What's new in the management of osteoporosis and prevention of fragility fractures?

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Abstract

With an increasingly aging population it has never been more important to reduce the burden of fragility fractures. Fragility fractures, especially those of spine and hip, affect an individual's morbidity and mortality and carry a significant economic burden. There has been a recent shift towards a more stratified approach to the management of fracture risk, using fracture assessment tools, in combination with assessment of bone mineral density using dual x-ray absorptiometry scanning. Primary and secondary fracture prevention will be outlined including the important role of fracture liaison services. The use of medications which reduce fracture risks are discussed including the use of Zoledronate in the immediate post hip fracture setting.

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INTRODUCTION

The economic burden of osteoporosis-related fracture is significant, costing approximately £4 billion per annum in the UK. It is estimated that one in two women and one in five men aged over 50 years will suffer an osteoporotic fracture in their lifetime. Bone mass is an established determinant of bone strength, and the bone mass of an individual in later life depends upon peak skeletal growth attained by the fourth decade and the subsequent rate of bone loss thereafter. Logically, fracture risk should be highest when bone mass is at its lowest.

In 1994 the World Health Organisation (WHO) defined osteoporosis as a bone mineral density (BMD) of at least 2.5 standard deviation below the mean peak bone mass (average for a young adult)-T-score- at the femoral neck in a post-menopausal woman measured by dual energy X-ray absorptiometry (DXA). The International Society of Clinical Densitometry further stated that osteoporosis could be diagnosed in men and postmenopausal women if the T score is <2.5 SD at the lumbar spine, total hip or femoral neck.

However, a major drawback of BMD assessment is that most fragility fractures will occur in individuals without BMD-defined osteoporosis. In other words, a BMD of ≤ -2.5 SD has high specificity for fracture risks, but the sensitivity is low (around 30-50%). Around two thirds of non-vertebral fractures occur in patients who do not have osteoporosis as per the WHO criteria. The low sensitivity of BMD is the principal reason that BMD testing for population-based screening is not recommended.

There has been a recent shift towards a more stratified approach to the management of osteoporosis, using fracture assessment tools, in combination with assessment of BMD using DXA scanning, to identify and target treatment at patients at highest risk of fracture (Scottish Intercollegiate Guidelines Network (SIGN) 2015). Risk calculators such as the web-based FRAX® algorithm have enabled assessment of an individual's fracture risk using clinical risk factors such as age and alcohol consumption. (1)

FRACTURE PREVENTION

The care of patients who may be at risk of osteoporosis and fracture, or those who have already sustained a fracture, can be complex as it requires identification, assessment and possible treatment of individuals who may be unaware of the need for treatment. Osteoporosis care is delivered by many specialities, often with no specific service having overall responsibility for the process of identifying such patients. Therefore, multifaceted systems of care that integrate all aspects of bone health and falls leading to fracture, are likely to deliver greater reductions in fractures than uncoordinated efforts.

Osteoporosis management can be divided into Primary fracture prevention (in those who have no previous fractures) and Secondary fracture prevention (in those with a previous fracture).

PRIMARY FRACTURE PREVENTION

This involves identifying individuals with risk factors for increased fracture risk (Table 1). Clinical risk factors such as drug therapy, coexisting diseases, lifestyle factors such as smoking and alcohol intake, and family history of hip fracture act in a cumulative manner to modulate fracture risk. Risks factors can be considered as modifiable (alcohol intake, low BMI, smoking status, or BMD) and non-modifiable (age, gender, ethnicity and co existing medical conditions).

QUANTIFYING THE RISK OF FRACTURE

Various tools have been developed to quantify the risk of fracture. The most widely used of these is the FRAX algorithm (1), but others have been developed such as QFracture.(2) The QFracture® and FRAX® risk assessment tools predict the absolute risk of hip fracture, and major osteoporotic fractures (spine, wrist, or humerus) over 10 years.

