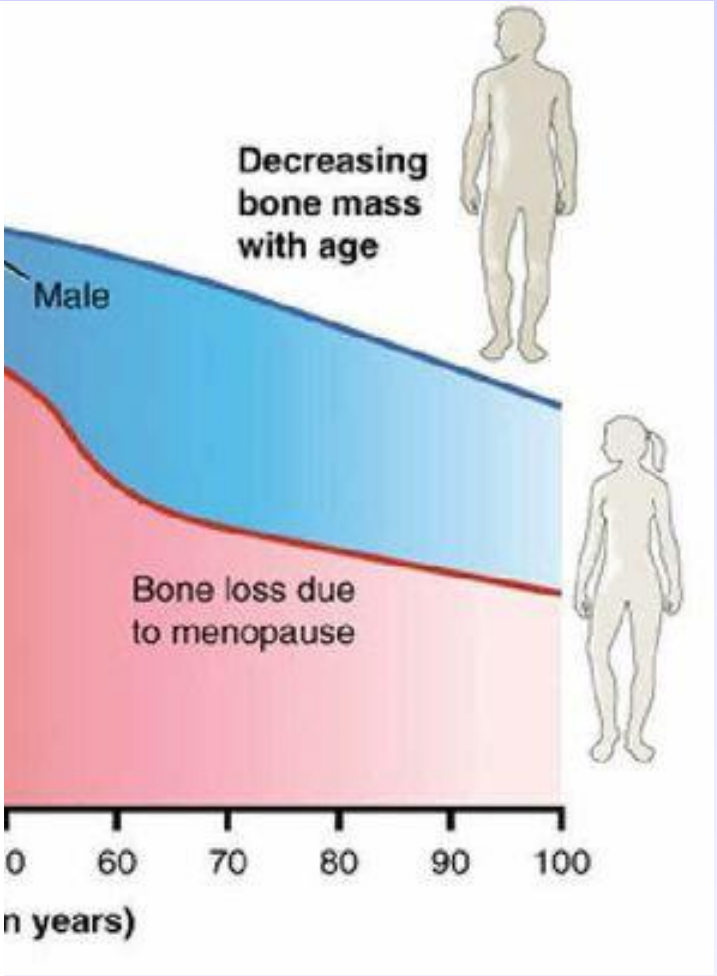
Low peak bone mass

- Malnutrition or severe during infancy, childhood or adolescence
- Anorexia nervosa
- Genetics
- Medications e.g. steroids

Risk factors for development of osteoporosis

- Low peak bone mass
- Accelerated bone loss

Low peak bone mass



Accelerated bone loss

- Medications e.g. steroids, aromatase inhibitors, some anti-convulsants
- Illnesses e.g. uncontrolled hyperthyroidism, cancer, inflammatory diseases such as rheumatoid arthritis
- Poor dietary intake of calcium/poor vitamin D e.g. poor diet, Coeliac's disease
- Early menopause

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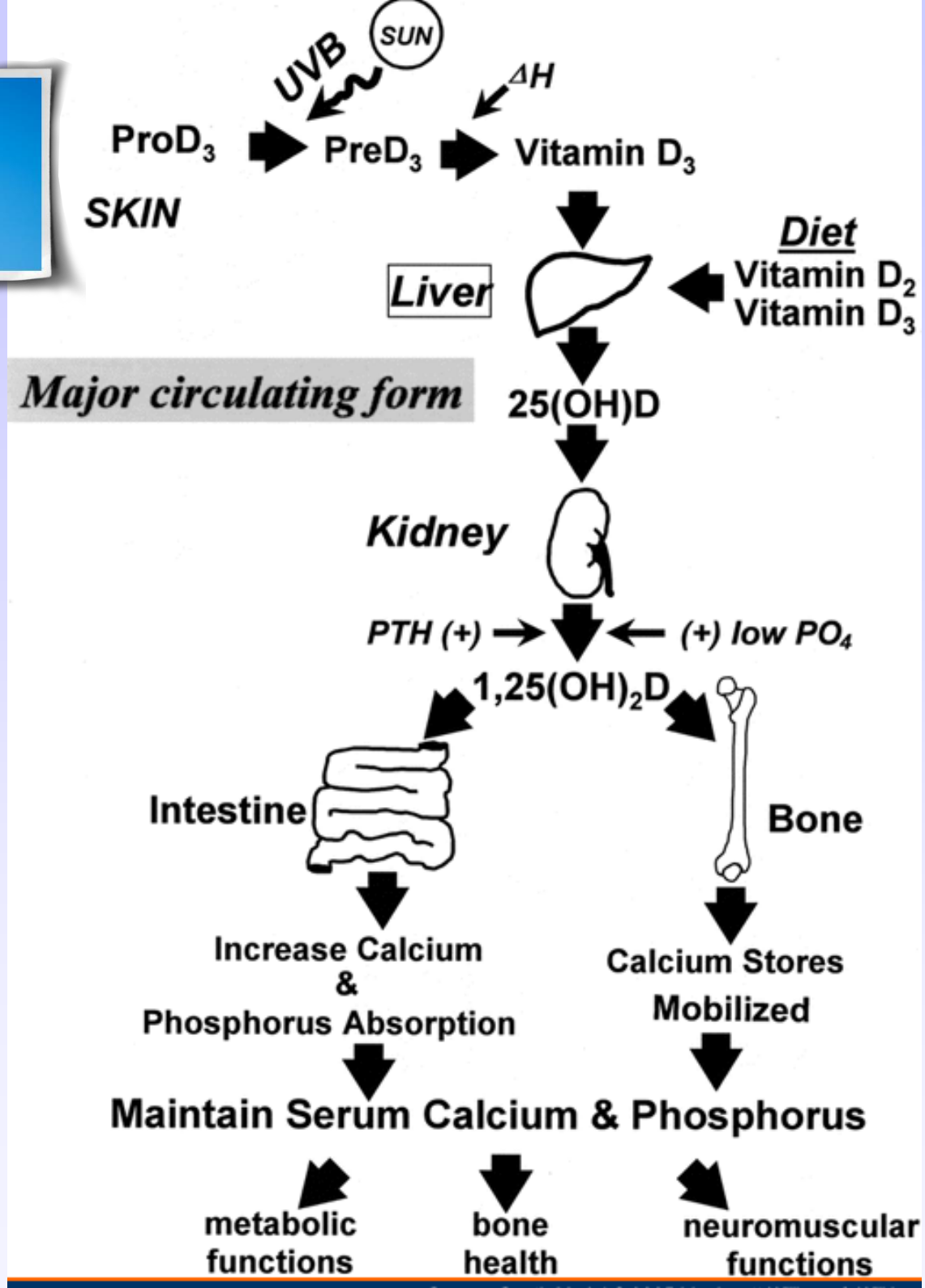
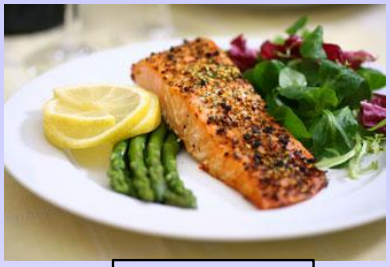
90%


UVB
SUN
ΔH
ProD3
PreD3
Vitamin D3
SKIN
Diet
Vitamin D2
Vitamin D3
Liver
Major circulating form
25(OH)D
Kidney
PTH (+)
(+) low PO4
1,25(OH)2D
Intestine
Bone
Increase Calcium
&
Phosphorus Absorption
Calcium Stores
Mobilized
Maintain Serum Calcium & Phosphorus
metabolic functions
bone health
neuromuscular functions



10%

Risk factors for developing low vitamin D

- Low sunlight exposure
  - Housebound
  - Dark skin
  - Use of suncream all the time
- Some medications
  - anticonvulsants
- Some long term conditions
  - Malabsorption states (Crohn's disease)
  - Liver and kidney diseases
- Some inherited conditions
  - Rare errors of metabolism

