BONE HEALTH

THE LEGACY OF LHRH THERAPY IN PROSTATE CANCER

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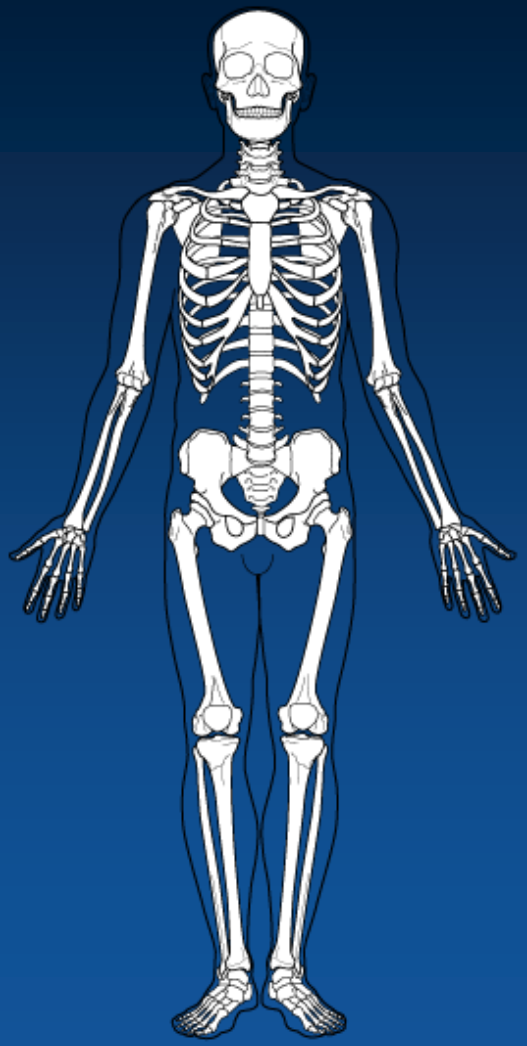
Functions of bone

Structural support
For heart, lungs and marrow

Protection of internal organs
From mechanical damage, particularly the brain, heart and lungs

Attachment of muscles
Bones act as levers for muscles, allowing voluntary movement

Mineral storage
The skeleton is the largest depot for minerals in the body; 99% of calcium, 85% of phosphorus and 50% of magnesium are stored in the bones



Production of blood cells
Red bone marrow produces blood cells in a process known as haematopoiesis

Storage of fatty acids
Yellow bone marrow contains a reserve of fat for consumption during starvation states

Acid-base balance
Bone buffers the blood against excessive pH changes by absorbing or releasing alkaline salts

Detoxification
Bone tissues can store heavy metals, such as lead, which can be gradually released and excreted

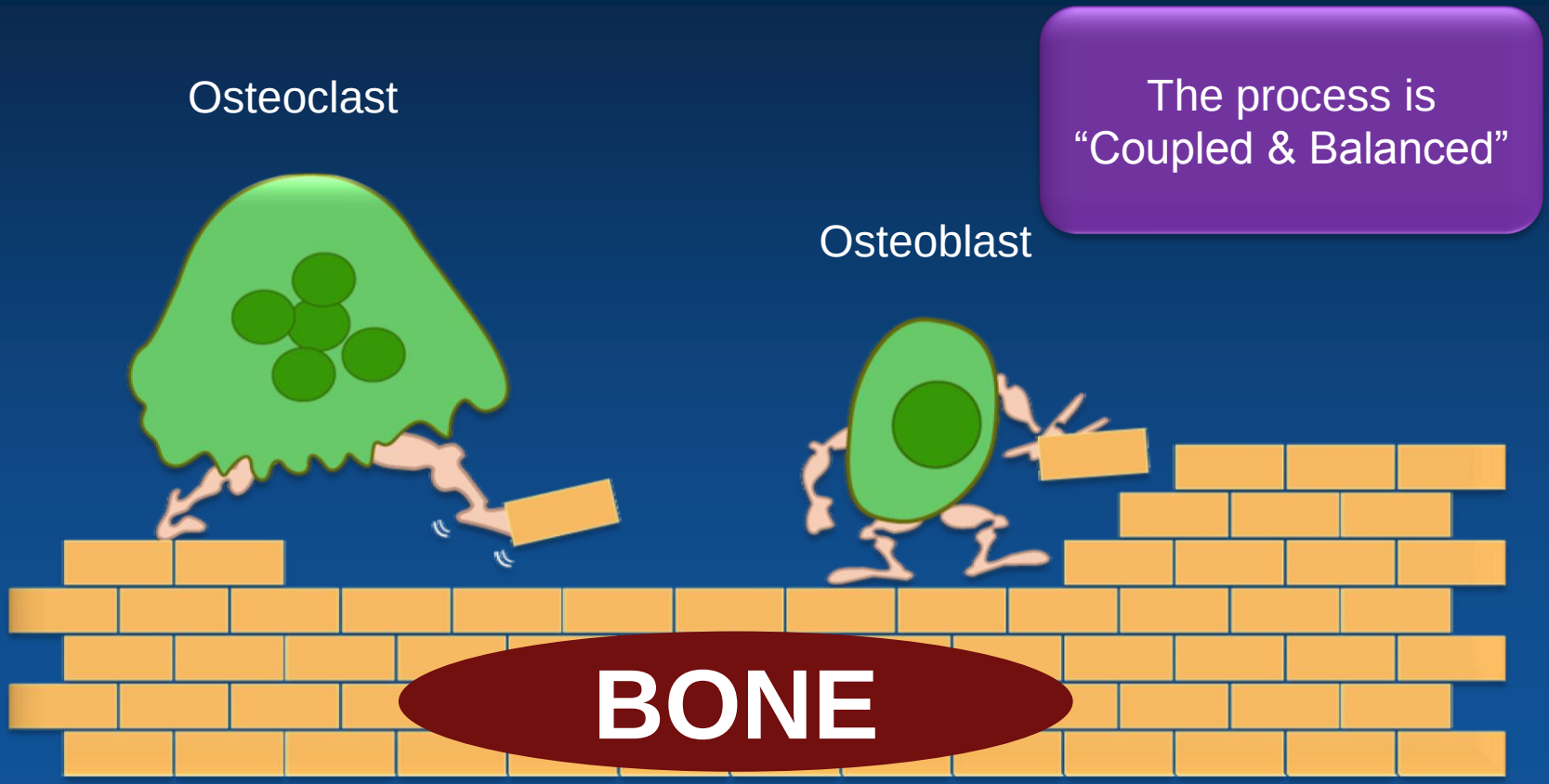
For normal bone health – a process called remodeling is required……

- To cope with constant mechanical stress
- To repair tiny fractures (Micro-fractures)
- Ensures skeletal integrity
- Maintains mineral homeostasis

Regulated by cytokines & systemic hormones!!!

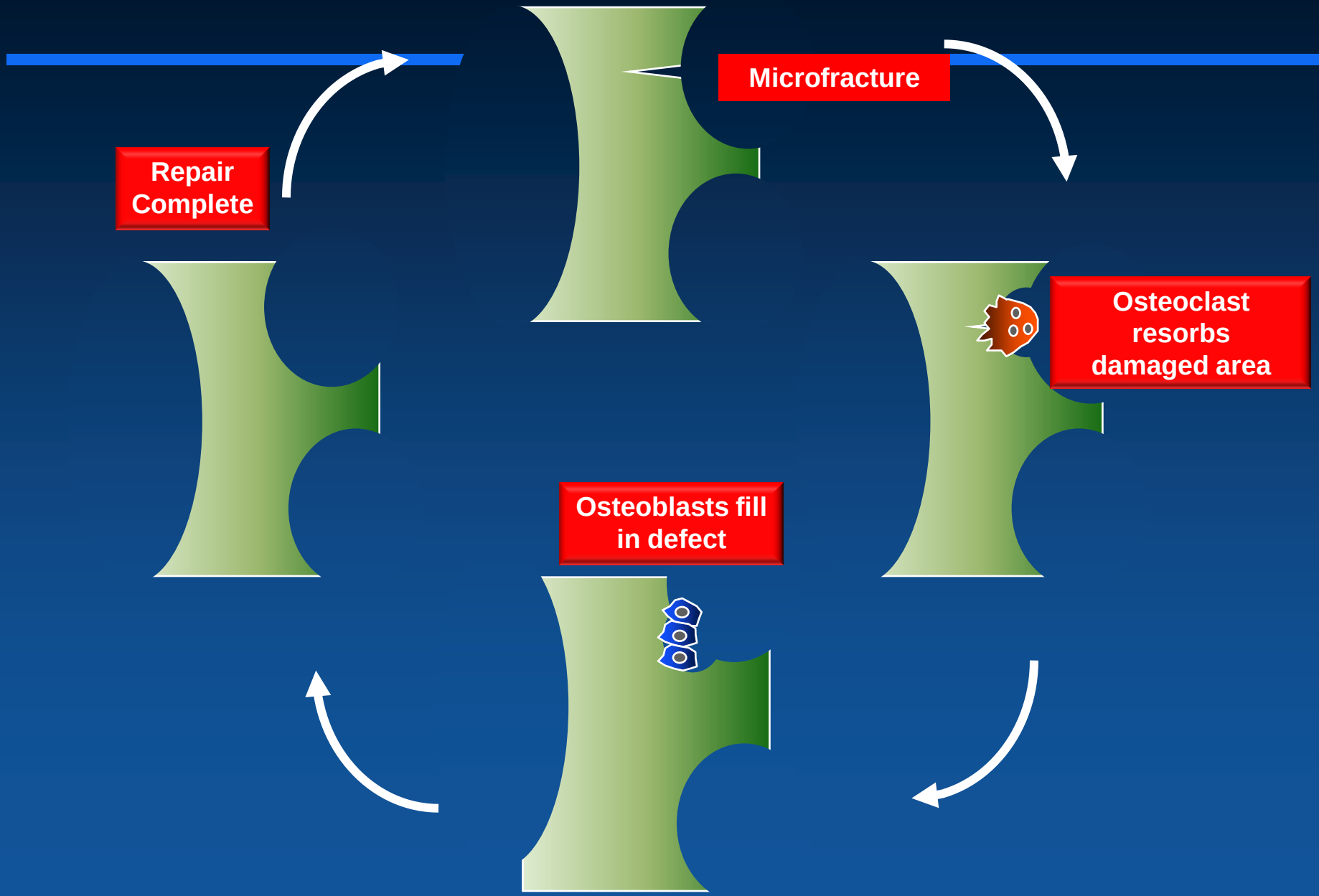
Continuous throughout life!!