FRAX®

The FRAX® algorithm was developed by analysis of several prospective population-based cohort studies in the UK, other countries in Europe, Canada, the USA and Japan. The FRAX risk-assessment tool was launched in 2008 and is freely available through a web-based portal for use in individuals aged 40-80. Fracture risk assessment is based on age, gender, BMI and on the presence or absence of previous

fracture, parental hip fracture, current smoking, and current use of glucocorticoids, Rheumatoid arthritis (RA), secondary osteoporosis and consumption of three or more units of alcohol per day. Previous fracture is defined as “a fracture in adult life occurring spontaneously, or a fracture from trauma which, in a healthy individual, would not have resulted in a fracture”. Secondary causes of osteoporosis include diabetes, osteogenesis imperfecta, untreated longstanding hyperthyroidism, hypogonadism or premature menopause, chronic malnutrition or malabsorption and chronic liver disease.

Femoral neck bone mineral density (BMD) can be optionally added to enhance fracture risk prediction. Fracture probability differs markedly in different regions of the world so that FRAX® is calibrated to those countries where the epidemiology of fracture and death is known (currently 64 countries). About 6 million calculations are performed yearly in 173 countries.

However, FRAX® calculations do not take account of dose-responses for several risk factors. For example the number of previous fractures, the severity of a vertebral fracture, the dose of steroid or amount of cigarette and alcohol consumption. It is not possible to combine all of these variables in a single algorithm and hence clinical judgement should always be applied. FRAX® 2, launched in June 2023, addresses some of these limitations, and there are also plans to update the original algorithm, taking into account the wealth of additional epidemiological and fracture data which has been collected since it was developed.

The concept of population-based screening programmes using the FRAX® assessment tool followed by DXA to recalculate risk or identify people with osteoporosis has been evaluated in several studies. Whilst some studies did show a reduction in hip fractures, such screening programmes have not been introduced into clinical practice.

Q FRACTURE ALGORITHM

QFracture, developed in 2009, is based on variables that are readily available in electronic healthcare records and validated in large primary care populations in the UK. It estimates an individual’s 10-year risk of developing both hip and major

osteoporotic fractures (including hip, spine and wrist), without BMD measurement. It is applicable to individuals aged 30–85 years. The clinical risk factors included in the QFracture algorithm are age, sex, BMI, smoking, alcohol intake, glucocorticoids, asthma, cardiovascular disease, history of falls, chronic liver disease, RA, type 2 diabetes and tricyclic antidepressants. Additional factors used in women only are: hormone replacement therapy, parental history of hip fracture, menopausal symptoms, gastrointestinal malabsorption and other endocrine disorders. (2)

The main strength of QFracture over other such calculators is that it has been extensively validated in the UK population and has been shown to be more accurate at predicting fractures in the UK population than FRAX. However, some of the variables and risk factors in QFracture cannot be altered by osteoporotic medications and QFracture does not have the option of adding BMD to the calculation.

Choice of fracture risk assessment tools and thresholds for further assessment and treatment based on 10-year fracture risk score vary across national guidelines and clinical judgement and local pathways should be considered. In England and Wales treatment thresholds are based on the National Osteoporosis Guideline Group (NOGG) guidance which is built into the FRAX tool. In Scotland, a 10-year risk of major osteoporotic fracture ≥ 10% assessed by either FRAX or QFracture is the threshold for further assessment. In people aged over 80 years of age, it is important to interpret the estimated 10-year fracture risk with some caution, as the short-term fracture risk maybe underestimated.

MEASUREMENT OF BONE MINERAL DENSITY -DUAL ENERGY X-RAY ABSORPTIOMETRY (DXA)

Measurement of BMD at the lumbar spine, femoral neck, total hip, and wrist have been shown to predict future fracture risks. Hip BMD has the greatest utility in predicting fractures, followed by spinal BMD. The gold standard tool for assessing BMD is a DXA scan. This low dose radiation technique (<10% of a CXR) is used both to diagnosis low BMD and assess response to therapy. Patients generally must be able to self-transfer onto the scanner (or with minimal assistance) and lie still for up to 5 minutes per image acquired. Standard scan appointments are between 20 and 30 minutes long and most DXA centres include patient questionnaires to enhance the DXA scan reporting accuracy. (images 1 and 2)

It is now standard practice to perform lateral morphometry of the spine during a DXA scan to identify vertebral fractures (image 3). Such images also detail degenerative changes in the spine and aortic calcification, both of which artificially elevate BMD. Taking these additional features into account improves the accuracy of the DXA scan report. Extended scanning of the femur appears to have a utility in picking up incipient atypical femoral shaft fractures (AFFs) providing the opportunity to prevent fracture (image 4).