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Current concepts

1. Fracture risk reduction

2. Medication is not for life

Current concepts

1. Fracture risk reduction

2. Medication is not for life

We no longer treat osteoporosis

instead

we reduce someone's risk of fracture

We no longer treat osteoporosis

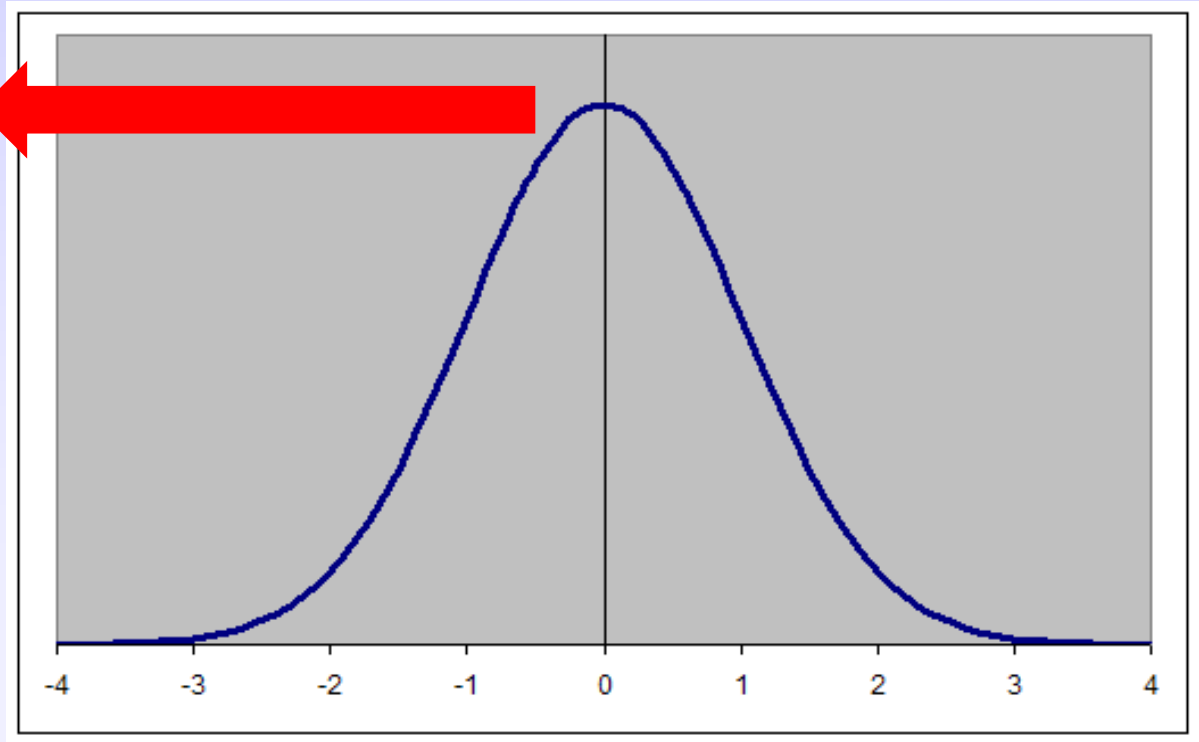
instead

we reduce someone's risk of fracture

Bone density for fracture risk identification

Increasing fracture risk

Number of people in a population



Bone density

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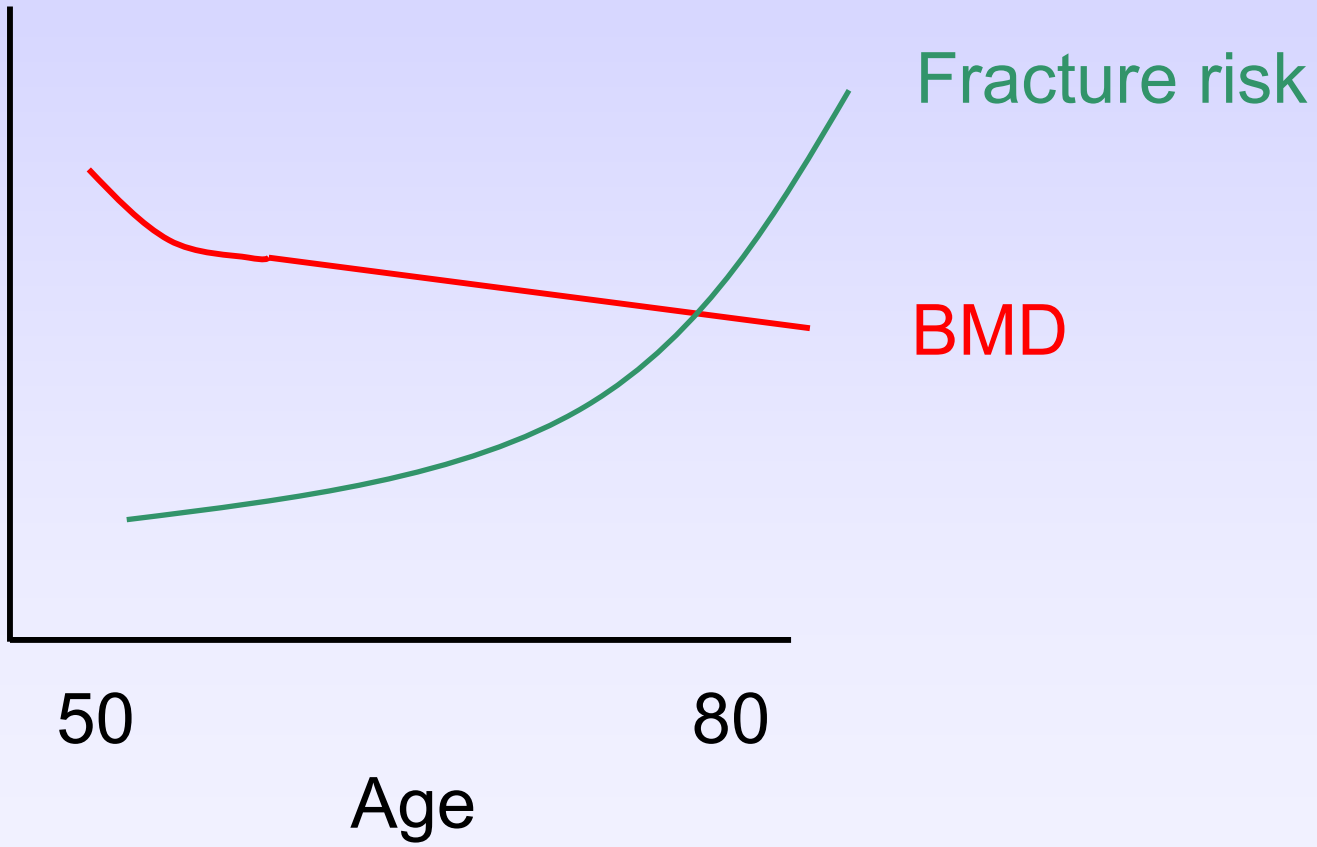
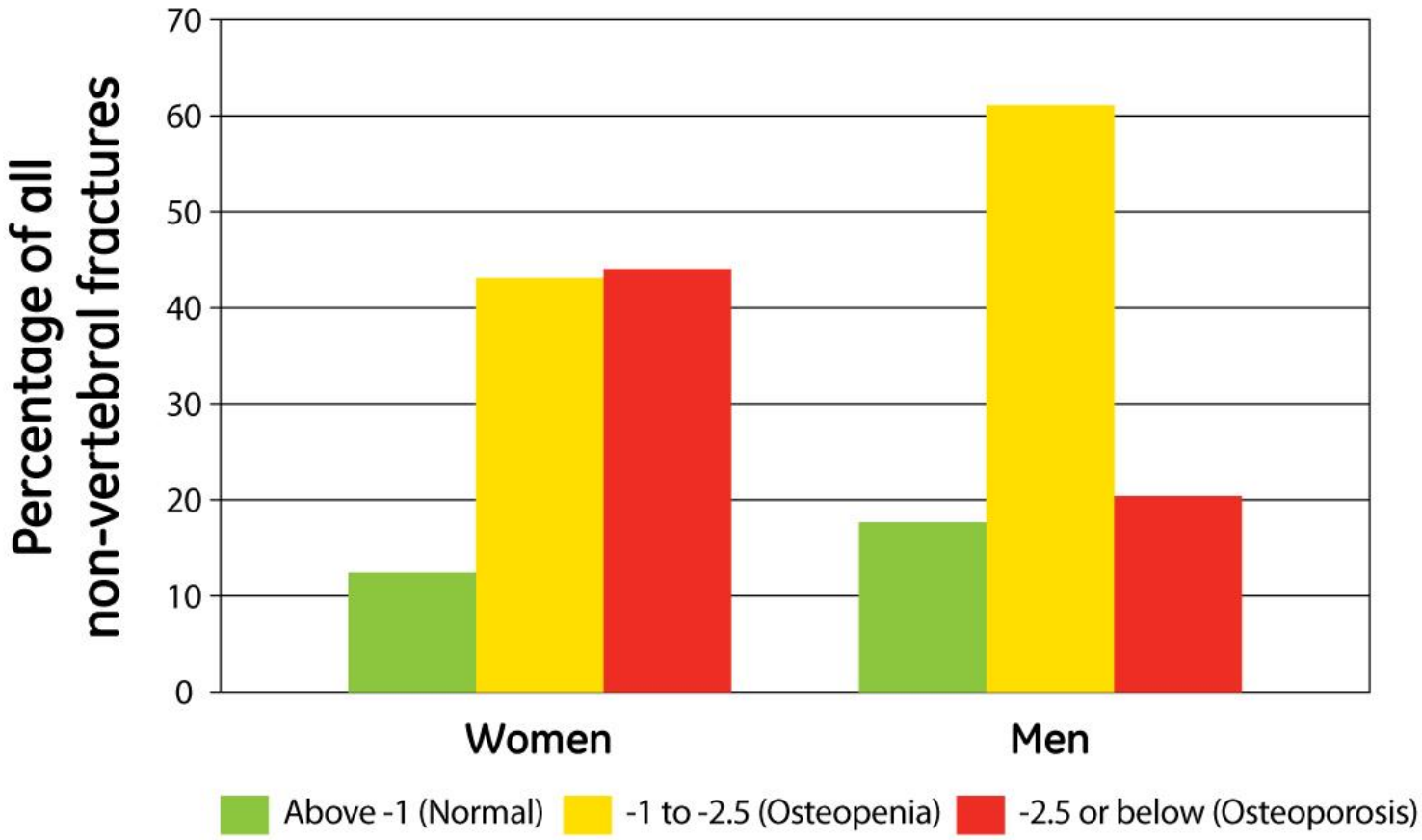
BMD does not fully explain the effect of age on fracture risk