Normal bone remodeling: Old/damaged bone is removed by osteoclast activity and replaced by osteoblast activity

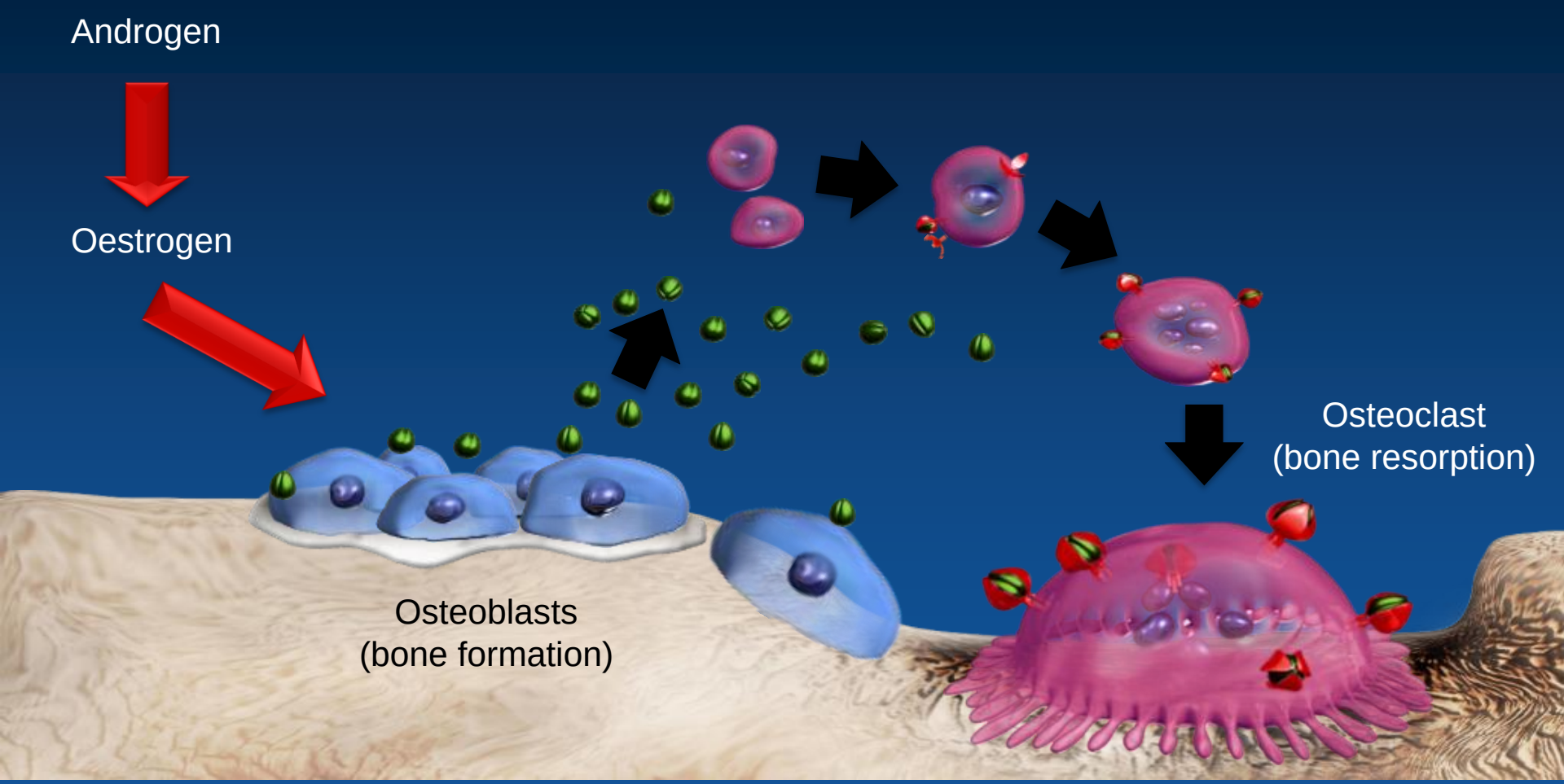


Adapted from Prof GR Mundy, Vanderbilt University

The Fracture Cycle



Androgen is a key mediator of bone formation…



Adapted from Boyle WJ *et al*. *Nature* 2003;423:337–42. Lewiecki. *Exper Opin Biol Ther* 2006;6:1041-50.

= RANK = RANK ligand

RANK, receptor activator of nuclear factor κ B

Androgen Deprivation Therapy (ADT).....

Prostate cancer

Androgen deprivation therapy (ADT):

- LHRHagonists
  - Leuprolide
  - Goserelin
  - Triptorelin
- LHRH antagonists
  - Degarelix
- Orchidectomy

ADT therapy in Prostate Cancer

Indications for ADT

Metastatic disease

- N+, M0 stage: Standard adjuvant therapy in more than 2 positive nodes to radiation therapy or radical prostatectomy as primary local therapy
- M+ stage: Standard option; mandatory in symptomatic patients

Locally advanced disease (T3-T4 stage)