Scanners tend to be static devices but mobile devices also exist. For example, NHS Grampian has a mobile bone density scanning service providing DXA services for areas of remote Aberdeenshire and the Orkney and Shetland isles.

In primary fracture prevention, the combined information from a DXA scan and fracture risk assessment determines requirement for medication to reduce fracture risks.

SECONDARY FRACTURE PREVENTION

Having a fracture increases an individual's risk of a subsequent fracture. Sustaining one low trauma fracture doubles the risk of having a further fracture. If the index fracture is a vertebral or hip fracture there is a 5-8 fold increased risk of fracture. The increased risk of fracture is greatest in the first 24 months post index fracture. Therefore, timely identification of low trauma fracture is essential to prevent subsequent fractures. There is a need to **i**dentify fractures, **i**nvestigate for osteoporosis and to **i**nitiate therapy-the three **I**'s of the Capture the Fracture programme (International Osteoporosis Foundation).

FRACTURE LIAISON SERVICES

Several secondary fracture prevention models of care have been evaluated. A meta-analysis of 44 studies found 4 models of care in secondary fracture prevention, with the more intensive interventions being found to be both clinically and cost-effective. (3)

The first such comprehensive secondary fracture prevention service (Fracture liaison service (FLS)) was set up in Glasgow, Scotland in 1999. This involved systematic

identification of new fractures by nurses attending fracture clinics and orthopaedic wards, diagnostic evaluation and treatment recommendations to the primary care physician for the secondary prevention of osteoporotic fractures. Several studies and meta-analysis have subsequently supported the clinical and cost effectiveness of FLS services based on the Glasgow model (4) which is now an internationally recognised model of care. However, local implementation of FLS models differ depending on local population needs, geography and resources. An example of which is the identification of fractures via x-ray reports and imaging.

The Royal Osteoporosis Society has developed 6 standards of care for FLS. In England and Wales, the Royal College of Physicians hosts a Fracture Liaison service database (FLS-DB). FLS-DB provides the ability to audit FLS services and evaluate patterns of assessment and treatment for osteoporosis and falls for patients who have sustained a fragility fracture. The audit's objective is to improve the quality of the clinical care delivered to patients who sustain fractures through effective measurement against ROS clinical Standards, feedback to providers and quality improvement initiatives. In Scotland there is universal coverage of FLS and a Scottish FLS audit similar to that in England and Wales is being considered.

MEDICATIONS TO REDUCE FRACTURE RISKS

It is considered essential that all patients at risk of fracture are calcium and vitamin D replete. Calcium and Vitamin D supplements themselves should not be considered as osteoporosis therapy but may be of value taken without other therapies in house bound elderly individuals.

Bone therapy can be divided into anti resoptive (reduce bone turnover) and anabolic (stimulating bone formation) therapies. All these medications exhibit fracture reduction efficacy, but vary in their mechanism of action, potency and time to efficacy.

ANTIRESOPTIVE THERAPIES.

BISPHOSPHONATES

Bisphosphonates are the main therapies used in the management of osteoporosis. Alendronate and risedronate are nitrogen containing bisphosphonates which have a potent inhibitory effect on osteoclastic bone resorption, a high affinity for binding bone mineral and a prolonged duration of action. Both treatments are oral, usually given as

a weekly medication. Therapeutic benefit is achieved after 6-12 months. Adherence/compliance with these medications can be difficult for individuals as they must be taken fasted, leaving a further 30 minutes before food and drink other than water and patient must remain with an upright posture (sitting or standing) during this time. Relative risk reduction for vertebral fractures is around 0.5, 0.6 for hip fracture reduction and 0.8 for non-vertebral fractures. (5, 6) Ibandronate is another a nitrogen containing bisphosphonate but appears to have a lower efficacy in hip fracture prevention.