Prevalence of fractures by osteoporosis risk categories



- there are multiple risk factors that can contribute to an individuals overall risk of osteoporosis and osteoporotic fracture **- only one of which is DXA**

Problems with the use of BMD tests alone:

• DXA is not widely available in many parts of the world

• BMD alone is not optimal for detection of individuals at high risk of fracture

• majority of fractures occur in people without osteoporotic BMD

Fracture risk identification

- We assess peoples future fracture risk, and treat if they are above the treatment threshold
- FRAX
- NICE CG146

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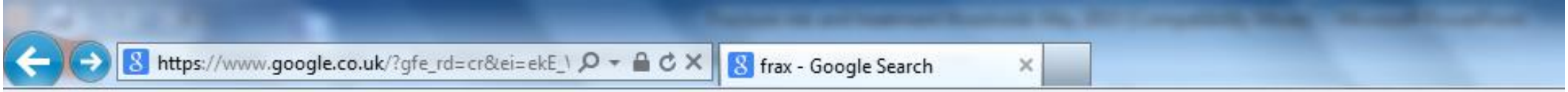

Google frax

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About 530,000 results (0.29 seconds)

Frax - University of Sheffield

www.shef.ac.uk/**FRAX**/

The **FRAX**® tool has been developed by WHO to evaluate fracture risk of patients. It is based on individual patient models that integrate the risks associated with ...

Calculation Tool

FRAX ® WHO Fracture Risk Assessment Tool. Home ...

Australia

Country: Australia. Name/ID: About the risk factors. Questionnaire: 1.

US

For USA use only. Consider FDA-approved medical therapies in ...

Brazil

Country: Brazil. Name/ID: About the risk factors. Questionnaire: 1.

Paper Charts

Charts of the FRAX® tool are available to download for office ...

English

US - Calculation Tool - FRAX tool - ...

More results from shef.ac.uk »

FRAX Information and Resources | International ...

www.iofbonehealth.org/osteoporosis.../**frax**-information-and-resources

FRAX WHO Fracture Risk Assessment website screenshot **FRAX** is a scientifically validated risk assessment tool, endorsed by the World Health Organization ...

FRAX - Wikipedia, the free encyclopedia

Welcome to FRAX®

The FRAX® tool has been developed by WHO to evaluate fracture risk of patients. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck.

Dr. John A Kanis
Professor Emeritus,
University of
Sheffield

The FRAX® models have been developed from studying population -based cohorts from Europe, North America, Asia and Australia. In their most sophisticated form, the FRAX® tool is computer-driven and is available on this site. Several simplified paper versions, based on the number of risk factors are also available, and can be downloaded for office use.

The FRAX® algorithms give the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).

FRAX De

Click here to
applications

Web Vers

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Links

www.iofbone

www.nof.org

www.jpof.or.j

www.esceo.c

FRAX avai
iPhone Ap

View in iTune

www.shef.ac.uk/FRAX/tool.aspx

shef.ac.uk

FRAX® WHO Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | English

Calculation Tool

Please answer the questions b

Country: UK

- Asia
- Europe
- Middle East & Africa
- North America
- Latin America
- Oceania

Armenia	Austria	Belgium
Croatia	Czech Republic	Denmark
Estonia	Finland	France
Germany	Greece	Hungary
Iceland	Ireland	Israel
Italy	Lithuania	Malta
Netherlands	Norway	Poland
Portugal	Romania	Russia
Slovakia	Spain	Sweden
Switzerland	Turkey	UK

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: Date of Birth: Y: M: D:
2. Sex ○ Male ○ Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture ◉ No ○ Yes
6. Parent Fractured Hip ◉ No ○ Yes
7. Current Smoking ◉ No ○ Yes
8. Glucocorticoids ◉ No ○ Yes
9. Rheumatoid arthritis ◉ No ○ Yes
10. Sec
11. Alc
12. Fem

Selec

Clear Calculate

Height Conversio

Inches → cm

Conve

02837621
Individuals with fracture assessed since 1st June

/FRAX/tool.aspx#

FRAX® WHO Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | English

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: UK Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: Date of Birth: Y: M: D:
2. Sex — Male / Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture — No / Yes
6. Parent Fractured Hip — No / Yes
7. Current Smoking — No / Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Secondary osteoporosis — No / Yes
11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm^2)