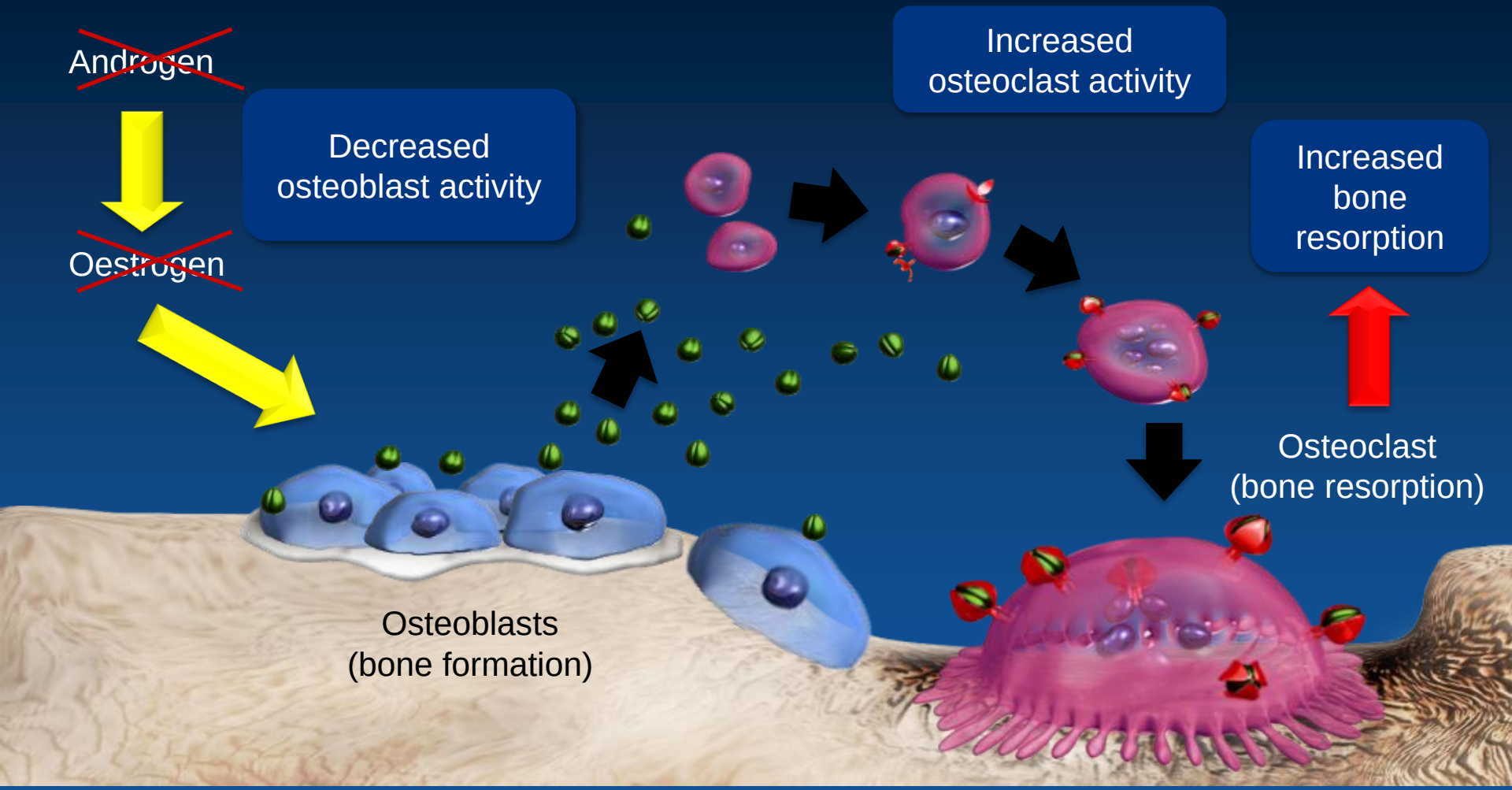
- Symptomatic patients
- Extensive T3-T4 disease
- High PSA level (>25-50 ng/mL)
- PSA-Doubling Time (DT) <1 yr
- As concomitant/adjuvant treatment (3 years) to radiation treatment; shown to have a survival advantage for risk patients

Selected patients with localised disease: (T1a –T2c stage)

- Symptomatic patients, who need palliation of symptoms, unfit for curative treatment
- For high-risk patients, neoadjuvant hormonal treatment and concomitant hormonal therapy plus radiotherapy result in increased overall survival

1 Mottet N et al. EAU guidelines on prostate cancer. 2014 . http://www.uroweb.org/guidelines/online-guidelines: (last accessed 4/2014)

ADT reduces osteoblast activity and increases bone resorption by osteoclasts

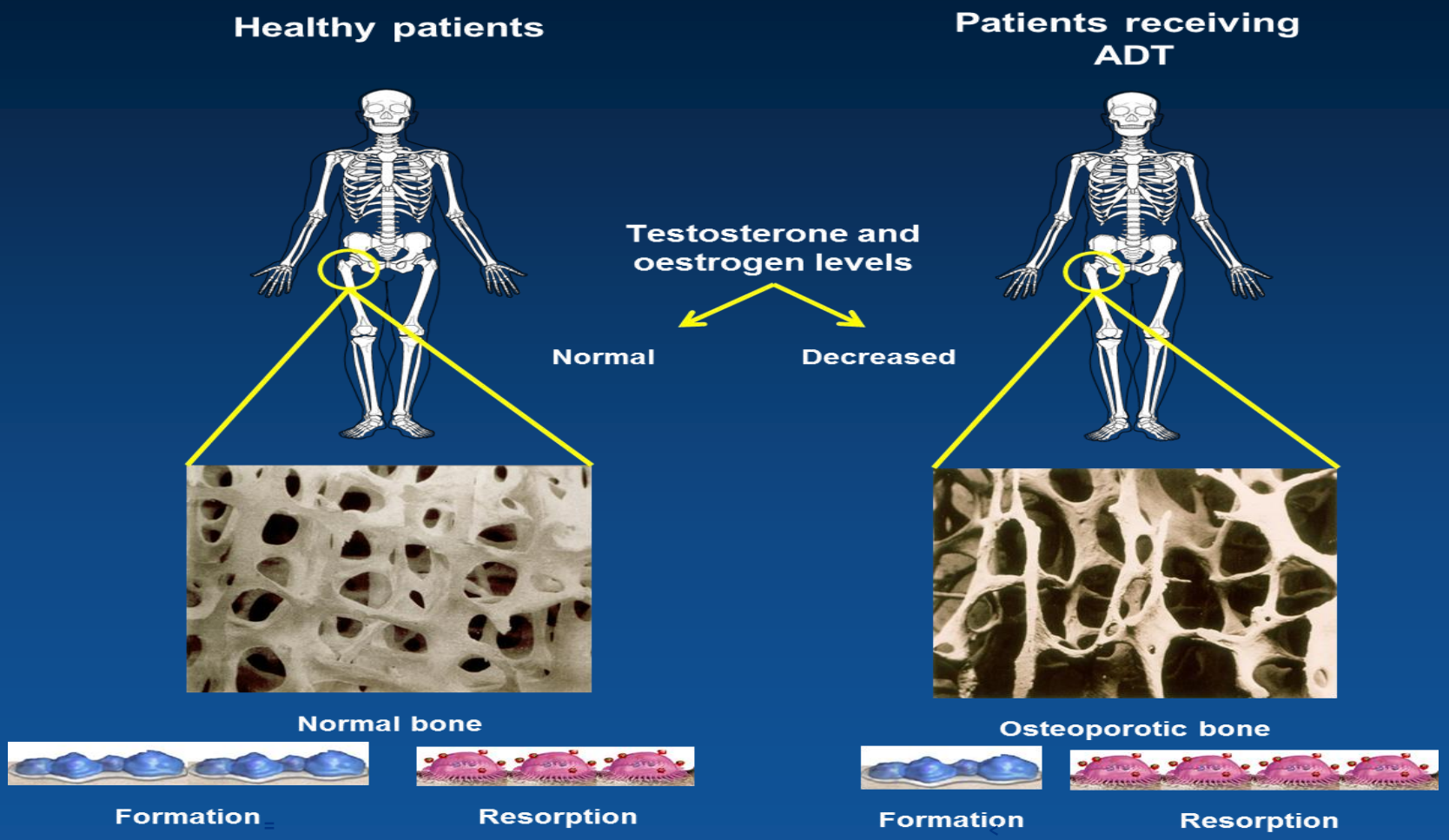


Adapted from Boyle WJ *et al*. *Nature* 2003;423:337–42. Lewiecki. *Exper Opin Biol Ther* 2006;6:1041-50.

= RANK = RANK ligand

ADT, androgen-deprivation therapy; RANK, receptor activator of nuclear factor κ B

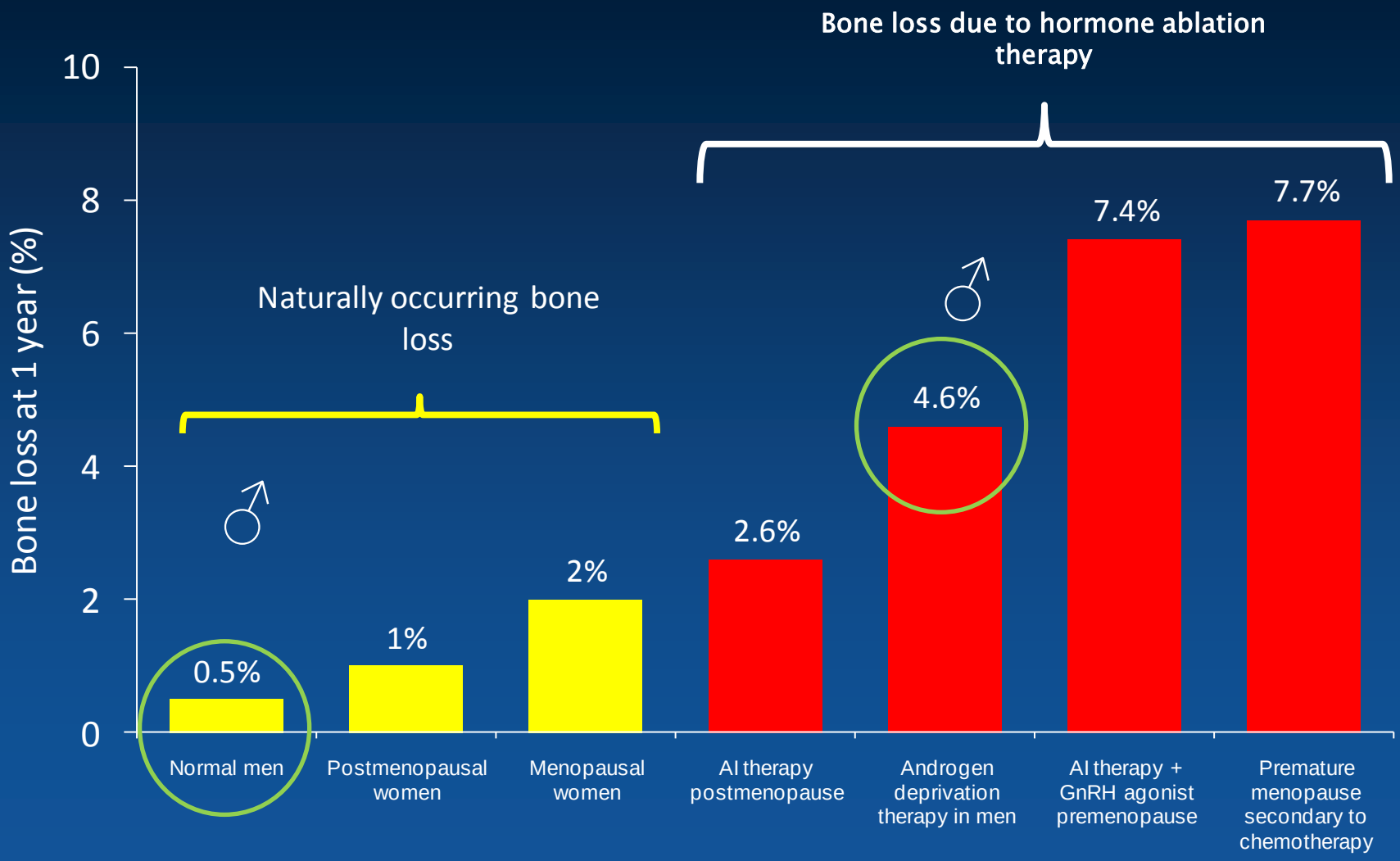
ADT results in a transition from normal bone formation to abnormal bone loss…….