Zoledronate is currently the most potent available bisphosphonate. It is delivered by an intravenous (IV) infusion on an annual basis usually for 3 years. Different regimes have been studied such as at 18 months intervals for 6 years. This is a faster acting agent, with fracture reduction seen within 1-3 months following treatment. Using the standard administration regime, relative risk reductions of 0.3 for vertebral fractures, 0.6 for hip fractures and 0.8 for non-vertebral fractures are observed. Zoledronate has been specifically investigated in patients (women and men) post hip fracture with evidence of reduction in further hip fractures and all-cause mortality (0.72, CI 0.56-0.93) (7)

Oral bisphosphonates are generally very safe medications. Alendronate can cause gastrointestinal (GI) upset and both oesophageal erosions and ulcers. Risedronate can also be associated with these issues but to a lesser extent and tends to be better tolerate in individuals with upper GI issues. Side effects of IV bisphosphonates include influenza-like symptoms which typically occur within 3 days of the infusion. These symptoms are usually mild and self-limiting, never exceeding 5 days duration. There appears to be a small increased risk of both uveitis and scleritis, particularly with IV zoledronate therapy. (1.1% and 0.1% for acute anterior uveitis and episcleritis)

Rare side-effects

Medication –related osteonecrosis of Jaw (MRONJ) is defined as exposed bone, or bone that can be probed through a fistula in the maxillofacial region that has persisted for more than 8 weeks and without a history of radiation therapy to the jaw or metastatic disease (8).The pathophysiology is not fully understood and is probably

multifactorial. ONJ is more prevalent in patients who have procedures which impact on bone, such as tooth extractions and possibly dental implants, but can occur spontaneously. Risk factors include cumulative bisphosphonate dosage and duration of treatment, concurrent periodontal disease, treatment with systemic steroids and people of Asian ethnicity. ONJ is also seen in people who have never used anti-resoptive therapies. The risk of ONJ is 0-2.3% where bisphosphonates are used in oncological diagnoses. With bisphosphonates for osteoporosis the risk is 0-0.1%, but probably increases with longer therapy duration. (9)

Atypical Femoral Fractures (AFF)

These are an uncommon type of stress fracture that occurs with little or no trauma in the mid shaft of the femur starting on the lateral border. Patients may experience pre fracture thigh pain and the issue is frequently bilateral with a requirement to prophylactically pin the non-fractured site. The fractures may be associated with poor fracture healing. They have been associated with anti-resorptive therapy. A large observational study indicated that such fractures occur in 13 per 10,000 patients untreated and in 31 per 10,000 treated with alendronate. There does appear to be an association with glucocorticoid therapy and the AFF issue seems to be a class effect. (10)

DENOSUMAB

Denosumab is a monoclonal antibody directed against the receptor activator of nuclear factory kappa B ligand (RANK Ligand) which is required for osteoclast differentiation and function. It has a potent inhibitory effect on osteoclastic bone resorption and is administered by a subcutaneous injection (60 mg every six months). Unlike bisphosphonates, the effect of denosumab on bone does not persist after treatment discontinuation. This results in a rebound in bone turnover on stopping therapy and associated increased fracture risk. Discontinuing denosumab must be planned with timely administration of further potent anti resoptive therapy to reduce the increase in bone turnover. Denosumab causes relative risk reductions of 0.32 for vertebral fracture, 0.8 for non-vertebral fractures and 0.6 for hip fractures. It is essential that patients are calcium and vitamin D replete prior to and during denosumab therapy to prevent symptomatic hypocalcaemia. (11)

HORMONE REPLACEMENT THERAPY (HRT)

HRT has been used to treat menopausal symptoms for over 50 years. Two large randomised controlled studies conducted by the Woman's health Initiative found a relative risk reduction of 0.4 for hip fracture after 7 years mean follow up. There was also a reduction in spinal and all fractures by around 0.6 and 0.8 respectively. HRT is an effective treatment to reduce fracture risk in postmenopausal women however the risks of adverse effects including cardiovascular disease and cancer risks increase in older women and therefore it is recommended for use in the younger postmenopausal woman only. (12)

RALOXIFENE

This selective oestrogen receptor antagonist reduces the risk of vertebral fractures but not of other fractures. It is associated with an increased risk of deep venous thrombosis but reduces by 50% the risk of oestrogen receptor positive invasive breast cancers. It can be considered as a treatment option in the prevention of vertebral fractures in post-menopausal women when other treatments are unsuitable or contraindicated

ANABOLIC THERAPIES

TERIPARATIDE (PARATHYROID HORMONE AGONISTS)