Select BMD

Clear Calculate

Print tool and information

Weight Conversion

Pounds → kg

Convert

Height Conversion

Inches → cm

Convert

02772627

Individuals with fracture risk assessed since 1st June 2011

www.nos.org.uk

National Osteoporosis

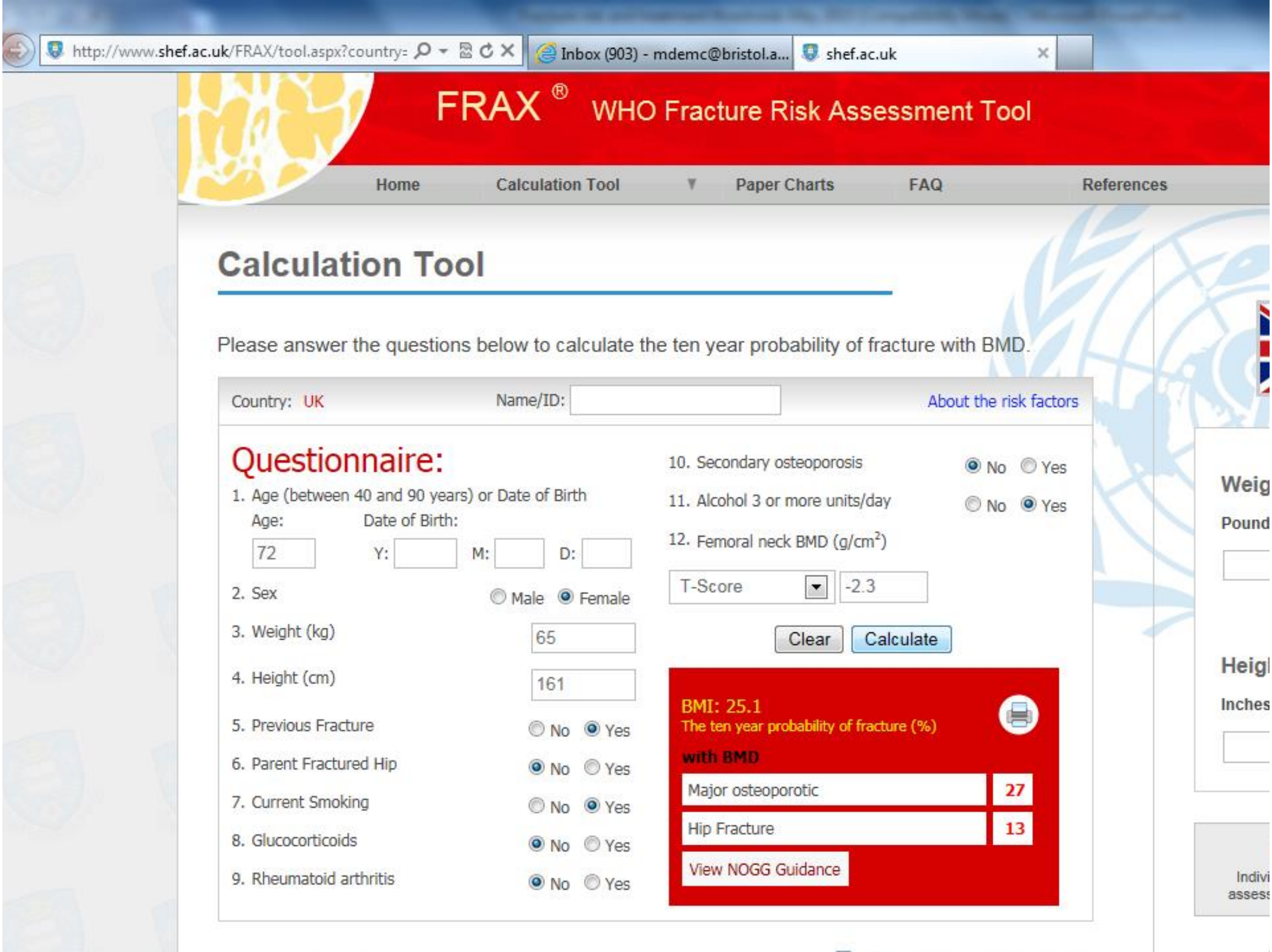
How was FRAX developed?
Choice of risk factors

Choice was governed by

- availability of data
- ease with which the risk factors could be used in Primary Care
- potential risk factors were examined by a series of meta-analyses

FRAX results

- Probability (%) of fracture over the next 10 years
  - Hip
  - Major osteoporotic fracture (hip, forearm, humerus, clinical vertebral)


http://www.shef.ac.uk/FRAX/tool.aspx?country=
Inbox (903) - mdemc@bristol.a...
shef.ac.uk
FRAX ® WHO Fracture Risk Assessment Tool
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Paper Charts
FAQ
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Calculation Tool
Please answer the questions below to calculate the ten year probability of fracture with BMD.
Country: UK
Name/ID:
About the risk factors
Questionnaire:
1. Age (between 40 and 90 years) or Date of Birth
Age:
Date of Birth:
72
Y:
M:
D:
2. Sex
Male
Female
3. Weight (kg)
65
4. Height (cm)
161
5. Previous Fracture
No
Yes
6. Parent Fractured Hip
No
Yes
7. Current Smoking
No
Yes
8. Glucocorticoids
No
Yes
9. Rheumatoid arthritis
No
Yes
10. Secondary osteoporosis
No
Yes
11. Alcohol 3 or more units/day
No
Yes
12. Femoral neck BMD (g/cm²)
T-Score
-2.3
Clear
Calculate
BMI: 25.1
The ten year probability of fracture (%)
with BMD
Major osteoporotic
27
Hip Fracture
13
View NOGG Guidance

Benefits and disadvantages of FRAX

Benefits

- Allows incorporation of clinical risk factors plus BMD in an easy on-line tool
- Valid in many countries
- Produces % that are understandable

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Disadvantages

- Most data is yes/no
- Doesn’t include falls
- Underestimates fracture risk with vertebral fractures

Fracture risk identification

- We assess peoples future fracture risk, and treat if they are above the treatment threshold
- FRAX
- NICE CG146

Osteoporosis: assessing the risk of fragility fracture

Issued: August 2012

NICE clinical guideline 146

guidance.nice.org.uk/cg146

University of BRISTOL

North Bristol NHS Trust

NICE CG146

- Targeting risk assessment
- Methods of risk assessment

NICE CG146: Targeting fracture risk assessment

- All women >65 and men >75
- Women 50-65 and men 50-75 in the presence of additional risk factors
- Do not routinely assess fracture risk in people <50

NICE CG146: Methods of fracture risk assessment

1. Use either FRAX or Qfracture without DXA

2. Then, consider BMD measurement with DXA in people whose fracture risk is in the region of an intervention threshold, and recalculate fracture risk

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Treatment thresholds

- Are no nationally agreed thresholds for intervention in the UK

- There are a range of treatment thresholds to chose from:
  - Bone density T score <-2.5
  - NOGG guidance
  - Fixed percentage cut-off (20% and/or 5%)