European Association of Urology Nurses : e-learning course: Bone Health and Urological Cancer 2012.

How quick is the effect?

Bone loss in men and women at 1 year



Higano CS. Nat Clin Pract Urol 2008;5:24-34; Eastell R, et al. J Bone Miner Res 2006;21:1215-23; Maillefert JF, et al.J Urol 1999;161:1219-22; Gnant M, et al. Lancet Oncol 2008;9:840-9; Shapiro CL, et al. J Clin Oncol 2001;19:3306-11.

However the problem already exists before ADT is started !!!

Prevalence of Osteoporosis at Baseline and Under ADT in Prostate Cancer: Cross-Sectional Data.

Duration of ADT (yr)	Patients (%)		
	Osteoporosis	Osteopenia	Normal
None	35.4	45.2	19.4
2	42.9	39.3	17.8
4	49.2	34.4	16.4
6	59.5	29.7	10.8
8	65.7	28.5	5.7
10	80.6	19.4	0

Morote J, et al. Urology. 2007;69:500-504.

What are the additional effects of ADT in men with prostate cancer??

Parameter	ADT only Effect
Body composition	
Weight	↑
Lean body mass	↓
Fat mass	↑
Cardiometabolic changes	
HDL and total cholesterol levels	↑
Triglyceride levels	↑
Insulin sensitivity	↓
Risk of incident diabetes mellitus	↑
Risk of cardiovascular disease	(↑)
Physical function	
Physical function	↓
Muscle strength	↓
Bone health	
Bone mineral density	↓
Osteoporosis incidence	↑
Risk of bone fracture	↑
Quality of life	
Overall	↓
Fatigue	↑
Cognitive function	(↓)
Sexual function	↓

Østergren, P. B. *et al*. (2016) *Nat. Rev. Urol.* doi:10.1038/nrurol.2016.67

ADT with GnRH agonists increases the risk of fatal myocardial infarction

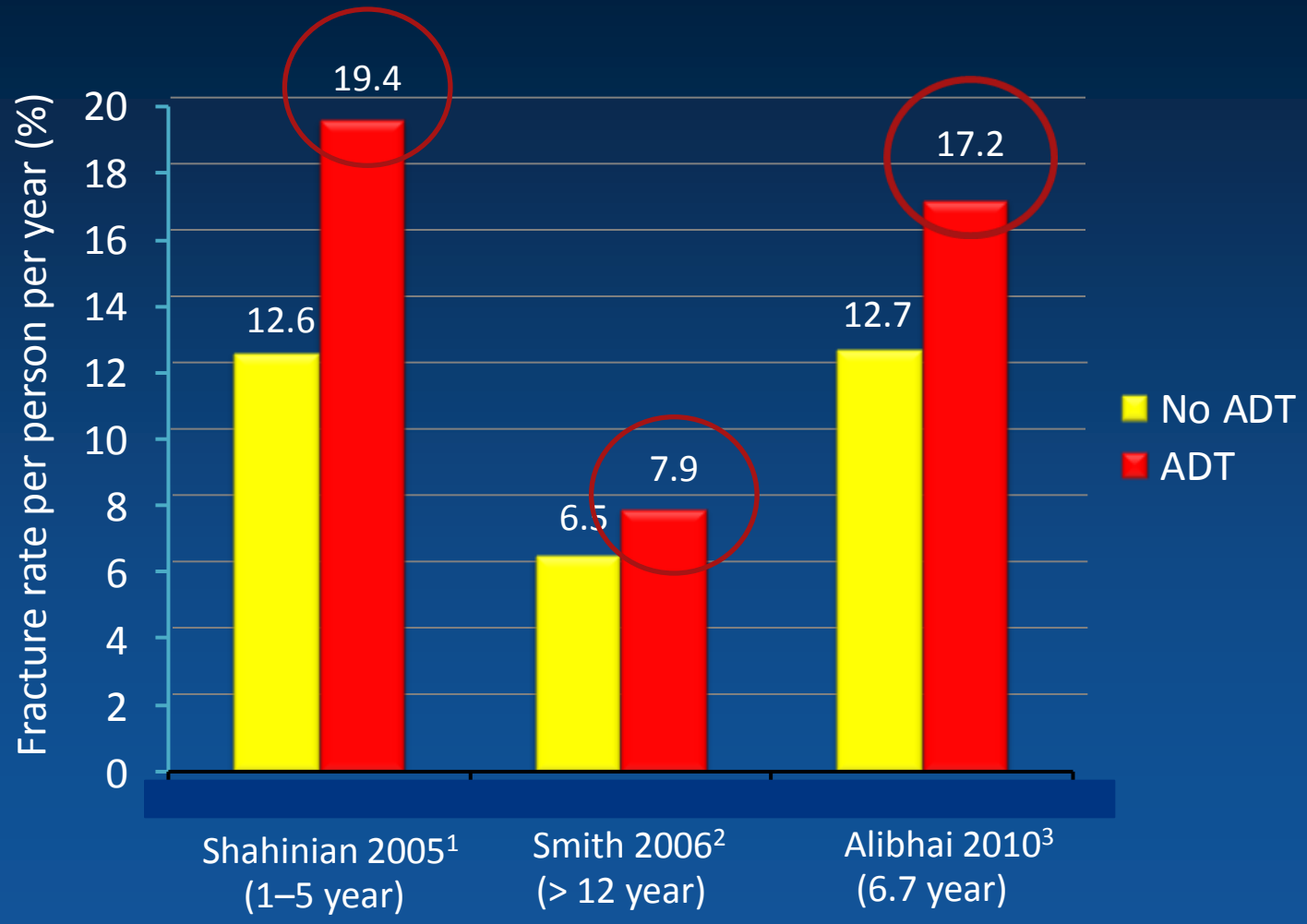
- Men aged ≥65 years receiving 6 months of ADT+RT had shorter times to fatal myocardial infarction compared with RT alone (p=0.017)[1]
- Patients with moderate or severe comorbidities had a greater risk of a fatal myocardial infarction when receiving RT + ADT compared with RT alone[2]

GnRH agonists: FDA warning

- October 2010: US FDA asks manufacturers of GnRH agonists to add extra safety information to drug labels
  - Increased risk of diabetes and certain CV diseases (heart attack, sudden cardiac death, stroke) in men with prostate cancer

1. D'Amico, et al. J Clin Oncol 2007;25:2420–5
2. D'Amico, et al. JAMA 2008;299:289–95.

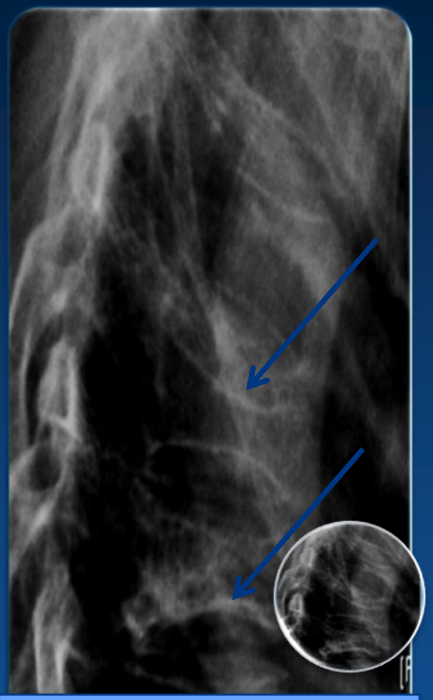
ADT consistently increases fracture risk in men with prostate cancer……