Teriparatide is the 1-34 terminal fragment of parathyroid hormone (PTH). Although sustained elevations of PTH lead to bone loss, as in hyperparathyroidism, intermittent exposure to Teriparatide once daily increases bone formation more than bone resorption resulting in an anabolic effect and increase in bone density. Maximum effects are in skeletal sites which are predominately composed of trabecular bone such as the spine. Teriparatide is associated with a relative risk reduction of 0.6 in all non-vertebral fractures and 0.3 for vertebral fractures. Teriparatide is recommended to prevent both vertebral and non-vertebral fractures in those with severe osteoporosis, and if the patient has 2 or more vertebral fractures can be recommended above bisphosphonate therapy in treatment naïve patients. Teriparatide is delivered by daily subcutaneous injection for a maximum of 2 years. On completion of therapy, bone loss will occur and further anti-resorptive therapy is required to maintain the increase in bone mass. Whilst Teriparatide is not licensed for fracture healing, there is some evidence to support fracture healing in AFF and MRONJ. (13)

ROMOSOZUMAB

Romosozumab is a monoclonal antibody that binds to and inhibits sclerostin. This increases bone formation, whilst decreases bone resorption. A relative risk reduction of 0.3 in further vertebral fractures and 0.6 in hip fractures has been observed in studies. Romosozumab is recommended for the prevention of further fractures in those with severe osteoporosis at imminent risk of further fracture. Of note there is a suspicion of additional cardiovascular events in those receiving Romosozumab who have suffered a previous myocardial infarction or stroke therefore it is not recommended for use in such individuals and cardiovascular risk assessment should be considered prior to initiation of therapy. Romosozumab is delivered as two subcutaneous injections delivered monthly for a period of 12 months, followed by antiresorptive therapy to maintain the increase in bone mass.(14)

PREVENTION OF FRACTURES AFTER HIP FRACTURE

In 1990, the number of hip fractures worldwide was estimated to be 1.66 million, including 1.19 million women and 463 000 men. Approximately 90% of these fractures occurred in individuals aged over 50 years, predominantly as the result of falls from standing height. In most populations, there is typically an exponential increase in the incidence of hip fracture with advancing age. Hip fractures in women outnumber those in men with a ratio of two to one. With an ageing population, the socioeconomic burden of hip fracture is likely to increase. In the UK around 79 000 individuals suffer hip fractures each year, with a cost in 2010 estimated at £3.5 billion projected to rise to £5.5 billion per year by 2025.

The mortality burden of hip fracture is significant, with a rate of approximately 8% in men and 3% in women aged above 50 years post fracture. In the UK, the observed 12-month survival rates post-hip fracture are significantly lower than the anticipated life expectancy of affected individuals (in men 63.3% observed vs. 90.0% expected and in women 74.9% observed vs. 91.1% expected). Death following hip fracture is not solely attributable to the fracture itself, coexisting illnesses and poor pre-fracture functional status are key determinants of post-fracture mortality risk. This is greatest immediately post-fracture, with a second hip fracture observed in 1 in 3 patients within 1.5 years of the index fracture. Of all fracture types, hip fractures are associated with the highest levels of morbidity.

For timely and effective fracture prevention in these individuals requires treatment which is well tolerated, easy to take and provides a rapid reduction in fracture risk. The compliance rates with oral bisphosphonates have long been recognised as problematic. UK GP prescribing data reveals that one year after a fragility fracture only a third of eligible patients (mean age 79) are on anti-osteoporosis treatment. There is a delay to efficacy with bisphosphonates of around 6-12 months depending on the agent used. NOGG recommends intravenous zoledronate as a first line bone therapy, especially after hip fracture and the Scottish Hip Fracture audit includes the use of IV zoledronate post hip fracture as a standard of care (number 11).