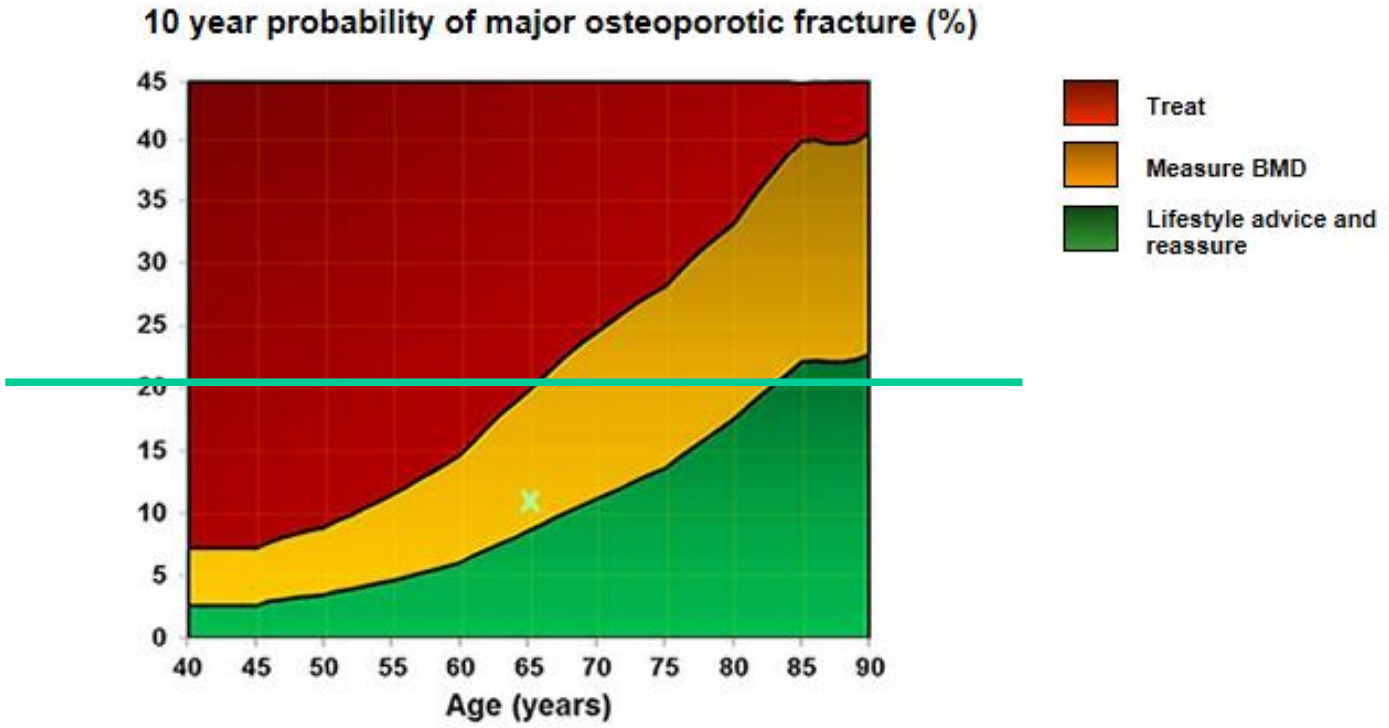
NATIONAL OSTEOPOROSIS GUIDELINE GROUP

Update

Graphs

Back to FRAX Home Back to NOGG Home Manual Data Entry FAQ Download Documents

Assessment threshold - Major fracture



Interpretation

Fracture risk reduction

- Goal is intervention to reduce fracture risk
  - Medications work by reducing risk by 20-70%
  - Don’t forget reducing falls risk through reducing some medications, assessing balance, sorting eyesight, removing bad footwear, small rugs etc

Current concepts

1. Fracture risk reduction

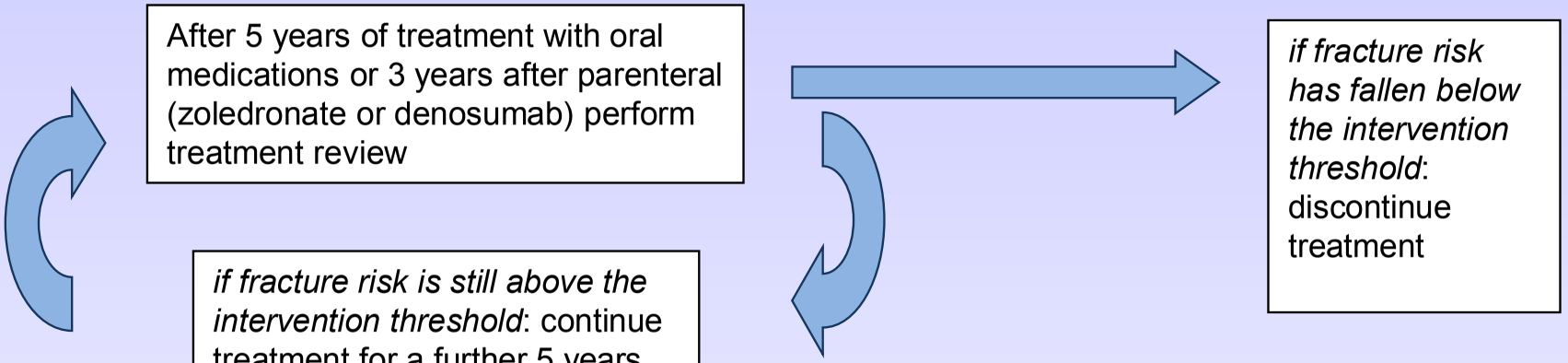
2. Medication is not for life

Length of time on treatment

- We are currently recommending oral medications for 5 years, and then reassessing need for ongoing treatment

- If fracture risk is still high (previous hip fracture, previous vertebral fracture, ongoing steroids) then continue for a further 5 years before reassessing

BNSSG guidelines



Medication	Recommended duration of drug holiday
alendronate	2-3 years
risedronate	1-2 years
ibandronate	1-2 years
zoledronic acid	>3 years
denosumab	6-12 months

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Alice, 76 years old

- Tripped at home on Wednesday afternoon after coming back in from the shops
- Just a stumble

- Put out her arm to save herself
- Broke her right wrist (Colles fracture)

- Neighbour drove her to A&E at Southmead Hospital
- Had an X-ray
- Put in a cast
- Given an appointment for Fracture Clinic the next day

Fracture clinic, Thursday morning

- Seen by the orthopaedic registrar
- X-ray reviewed, reassured, rebooked for 6 weeks

- Whilst in waiting room, approached by the Fracture Liaison Nurse
- Discussed osteoporosis
- Told she will be sent for a DXA scan in 12 weeks time
- May need some treatment to reduce her risk of breaking more bones

DXA appointment

- Given an appointment at Southmead Hospital
- Told to attend, not wearing much metal (no underwired bra, no heavy necklaces, belt removed)
- Needed to complete a questionnaire beforehand

Result of questionnaire

- Height: 154.2cm
- Weight: 70kg

- Never smoked
- Likes her brandy – has two glasses per week
- No previous fracture
- Mum broke her hip in her 70s
- No steroids
- No rheumatoid arthritis
- No other secondary causes

Result of FRAX

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: UK Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 76 Date of Birth: Y: M: D:
2. Sex — Male / Female
3. Weight (kg): 70
4. Height (cm): 154.2
5. Previous Fracture — No / Yes
6. Parent Fractured Hip — No / Yes
7. Current Smoking — No / Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Secondary osteoporosis — No / Yes
11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm^2): T-Score -3.3