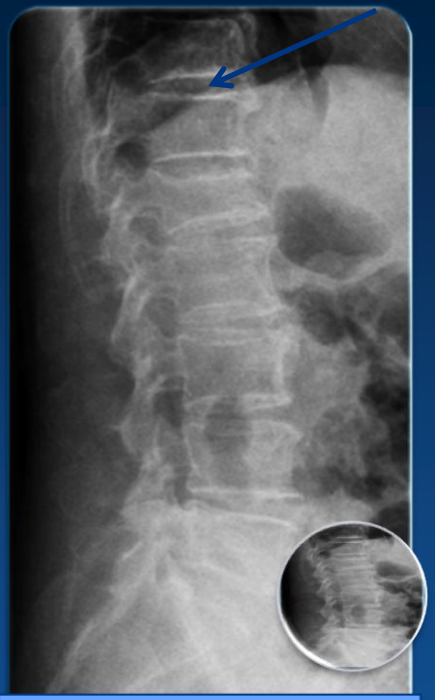
1. Shahinian VB *et al. N Engl J Med* 2005;352:154–64. 2. Smith MR *et al. J Clin Oncol* 2005;23:7897–903. 3. Alibhai SMH *et al. J Urol* 2010;184:918–24.

ADT, androgen-deprivation therapy

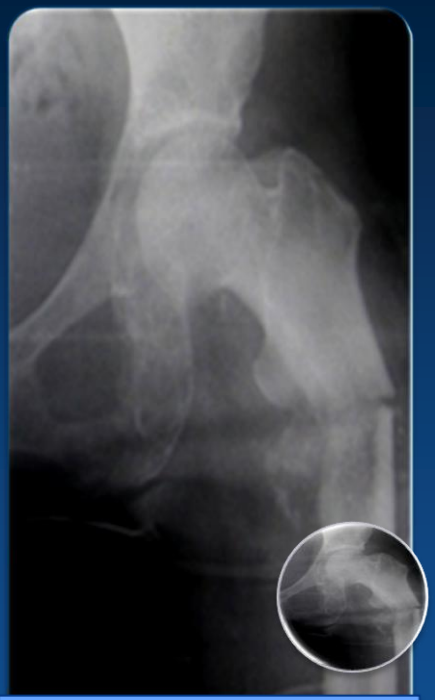
Effects of osteoporosis: Vertebral and hip fractures



Osteoporotic compression fractures



Osteoporotic compression fracture with ‘wedge’ deformity



Osteoporotic fracture of the left femur

EAUN e-learning bone health course 2013.
Available at: http://www.uroweb.org/nurses/educational-resources-for-nurses/

Hip Fractures Impact Mortality and Life Expectancy

- 1-2 yr mortality in men is ~ 30% to 38% [1-3]
  - Hip fracture affects life expectancy dramatically[4,5]
    - Aged 60-69 yrs: 11.5 yrs of decreased life expectancy
    - Aged 70-79 yrs: 5.0 yrs of decreased life expectancy

1. Forsen L, et al. Osteoporosis Int. 1999;10:73-78. 2. Schurch MA, et al. J Bone Miner Res. 1996;11: 1935-1942. 3. Soderqvist A, et al. Gerontology. 2009;55:496-504. 4. Cree M, et al. J Am Geriatr Soc. 2000;48:283-288. 5. Center JR, et al. Lancet. 1999;353:878-882.

PROSTATE CANCER GUIDELINES (2016)
HORMONAL THERAPY

6.8.7.1.3.1.Non-metastatic bone fractures

Due to increased bone turnover and decreased BMD in a time-dependent manner, ADT use is linked to an increased risk of fracture (up to 45% relative risk with long-term ADT) Hip fractures in men are associated with a significant risk of death.

- *Evaluation of BMD should be performed by dual emission X-ray absorptiometry (DEXA) before starting long-term ADT.*
- *Treatment :* with denosumab or bisphosphonates

❖ **Lifestyle changes before starting long-term androgen-deprivation therapy**

Patients should be encouraged to adopt lifestyle changes, e.g. increased physical activity, cessation of smoking, decreased alcohol consumption, and to normalise their BMI.

Calcium and vitamin D supplements should be considered if low values are detected (normal values: calcium: 2.2-2.6 nmol/L,vitamin D: 100-160 nmol/L). A daily intake of at least 1,200 mg/day of calcium and 1,000 UI of vitamin D is useful.

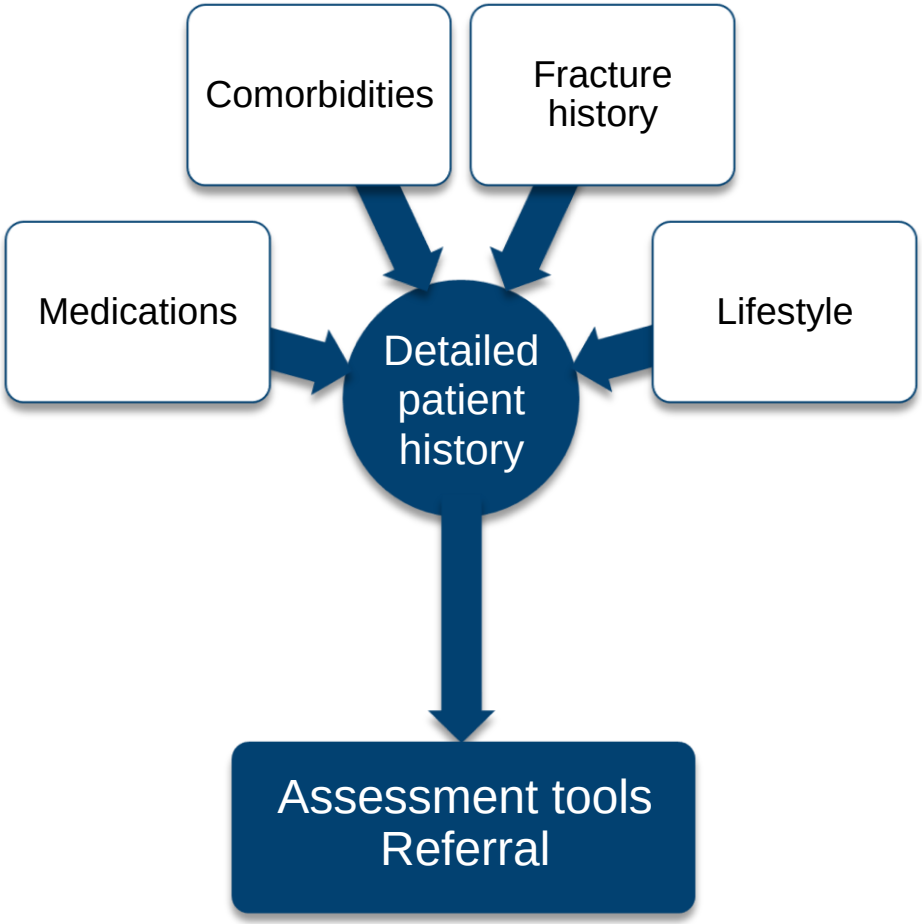
6.8.7.1.3.4.Fatigue

Regular exercise appears to be the best protective measure with prolonged efficacy and improved specific survival.

http://uroweb.org/guideline/prostate-cancer (2016)

Assessment and monitoring

Nurses have a key role in fracture risk assessment



Tanna N. Nurs Times 2009;105:28−31.

Detailed patient history

Major risk factors

- Hypogonadism (hormone ablation therapy)
- Prior fragility fracture (after age 40 yrs)
- Age (> 65 yrs)
- Low bone mineral density (T-score < -2.5)
- Family history of fracture
- Vertebral compression fracture
- Osteopaenia apparent on X-ray

Most major risk factors result from:

- Medications
- Comorbidities

Less likely to be modifiable

Saad F, et al. J Clin Oncol 2008;26:5465−76;
Tanna N. Nurs Times 2009;105:28−31.