As Zoledronate is delivered by an intravenous infusion usually on an annual basis. This removes compliance/adherence issues. The effects of Zoledronic acid on recurrent fractures were investigated in 2,127 men and women > 50 years with hip fracture. Around three quarters of the individuals in the trial were women. Patients were included in the study if they were unable or unwilling to take oral bisphosphonates. (7)

Individuals were excluded if they had a hypersensitivity to bisphosphonate, creatinine clearance <30mls/min, low serum calcium, active cancer, other metabolic bone disease, and life expectancy < 6 months. IV Zoledronate was given within 90 days of surgically repaired hip fracture and then 12 monthly for a maximum of 3 infusions. All participants were given a loading dose of vitamin D (50,000 to 125,000IU orally or IM) 14 days before first infusion and thereafter treated with daily oral calcium and vitamin D supplementation

The risk of vertebral fractures was reduced in the Zoledronic acid group (HR 0.54, 95% CI 0.32 to 0.92), as were non-vertebral fracture risks (HR 0.73, 95% CI 0.55 to 0.98). The risk of hip fracture was reduced but not significantly (HR 0.70, 95% CI 0.41 to 1.19). All-cause mortality was also significantly reduced in the Zoledronic acid group (HR 0.72, 95% CI 0.56 to 0.93). The fracture reduction effect is present by 3 months post infusion, providing benefits even to those with challenging life expectancy.

It should also be noted that patients receiving only one of the planned three infusions experienced a similar relative fracture risk reduction to those who achieved all three infusions.

In 2016, 181 women living in a long-term care facility were given IV zoledronate therapy. In this 2-year, randomized, placebo-controlled, double-blinded study the participants had either T-score < −2.0 at the spine, hip or radius, or prior vertebral or hip fracture. The mean age in the study was 85.4+/- 0.6 and the patients' physical and cognitive function were equal in the treatment and control groups. One dose of IV Zoledronic acid improved BMD over 2 years. No significant differences in adverse events were seen between groups. IV Zoledronate therapy appears safe for use in the frail elderly.

The licence for IV zoledronate states that it should not be used in the first 2 weeks post fracture, largely because there were not significant participants in the original licencing study who had IV zoledronate within two weeks and therefore safety and efficacy data is not available. It is recognised that IV zoledronate should preferable be given in the immediate post hip fracture phase whilst the patient remains an inpatient to achieve future fracture prevention as soon as feasible. Bringing frail elderly patients post hip fracture back for infusions of Zoledronate is likely to be delayed if it ever occurs. Post marketing experience of using IV zoledronate in the first two weeks after surgery shows it is well tolerated and not associated with the acute phase response commonly seen in the outpatient setting with IV zoledronate. Systematic reviews and meta- analysis of early post-surgery administration (10 studies and 28,888 patients) has shown no evidence of non-union or delayed radiological or clinical fracture healing and shows comparable BMD gains over 12 months compared to standard regimes.

It is important that patients are calcium and vitamin D replete prior to receiving an IV zoledronate infusion to reduce the risk of symptomatic hypocalcaemia. In the acute hip fracture setting checking vitamin D levels will cause delays and may give inaccurate results in the acute phase post fracture. Vitamin D deficiency is common in the hip fracture population therefore high dose loading of vitamin D provides an appropriate approach, with risks of hypercalcaemia being very rare. A loading dose of 150,000-250,000 IU of vitamin D is recommended given either as a split or single dose regime. Only in hypercalcaemic patients should this be avoided.

IV zoledronate should not be given to patients whose eGFR is <35 ml/min in the acute post hip fracture setting and this should be calculated by the Cockcroft-Gault formula. Standard laboratory measures are based on age and sex and do not consider body

weight which can be very low in this patient population. Figure 4 indicates the algorithm for giving IV zoledronate post hip fracture adopted in Scotland.

The risk of osteonecrosis of jaw (ONJ) is very low in bisphosphonate naive patients, with one study identifying a single case post IV zoledronate in around 6000 patients. In the age group of people suffering a hip fracture dental issues are common so all patients should be encouraged to seek routine dental care, however the low absolute risk of MRONJ needs to be balanced against the high absolute risks of future imminent fracture.

A review article in Age and Aging (15) gives a full review of the issues around giving IV zoledronate therapy post hip fracture, a proposed algorithm and full references.

CONCLUSION

Osteoporosis is a very common and usually silent condition which predisposes affected individuals to fragility fractures with associated morbidity and mortality. Reducing fracture risk can be divided into primary and secondary fracture prevention. This should make use of fracture risk assessment tools to estimate fracture risks and systems of care such as FLS in those who have already sustained a fracture. DXA scans remain an important investigation but in certain situations such as the frail elderly and in those who have suffered vertebral and hip fractures a DXA scan should not delay treatment.