Clear | Calculate

BMI: 29.4

The ten year probability of fracture (%) with BMD

Major osteoporotic	56
Hip Fracture	45

View NOGG Guidance

If you have a TBS value, click here: Adjust with TBS

Print tool and information

Weight Conversi

Pounds → kg Conve

Height Conversi

Inches → cm Conve

03991912

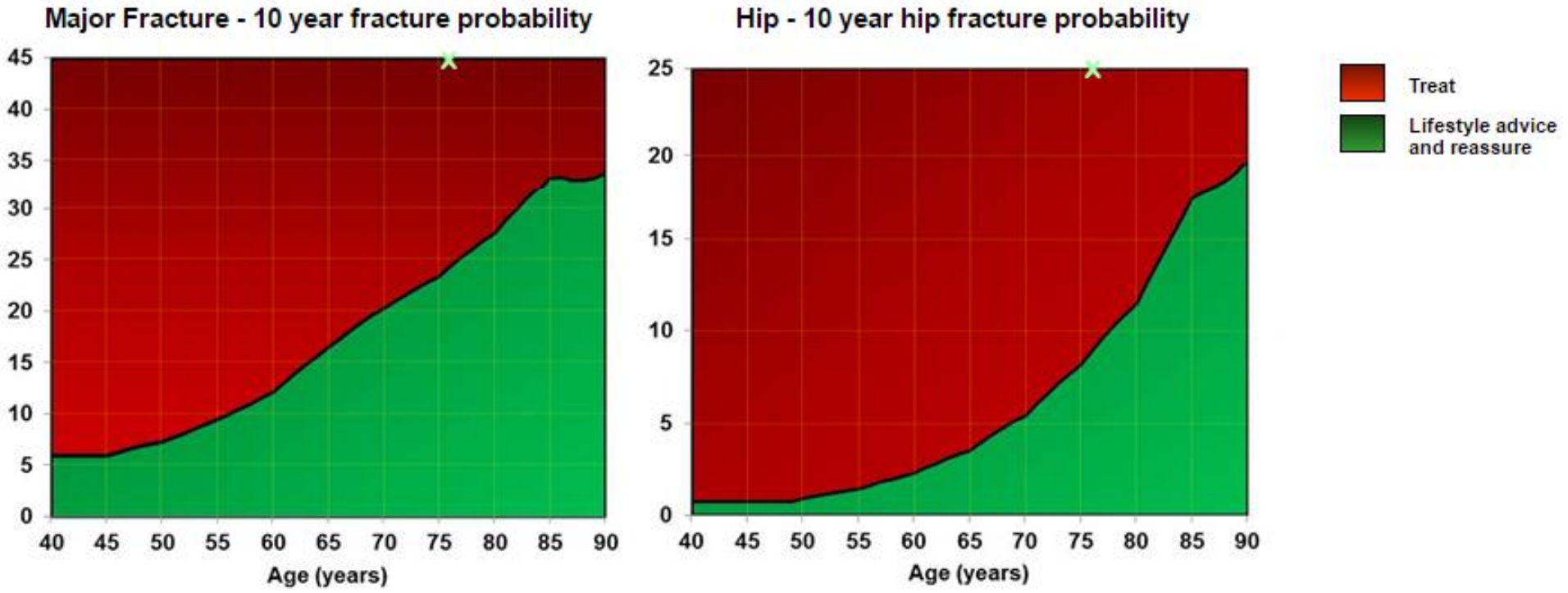
Individuals with fracture assessed since 1st June

www.nos.org.uk

National Osteoporo Society

Risk factors

Intervention Threshold



Treatment is recommended in the majority of elderly women with a prior fracture, even if the probability lies below the intervention threshold after BMD measurement.

Interpretation

The intervention thresholds depicted by the lines between the green and red areas above are the 10 year probabilities of a major osteoporotic fracture (left graph) or a hip fracture (right graph) in women with a prior fracture.

- In individuals with probabilities of a major osteoporotic fracture **and/or** hip fracture AT or ABOVE the intervention threshold, treatment should be strongly considered.
- Where both probabilities fall below the treatment threshold, a further assessment is recommended in 5 years or less depending on the clinical context.

NB - These thresholds are for guidance only and the final decision to initiate therapeutic intervention lies with the individual clinician

Report arrives at GP surgery

- Recommendations: high risk of future fracture. Recommend treatment with bisphosphonate plus ensure adequate calcium and vitamin D intake

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Fracture risk reduction

- NICE guidance
- The reality
  - First line treatment
  - Second line agents

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Fracture risk reduction according to NICE

- TA 160 = primary prevention
- TA 161 = secondary prevention
- TA 204 = denosumab
- TA 279 = surgical interventions for vertebral fractures

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- TA 160 = primary prevention
- TA 161 = secondary prevention
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- Only covers postmenopausal women
- Does not cover intravenous zoledronate
- Contradict themselves, very complicated

NICE 161 (secondary fracture prevention) – important for Alice

- first line treatment is generic alendronate
- if tolerability issues, unable to comply with instructions for use or contra-indication, and low BMD can switch to risedronate or etidronate
- if also cannot tolerate either risedronate or etidronate and very low BMD can switch to strontium ranelate or raloxifene

TA 161 continued

- if cannot tolerate either alendronate and risedronate or etidronate can switch to denosumab under NICE TAG 204 (no BMD requirements but must be at increased risk of fracture)

- if cannot tolerate either alendronate and risedronate or etidronate OR have a contra-indication or intolerant of Strontium ranelate OR who have had an unsatisfactory respense to alendronate, risedronate or etidronate (another fragility fracture despite adhering fully to treatment for 1 year AND evidence of a decline in BMD below pre-treatment level)

TA 161 continued

AND

- aged 65+ with a T score of <-4 or <-3.5 plus more than 2 fractures; aged 55-64 with a T score of <-4 and more than 2 fractures

  can have teriparatide

Fracture risk reduction

- NICE guidance
- The reality
  - First line treatment
  - Second line agents

First line agents

- Oral alendronate – weekly preparation with calcium/vitamin D supplements
- If intolerant (or treatment failure) then have a low threshold for switching to second line agents

Fracture risk reduction

- NICE guidance
- The reality
  - First line treatment
  - Second line agents

Second line agents

- IV Zoledronate
  - Advantages: cheap, once per year
  - Disadvantages: often can only be given in secondary care

- S/C denosumab
  - Advantages: given in primary care, twice a year
  - Disadvantages: very rapid off-set – need a plan of what to give afterwards

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Vitamin D

Depends on the level

- 25-OH vitamin D >50nmol/L = sufficient
- 25-OH vitamin D 30-50 = deficient and needs supplementation (may need replacement)
- 25-OH vitamin D <30 = severely deficient and needs replacement then supplementation

Supplementation

- = maintenance treatment with 800IU vitamin D3 +/- calcium daily for the foreseeable future

Replacement

- = 100,000 to 300,000IU vitamin D3 over some weeks

Maintenance treatment with vitamin D3

First line

- Adcal D3 Chewable Tablets = calcium carbonate 1.5g plus colecalciferol 400IU

Alternatives

- Adcal D3 Dissolve or Caplets

Important points

- Cannot use Chewable Tablets or Dissolve if peanut/soya allergy
- There are alternative agents for vegans

Replacement of vitamin D3

- Best to use oral route if possible (IM is possible, but not brilliantly absorbed)

<u>Typical regime to give 300,000IU</u>

= 2 x 20,000IU weekly for 7 weeks

- Should recheck calcium levels one month after replacing vitamin D3 like this

<u>Typical regime to give 100,000IU</u>

- If deficient, and needs parenteral treatment with denosumab or zoledronic acid

= 1 x 20,000IU per week for 5 weeks

- What is osteoporosis
- What is the role of vitamin D
- Current concepts of fracture risk reduction
- Example of patient pathway
- Drug treatment regimes
  - To reduce fracture risk
  - To replace/supplement vitamin D
- Case studies

Small Group Work

Case 1

- Mrs Sheila Brown, 72 year old retired housewife, with a recent low trauma fracture of her humerus, also has rheumatoid arthritis, and has had high dose corticosteroids on and off for many years.
- She has additional problems with quite bad indigestion, and she takes daily PPI and additional gaviscon as needed.

- She comes in with a new prescription for generic alendronate.

Case 1

1. How would you advise her to take the alendronic acid?
2. What are the issues around starting her on generic alendronate?
3. Are there alternatives that could be considered?
4. How long should she stay on treatment?
5. Where can she get more information on osteoporosis?
6. What lifestyle advice would you give her?

Bisphosphonates and indigestion

- Upper GI symptoms was an exclusion criteria in most of the phase III clinical trials of BPs

- In an observational cohort of 12,000 UK patients, the most common reasons for stopping oral nitrogen-containing BPs were dyspepsia, oesophagitis, oesophageal reflux, duodenitis, gastritis, heartburn or nausea[1]

[1] Biswas PN et al (2003) Osteop Int 14:507-514

- Nitrogen-containing BPs
  - Pamidronate (APD, Aredia)
  - Neridronate (Nerixia)
  - Olpadronate
  - Alendronate (Fosamax)
  - Ibandronate (Boniva)
  - Risedronate (Actonel)
  - Zoledronate (Zometa, Aclasta)

- Non-nitrogen-containing BPs
  - Etidronate (Didronel)
  - Clodronate (Bonefos, Loron)
  - Tiludronate (Skelid)

Alendronate vs Risedronate

- Is a long standing discussion regarding the GI tolerability of risedronate vs alendronate
- Endoscopic studies of patients randomised to either daily risedronate or daily alendronate showed a lower degree of upper GI erosions with daily risedronate[1]
- Large randomised 12-month head-to-head comparison of weekly alendronate vs weekly risedronate in 1053 patients showed no difference in the frequency of upper GI symptoms or outcomes[2]
- The US prescription study showed no difference in GI outcomes between oral risedronate or alendronate[3], but the likelihood of switching therapy was lower with risedronate