Detailed patient history

Minor risk factors

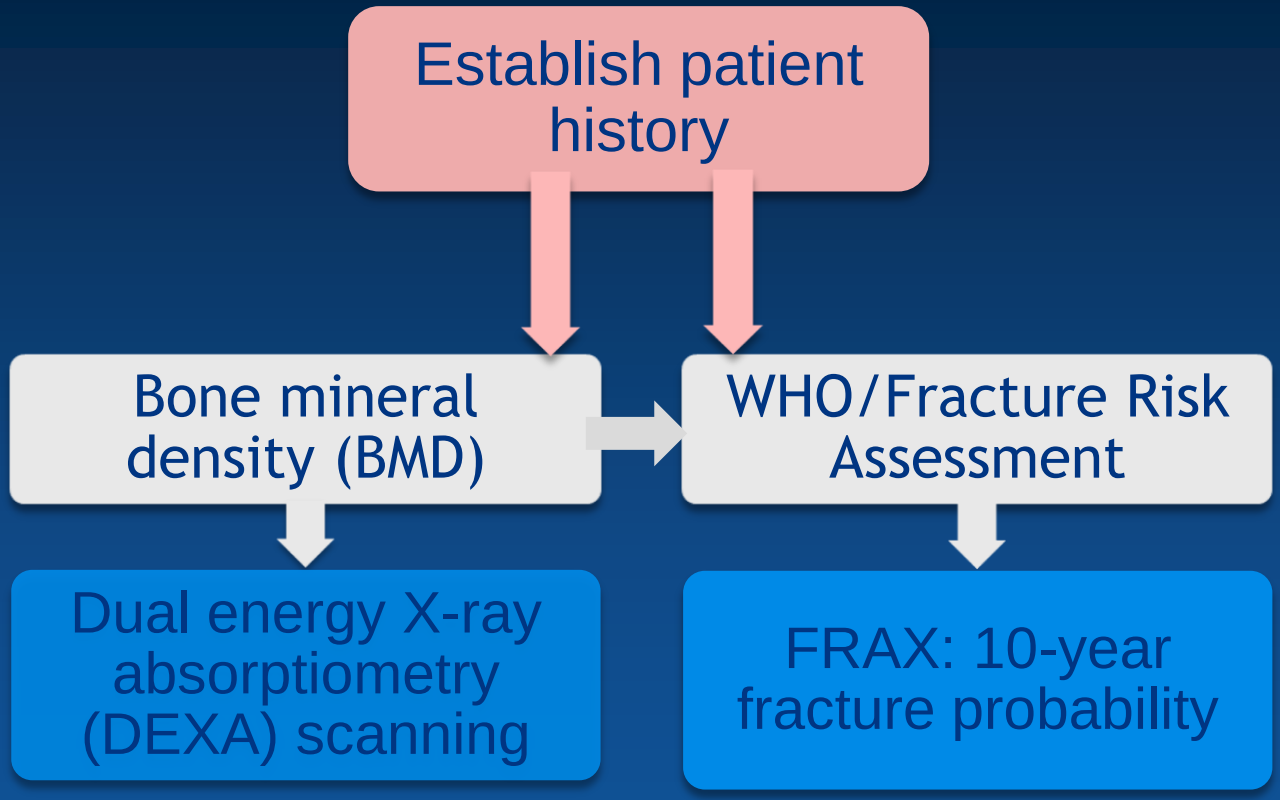
- Rheumatoid arthritis
- Low dietary calcium and vitamin D
- Smoker
- Excessive alcohol intake (> 2 units per day)
- Excessive caffeine intake (> 4 cups/day)
- Weight (< 57 kg)
- Weight loss (> 10% of weight at age 25 yrs)

Most minor risk factors result from lifestyle choices

More likely to be modifiable

Saad F, et al. J Clin Oncol 2008;26:5465−76;
Tanna N. Nurs Times 2009;105:28−31.

Assessment tools



WHO Fracture Risk Assessment tool. Available at: http://www.shef.ac.uk/FRAX (Accessed Aug 2014).

Bone Mineral Density (BMD)

Refers to the bone mineral content of a specific bone or bones, usually the spine & hip.

Average bone mineral density = BMC / W [g/cm^2]

- BMC = bone mineral content = g/cm
- W = width at the scanned line

- The bone mineral content of these bones is then compared to the young normal reference mean (aged 30) and same sex – to get the T-Score

- The resulting comparison is used to determine risk for fractures and the stage of osteoporosis (if any) in an individual.

www.nos.org.uk/for-people-and-families/osteoporosis-treatment-options/osteoporosis-scans-and-tests/ (accessed 9/3/2017)

Measuring Bone Mineral Density (BMD)

- *DEXA* (Dual-energy X-ray absorptiometry) *scanning provides an estimate of BMD*
- low BMD scores can accurately predict the risk of future fracture

- Axial DEXA - Gold standard

  Measures spine - Most sensitive to early bone loss

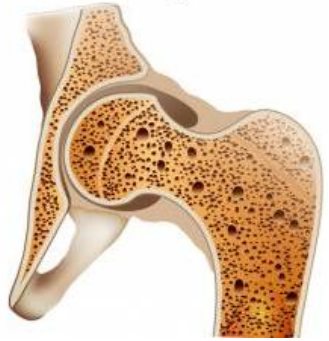
  Hip :

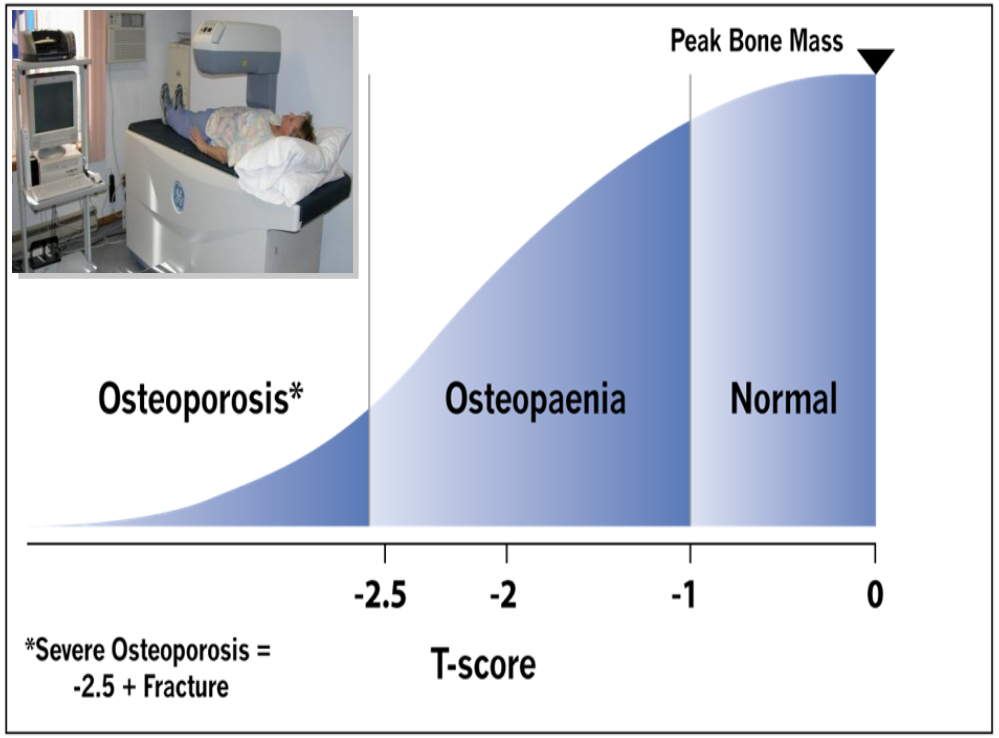
  - Best predicts hip fracture and fracture at other skeletal sites
  - Preferential for decision making

Berry SD, Samelson EJ, Pencina MJ, et al. *JAMA.* 2013;310:1256-1262

T-score: interpreting DEXA results

Osteoporosis





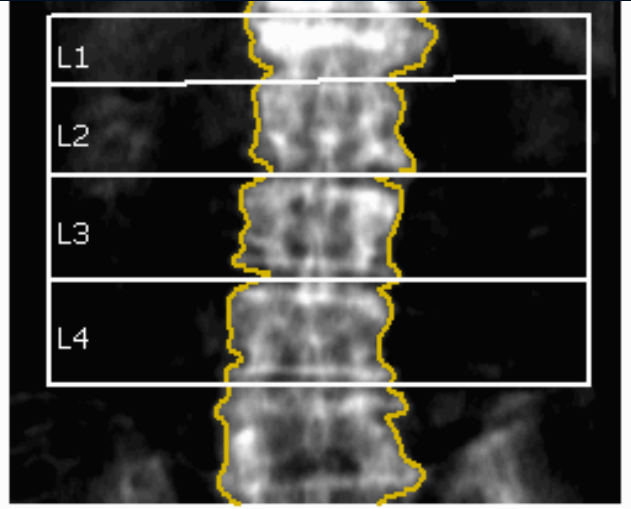
Normal bone

T-score

The number of standard deviations that separate the patient from the mean value of a healthy population.

Every unit decrease (deviation) is associated with 10−12% loss of bone density

World Health Organization. Guidelines for preclinical evaluation and clinical trials in osteoporosis, 1998.



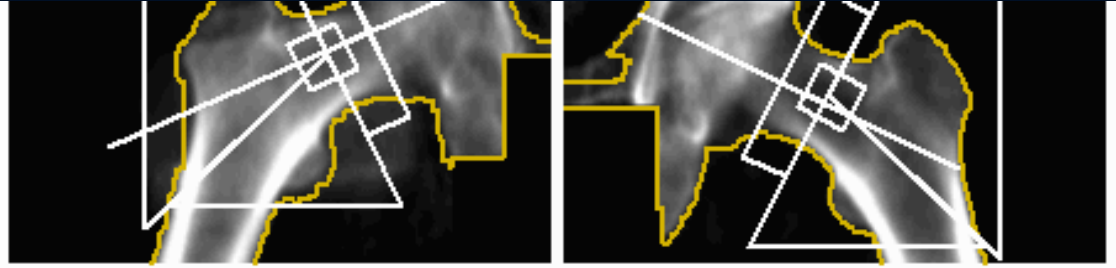
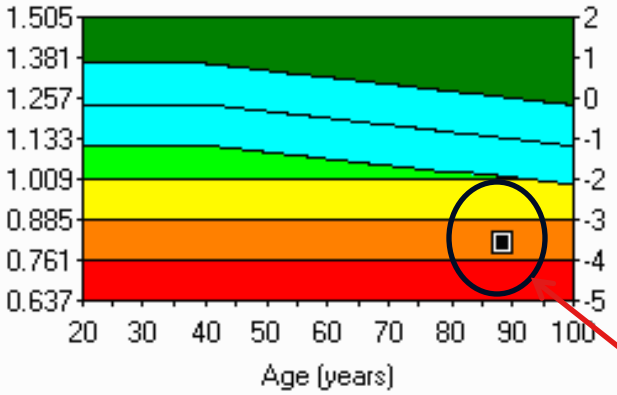


Image not for diagnosis

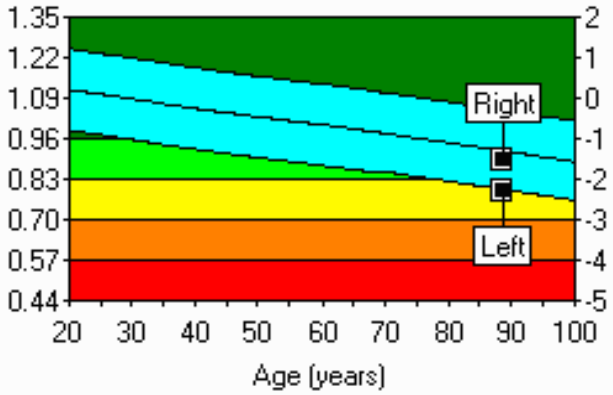
HAL chart results unavailable

Image not for diagnosis

Densitometry Reference: AP Spine L2-L4



Densitometry Reference: DualFemur Total



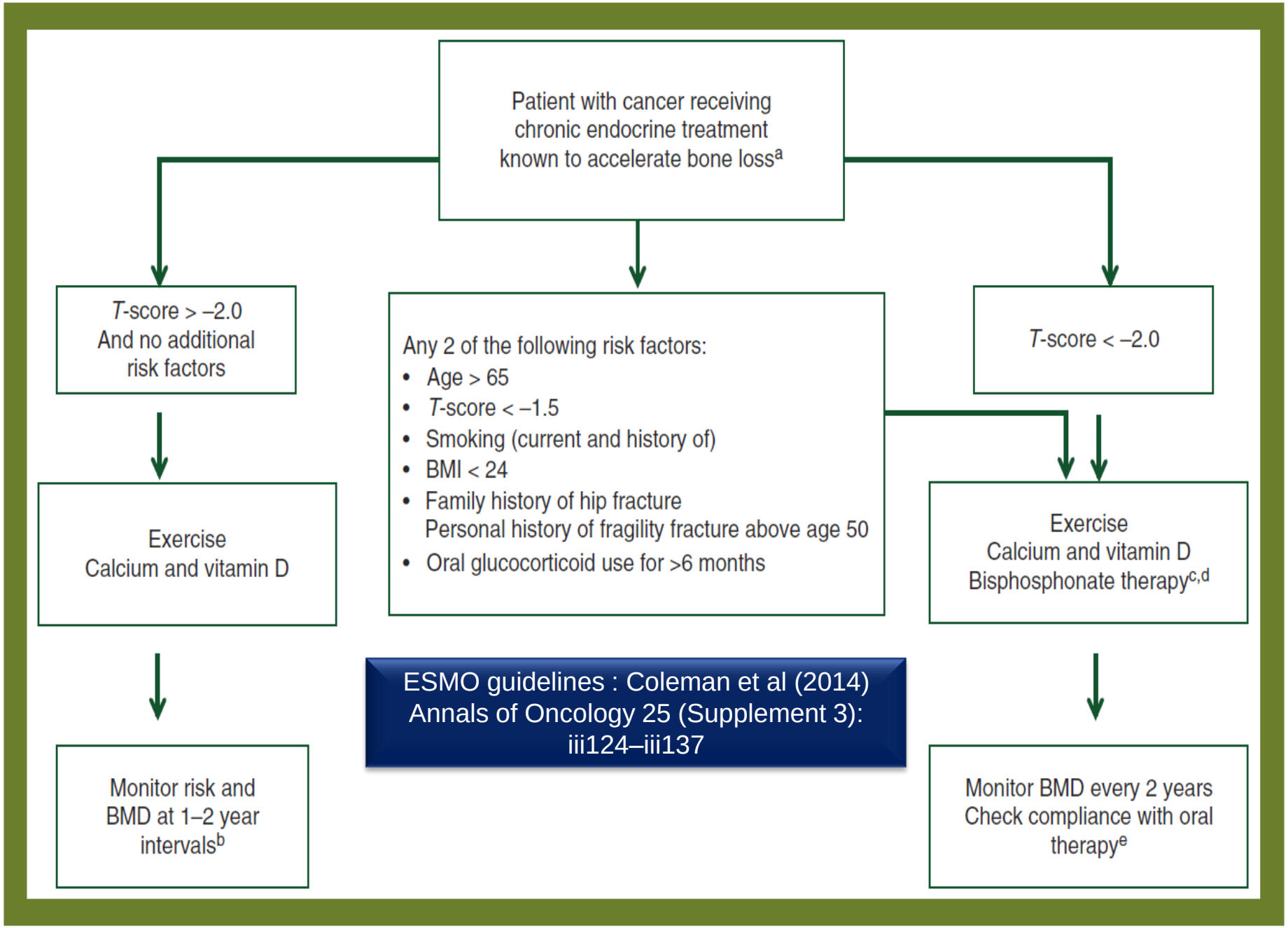
Region	BMD [1] (g/cm²)	Young-Adult [2,7] T-Score	Age-Matched [3] Z-Score	WHO Classification [11]
AP Spine L2-L4	0.808	-3.6	-2.8	-
DualFemur Total				
Left	0.792	-2.3	-1.0	-
Right	0.898	-1.5	-0.2	-
Mean	0.845	-1.9	-0.6	-
Difference	0.105	0.8	0.8	-

Bone Targeted treatments - ADT bone loss

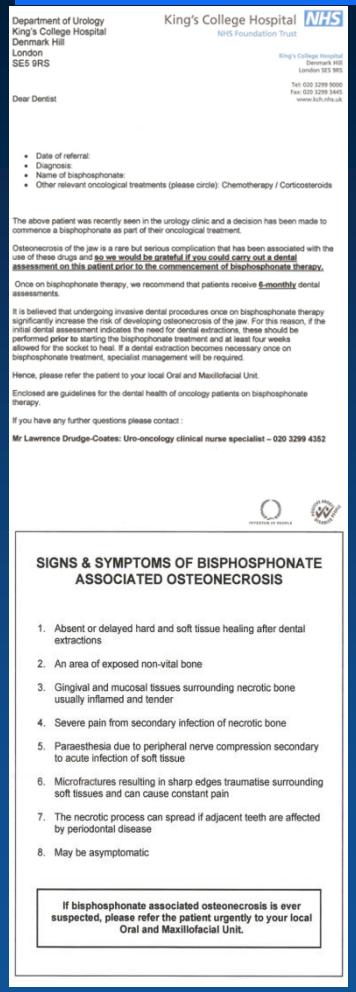
Preventing ADT bone loss :

- Zoledronic acid – 5mg annually (IV)
  - (increase BMD)
- Alendronate – 70mg weekly (PO)
  - (Increase BMD)
- Denosumab – 60mg every 6 months (S/C)
  - (Increase BMD & lower rate of new vertebral fracture 1.5% vs 3.9% with placebo)
- Calcium and vitamin D supplementation.
- Dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment.