[1] Thomson AB et al (2002) J Rheum 29:1965-1974
[2] Rosen CJ et al (2005) JBMR 20:141-151
[3] Cadarette SM et al (2009) Osteop Int 20:1735-1747

PPI use and fracture

- There is weak evidence for an association between use of PPI and fractures from observational studies[1-3]
- This probably represents confounding with adherence, although PPIs can affect magnesium balance
- A re-analysis of 3 RCTs with risedronate[4] shows that regardless of concommitant use of PPIs (8% did) risedronate reduced risk of new VFs compared to placebo

[1] Khalili H et al (2012) BMJ 344:e372
[2] Yang YX et al (2006) JAMA 296:2947-2953
[3] Targownik LE at al (2011) Expert Opin Drug Saf 10:901-912
[4] Roux C et al (2012) Osteop Int 23:277-284

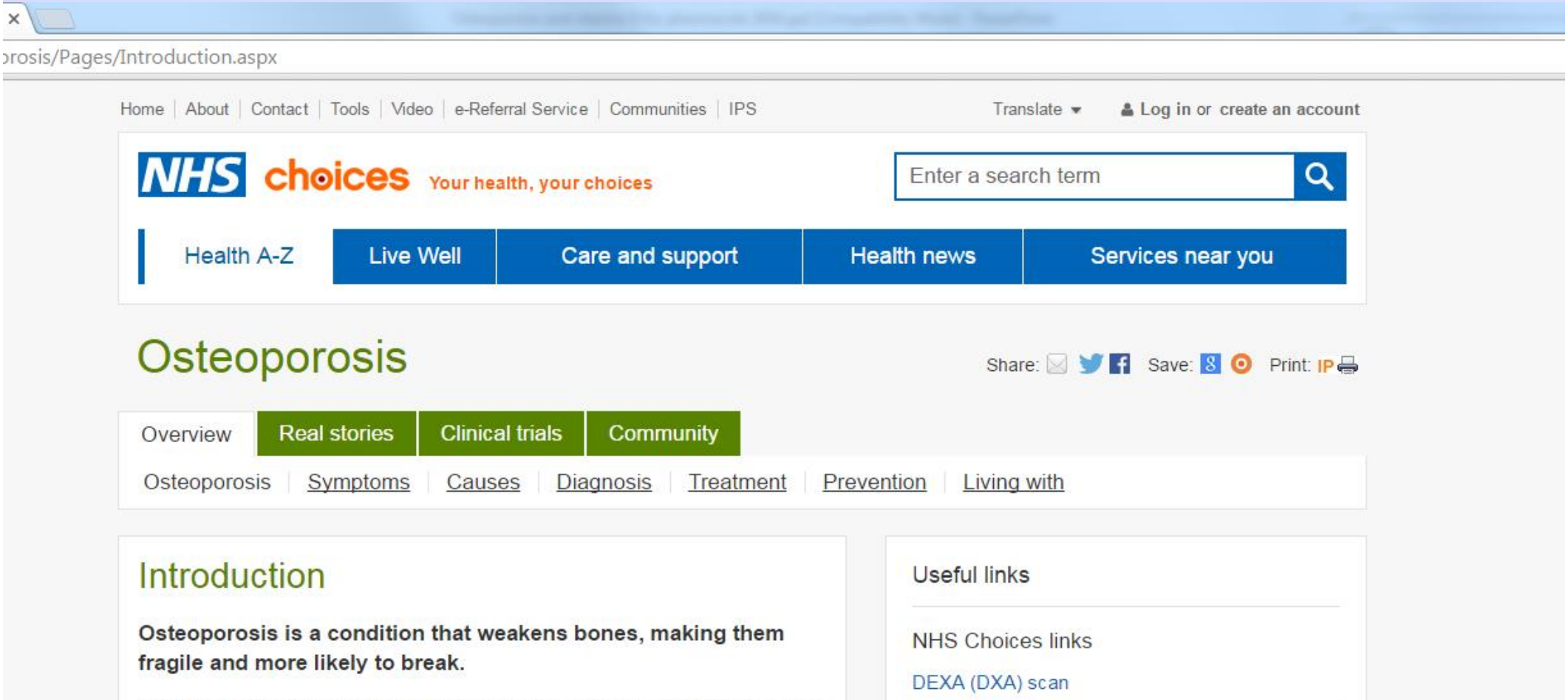
Prevention of glucocorticoid induced osteoporosis

- Very important
- Steroids are directly ‘toxic’ to bones by inhibiting osteoblasts and stimulating osteoclasts

- Can use FRAX to decide on treatment
- Bisphosphonates are first line

Information on osteoporosis

- NHS choices
  - On-line resource



Information on osteoporosis

- NHS choices
  - On-line resource
- National Osteoporosis Society
  - On-line resource
  - Also have a helpline run by nurses
  - Will send out an information pack if requested

Help & Support

View details of our Support Groups and Helpline Services below

Helpline Services

Forum

Case 2

- Mrs Rachael Jones, 71 year old retired banker has had a fractured humerus, seen by FLS and recommended to take generic alendronate with calcium and vitamin D supplementation. Her PMH includes a basal cell carcinoma, a deep vein thrombosis and a heart attack

- She comes in with a new prescription for alendronic acid and Adcal D3

- She has read that calcium and vitamin D supplements give you heart attacks and cancer, and bisphosphonates give you atrial fibrillation and is worried about taking them

1. What advice would you give her?
2. Can she get enough calcium and vitamin D from her diet?
3. Is there an alternative medication to reduce her fracture risk?

Ca/vit D and risk of MI

- An RCT of 1471 postmenopausal women were randomised to Ca supplements or placebo[1] and MI was more commonly reported in the calcium group (45 events in 31 women, vs 19 events in 14 women, P=0.01)
- A meta-analysis of 11 RCTs consisting of around 12,000 participants showed a 30% increase in the incidence of MI with results consistent across trials. The risk of MI with calcium tended to be greater in those with dietary calcium intake above the median, and was independent of age, sex and type of supplement
- A study of 1601 men and women aged 50-81 from Germany found regular calcium supplementation was associated with AF[3], but that vitamin D was associated with lower cardiovascular outcomes

[1] Bolland MJ et al (2008) BMJ 33:262-266
[2] Bolland MJ et al (2010) BMJ 341:3691
[3] Thiele I et al (2015) Atherosclerosis 241(2):743-751.

Ca/vit D and risk of MI

Is increasing evidence that calcium supplementation may be associated with a small weak increase in cardiovascular disease outcomes

This may outweigh any benefits

My advice – recommend patients obtain calcium through their diet, rather than tablets, unless absolutely necessary

[1] Bolland MJ et al (2008) BMJ 33:262-266
[2] Bolland MJ et al (2010) BMJ 341:3691
[3] Thiele I et al (2015) Atherosclerosis 241(2):743-751.

Ca/vit D and risk of cancer

- A re-analysis of the WHI showed Ca/vit D supplements in those who were not taking additional personal supplements at randomisation decreased the risk of total, breast and colorectal cancers[1]
- A further analysis by different authors showed Ca/vit D did not reduce invasive cancer incidence or mortality. Significant interactions were found between FH of cancer, personal supplement use, smoking and randomisation group

[1] Bolland NJ et al (2011) Am J Clin Nutr 94:1144-1149
[2] Mehler PS et al (2009) Int J Eating Dis 42:195-201

Ca/vit D and risk of cancer

No good evidence of an association

[1] Bolland NJ et al (2011) Am J Clin Nutr 94:1144-1149
[2] Mehler PS et al (2009) Int J Eating Dis 42:195-201

BPs and atrial fibrillation

- The HORIZON trial[1] of iv Zol showed increased incidence of arrhythmia in the treated patients compared to controls (6.9% vs 5.3%, P=0.003). Also, the risk of severe AF defined as fatal, life threatening or resulting in hospitalisation or disability, was also higher in the Zol group. The arrhythmias occurred more than 30 days after the infusion
- Many other studies have not confirmed this: extension of the HORIZON trial into older adults, retrospective analysis of the main RCTs of oral BPs, analysis of the Danish medical database (although one did!), US databases, UK GP database
- However, two meta-analyses have shown contradictory findings[2,3]

[1] Black DM et al (2007) NEJM 356:1809-1822
[2] Loke YK et al (2009) Drug Saf 32:219-228
[3] Bhuriya R et al (2010) Int J Cardiol 142:213-217

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Calcium in the diet

- What is the recommended daily intake of calcium for adults?