EAU guidelines Prostate Cancer - http://uroweb.org/guideline/prostate-cancer (2016),www.medicines.org.uk/emc/medicine/23127/2843/18171 (2017). Greenspan S et al (2008) *J Clin Oncol* **26**: 4426–4434. Smith MR et al (2009) *N Engl J Med* ; **361**: 745–755. Smith MR (2003) *J Urol* 2003; **169**: 2008–2012.


Patient with cancer receiving chronic endocrine treatment known to accelerate bone loss[a]
T-score > –2.0 And no additional risk factors
Any 2 of the following risk factors:
• Age > 65
• T-score < –1.5
• Smoking (current and history of)
• BMI < 24
• Family history of hip fracture
Personal history of fragility fracture above age 50
• Oral glucocorticoid use for >6 months
T-score < –2.0
Exercise
Calcium and vitamin D
Exercise
Calcium and vitamin D
Bisphosphonate therapy[c,d]
ESMO guidelines : Coleman et al (2014) Annals of Oncology 25 (Supplement 3): iii124–iii137
Monitor risk and BMD at 1–2 year intervals[b]
Monitor BMD every 2 years
Check compliance with oral therapy[e]

Dental Assessment



Department of Urology
King's College Hospital
Denmark Hill
London
SE5 9RS

King's College Hospital NHS
NHS Foundation Trust

Dear Dentist

- Date of referral:
- Diagnosis:
- Name of bisphosphonate:
- Other relevant oncological treatments (please circle): Chemotherapy / Corticosteroids

The above patient was recently seen in the urology clinic and a decision has been made to commence a bisphophonate as part of their oncological treatment.

Osteonecrosis of the jaw is a rare but serious complication that has been associated with the use of these drugs and **so we would be grateful if you could carry out a dental assessment on this patient prior to the commencement of bisphosphonate therapy.**

Once on bisphophonate therapy, we recommend that patients receive **6-monthly** dental assessments.

It is believed that undergoing invasive dental procedures once on bisphosphonate therapy significantly increase the risk of developing osteonecrosis of the jaw. For this reason, if the initial dental assessment indicates the need for dental extractions, these should be performed **prior to** starting the bisphophonate treatment and at least four weeks allowed for the socket to heal. If a dental extraction becomes necessary once on bisphosphonate treatment, specialist management will be required.

Hence, please refer the patient to your local Oral and Maxillofacial Unit.

Enclosed are guidelines for the dental health of oncology patients on bisphosphonate therapy.

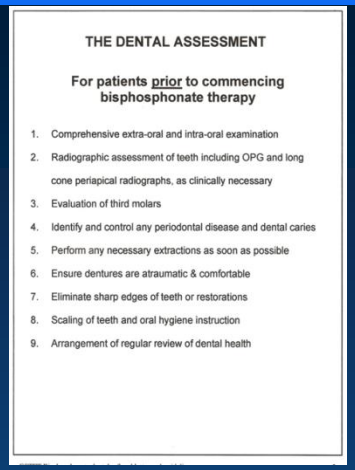
If you have any further questions please contact :

Mr Lawrence Drudge-Coates: Uro-oncology clinical nurse specialist – 020 3299 4352

SIGNS & SYMPTOMS OF BISPHOSPHONATE ASSOCIATED OSTEONECROSIS

1. Absent or delayed hard and soft tissue healing after dental extractions
2. An area of exposed non-vital bone
3. Gingival and mucosal tissues surrounding necrotic bone usually inflamed and tender
4. Severe pain from secondary infection of necrotic bone
5. Paraesthesia due to peripheral nerve compression secondary to acute infection of soft tissue
6. Microfractures resulting in sharp edges traumatise surrounding soft tissues and can cause constant pain
7. The necrotic process can spread if adjacent teeth are affected by periodontal disease
8. May be asymptomatic

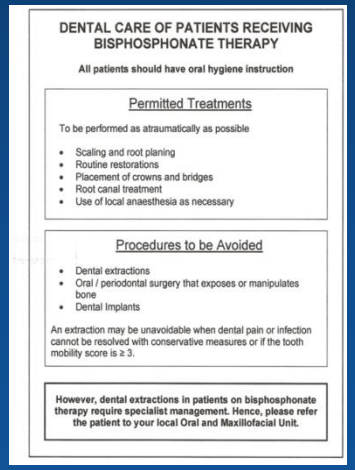
If bisphosphonate associated osteonecrosis is ever suspected, please refer the patient urgently to your local Oral and Maxillofacial Unit.



THE DENTAL ASSESSMENT

For patients prior to commencing bisphosphonate therapy

1. Comprehensive extra-oral and intra-oral examination
2. Radiographic assessment of teeth including OPG and long cone periapical radiographs, as clinically necessary
3. Evaluation of third molars
4. Identify and control any periodontal disease and dental caries
5. Perform any necessary extractions as soon as possible
6. Ensure dentures are atraumatic & comfortable
7. Eliminate sharp edges of teeth or restorations
8. Scaling of teeth and oral hygiene instruction
9. Arrangement of regular review of dental health



DENTAL CARE OF PATIENTS RECEIVING BISPHOSPHONATE THERAPY

All patients should have oral hygiene instruction

Permitted Treatments

To be performed as atraumatically as possible

- Scaling and root planing
- Routine restorations
- Placement of crowns and bridges
- Root canal treatment
- Use of local anaesthesia as necessary

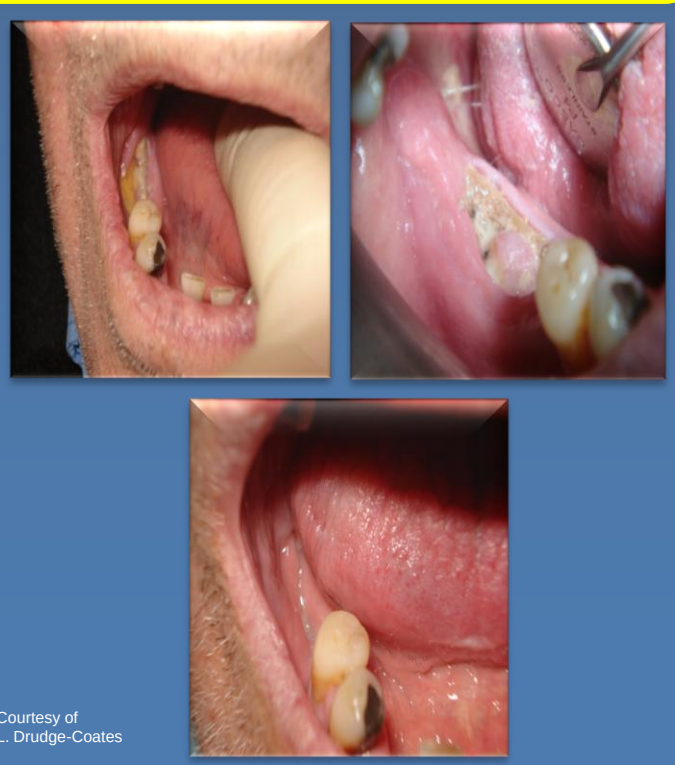
Procedures to be Avoided

- Dental extractions
- Oral / periodontal surgery that exposes or manipulates bone
- Dental Implants

An extraction may be unavoidable when dental pain or infection cannot be resolved with conservative measures or if the tooth mobility score is ≥ 3.

However, dental extractions in patients on bisphosphonate therapy require specialist management. Hence, please refer the patient to your local Oral and Maxillofacial Unit.

ONJ patient management



Courtesy of
L. Drudge-Coates

And in mCRPC??

Treatment-Related Physical Dysfunction Associated With First-Line Targeted Therapies in mCRPC

Agent	Target	Asthenic Conditions[a]	Falls	Sarcopenia
Androgen receptor–directed				
Abiraterone	CYP17[b]	Fatigue, 39%-44% Asthenia, 13%	5.9%	3%-4%[c]
Enzalutamide	Androgen receptor	Fatigue, 36%-51%	6.4%	NR

CYP17, cytochrome P-450 isoform 17 [a] Include fatigue and asthenia [b] Enzyme required for androgen biosynthesis [c] Retrospective analysis.

Glass O.K *et al*. (2016) *Clin Adv in Haem & Onc*. 14(6) : 436-446. Beer TM, et al (2014) *N Engl J Med*.371(5):424-433. de Bono JS, et al (2011) *N Engl J Med*.364(21):1995-2005. Scher HI et al (2012) *N Engl J Med*.367(13):1187-1197.

Conclusions

Proper identification, monitoring and treatment of bone loss is central to the management of men on androgen deprivation therapy (ADT) in which urology nurses can play a central part as apart of a multi-professional approach

- Prevent skeletal complications
- Avoid/reduce risk of disability
- Reduce morbidity and mortality
- Optimise quality of life.


Thank you for
your attention!