Age	Daily RNI (Reference Nutrient Intake)
0-12 months (non breast fed only)	525mg
1-3 years	350mg
4-6 years	450mg
7-10 years	550mg
11-18 years boys/girls	1000/800mg
Adults (19+) years	**700mg**
Pregnant women	700mg
Breast feeding women	700mg + 550mg

Foods that contain 700mg calcium

- 568mls (1 pint) milk = 682 mg calcium
- 50g cheddar = 370 mg
- 200mls yoghurt = 280 mg

- Pilchards in tomato sauce 200g (half a big tin) = 500 mg
- Tinned salmon 200g = 180 mg calcium

- 100g kale = 150mg calcium
- 100g broccoli = 40mg

- 100g calcium enriched tofu = 510mg calcium

Foods that contain 700mg calcium

- 100g (2 slices) white bread = 177mg calcium
- 100g wholemeal bread = 106mg

- 100g dried figs = 250mg calcium

- Cheese omelette – is only in the cheese, so depends how much you use

Alternative medications for someone with previous DVT and MI

= difficult

- Strontium
- Raloxifene
- Iv zoledronic acid
- s/c denosumab

Alternative medications for someone with previous DVT and MI

= difficult

- Strontium
- Raloxifene
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Strontium

- Are granules, to be dissolves in water, and drunk once per day, preferably at night
- A big issue is that after a few doses, we will be unable to accurately assess their DXA scan again
- Have many contraindications now
  - Cerebrovascular disease
  - Previous or current venous thromboembolic disease
  - Ischaemic heart disease
  - Peripheral arterial disease
  - Immobilisation
  - Uncontrolled hypertension

Alternative medications for someone with previous DVT and MI

= difficult

- Strontium
- Raloxifene
- Iv zoledronic acid
- s/c denosumab

Raloxifene

- Only for postmenopausal women
- Contraindications
  - Previous or current venous thromboembolic disease
  - Cholestatsis
  - Unexplained uterine bleeding
  - Endometrial cancer
- Cautions
  - Breast cancer
  - Risk factors for stroke
  - Risk factors for DVT - immobilisation

Alternative medications for someone with previous DVT and MI

= difficult

- Strontium
- Raloxifene
- Iv zoledronic acid
- s/c denosumab

Case 3

- Mr John Gould, a 75 year old retired administrator, on alendronic acid for 4 years after a fractured wrist, comes in to collect his repeat prescription

- He mentions that his dentist has told him that alendronic acid is very bad for his teeth, and he is wondering about stopping it because he needs to have a tooth removed

1. What advice would you give him?
2. What is the link between bisphosphonates and Osteonecrosis of the Jaw (ONJ)?
3. Where can he get more information?

ONJ and bisphosphonates

ONJ and bisphosphonates

- Is seen following IV administration of BPs for malignancy: 4mg iv Zol every 3-4 weeks in patients with multiple myeloma or bony metastases
- Similarly seen with high dose denosumab for cancer

- Association with oral BPs is much lower. A study of 8572 people using oral BPs[1] found and adjudicated 9 cases of ONJ, giving an event rate of 28 per 100,000 patient years = similar to the background population

- There is lack of understanding of pathology of ONJ: what about steroids, infection?

[1] Lo JC et al (2010) J Oral Max Surg 68:243-253

Current recommendations for people on bisphosphonates who need dental work

- Based on a pan-Bristol consensus meeting with representatives from the dental hospital (Chris Bell), BRI, Southmead, orthogeriatricians, bone physicians

- Do not stop oral bisphosphonates

- For IV zol and denosumab – try not to do anything other than cleaning within 8 weeks
- Encourage good oral hygiene with regular dental reviews

Case 4

- The daughter of Mrs Brenda McCormack, a 72 year old lady on alendronic acid, attends to collect her mothers repeat prescription.
- She mentions that her mum has recently broken her hip and she has been told it was ‘Atypical’
- She asks for advice about whether her mum should continue on the alendronic acid

1. What are Atypical Femoral Fractures?
2. What advice would you give her daughter?
3. What are links between Atypical Femoral Fractures and bisphosphonates?

AFF

- Is a formal definition of AFF based on symptoms, signs, and radiological and other clinical features[1]

[1] Shane E et al (2011) JBMR 25:2267-2294

Incidence of AFF

- AFF account for 0.41% to 0.69% of all hip fractures occurring in people older than aged 50
- Account for 7-12.9% of all subtrochanteric and shaft fractures

- They do not have a diagnostic code of their own, so epidemiology is difficult.

Link between AFF and bisphosphonates

- Some weak evidence based on radiological studies without good prescription data, and pharmacoepidemiology studies without radiology
- Is no increased risk of subtrochanteric or shaft fractures in those on bisphosphonate[1]
- AFFs also occur in those not on BPs

[1] Abrahamsen B et al (2012) Curr Rheumatol Rep 14:212-216

Management of AFF if on a bisphosphonate

- Stop the bisphosphonate until healed

- Incomplete fractures:
  - prophylactic surgical fixation, as many progress to complete fractures with conservative treatment[1]
  - is some evidence for teriparatide, but would need exceptional funding[2]

- Complete fractures managed surgically that do not unite:
  - is some evidence from case series for teriparatide, but will need exceptional funding[3]

[1] Banffy R et al (2011) Clin Orthop Relat Res 469:2028-2034
[2] Shane E et al (2011) JBMR 25:2267-2294
[3] Gomberg SJ et al (2011) JCEM 96:1627-1632

Management of osteoporosis in someone who had an AFF

- Unknown
- Probably sensible not to out them back on an anti-resorptive

- Check they still need treatment – FRAX, DXA scan, risk factors
- Consider alternative agents such as strontium (teriparatide if bone density very low)

Case 5

- Mrs Jocelyn Farnam-Smith, a 78 year old retired barrister, has been on alendronic acid for 8 years.
- She attends to collect her repeat prescription, but asks for some advice
- She has noticed her hearing getting worse over the past 5 years, and wonders if it's related to her bisphosphonate, as she understands it can damage the bones in the ears

1. What are links between bisphosphonates and osteonecrosis of the external auditory canal?
2. What advice would you give her?

Osteonecrosis of the external auditory canal

- Is a recent MHRA alert (Dec 2015) for bisphosphonates
- “has been reported very rarely”
- Consider this in people who have ear symptoms, including chronic ear infections, or suspected cholesteatoma
- Risk factors for developing osteonecrosis of the external auditory canal include: steroid use, chemotherapy, infection, an ear operation, or cotton-bud use.

Summary

- Osteoporosis – definition and risk factors
- Vitamin D metabolism pathway
- Identification of fracture risk
- Treatments available
  - NICE guidance, the reality, length of time on treatment, difficulties in older people with cardiovascular disease or previous DVTs
- Bisphosphonates
  - Indigestion and PPI use, Atypical femoral fractures, ONJ, Osteonecrosis of the external auditory canal
- Calcium and vitamin D supplementation/replacement
  - Recommended amounts, links with cardiovascular disease and cancer
- Sources of further information for patients

Thank you

University of BRISTOL

North Bristol NHS Trust