There are now several different types of therapy for osteoporosis which reduce fracture risk. They differ in their mechanism of action and potency but if the individual is at high risk of fracture, it is essential they are commenced on a treatment that will reduce fracture risk. Additionally, systems to encourage adherence/compliance with these medications are established.

Individuals with a hip fracture are at significant risk of suffering a subsequent fracture, including further hip fracture. IV zoledronate given during the hospital stay provides the most effective and timely means of reducing that future fracture risk.

REFERENCES

1. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 2008;19(4):385-97
2. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ 2012;344:e3427
3. Ganda K, Puech M, Chen JS, Speerin R, Bleasel J, Center JR, et al. Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. Osteoporos Int 2012;24(2):393-406
4. McLellan AR, Wolowacz SE, Zimovetz EA, Beard SM, Lock S, McCrink L, et al. Fracture liaison services for the evaluation and management of patients with osteoporotic fracture: a costeffectiveness evaluation based on data collected over 8 years of service provision. Osteoporos Int 2011;22(7):2083-98.
5. Cummings SR, Black DM, Thompson DE, Applegate WB, BarrettConnor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280(24):2077-82
6. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women: hip intervention program study group. N Engl J Med 2001;344(5):333-40.
7. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357(18): 1799-809
8. Ruggiero SL, Dobson TB, Fantasia J et al. American association of Oral and Maxillofacial Surgeons position paper on medication related osteonecrosis of the jaw 2014 update. Journal of Oral and Maxillofacial Surgery 2014 ; 72(10): 1938-1956
9. Chamizo Carmona E, Gallego Flores A, Loza Santamaria E, Herrero Olea A, Rosario Lozano MP. Systematic literature review of bisphosphonates and osteonecrosis of the jaw in patients with osteoporosis. Reumatol Clin 2013;9(3):172-7.
10. Abrahamsen B, Eiken P, Eastell R. Cumulative alendronate dose and the long-term absolute risk of subtrochanteric and diaphyseal femur fractures: a register-based national cohort analysis. J Clin Endocrinol Metab 2010;95(12):5258-65.
11. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2012 Jul 11;(7):CD004143. doi: 10.1002/14651858.CD004143.pub4. Update in: Cochrane Database Syst Rev. 2017 Jan 17;1:CD004143. PMID: 22786488.
12. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. New England Journal of Medicine 2009;361(8):756-65
13. Oswald AJ, Berg K, Ralston SH, Riches PL. Long-term effects of teriparatide followed by antiresorptive therapy on clinical outcomes in patients with severe spinal osteoporosis. Calcif Tissue Int 2019;105(2):148-55
14. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016;375(16): 1532-43
15. Johansen A, Opinder S, Dockery F, Black AJ, MacLullich AMJ, Javaid MK et Call to action: A five nation's consensus on the use of intravenous zoledronate after hip fracture https://doi.org/10.1093/ageing/afad172

Suggest further reading

SIGN Guideline 142: Management of osteoporosis and prevention of fragility fracture
www.sign.ac.uk/media/1812/sign-142-osteoporosis-v3.pdf

Royal Osteoporosis Society: effective Secondary Prevention of Fragility Fractures-Clinical Standard for Fracture Liaison services
theros.org.uk/media/1eubz33w/ros-clinical-standards-for-fracture-liaison-services-august-2019.pdf

National Institute for Health and Care Excellence (NICE).
Technology appraisal guidance [TA464, Bisphosphonates for treating osteoporosis.
https://www.nice.org.uk/guidance/ta464
National Institute for Health and Care Excellence. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended). London: NICE; 2011. (NICE TA161).
http://www.nice.org.uk/guidance/ta161
National Institute for Health and Care Excellence. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amendment). London: NICE; 2011. (NICE TA160).
http://www.nice.org.uk/guidance/ta160

BOX 1

‘Osteoporosis’

Term ‘osteoporosis’ was first used in France in the 1820s to describe post-mortem bones with abnormal hollow spaces.

Entered English terminology by 1885 but lacked a specific description until Fuller Albright’s work in Boston in the 1940s.

It is the commonest metabolic bone disease in the developed world and is characterised by low bone mass and micro architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risks.

With a worldwide ageing population, the importance of the prevention and management of osteoporotic fragility fractures is increasing over time.

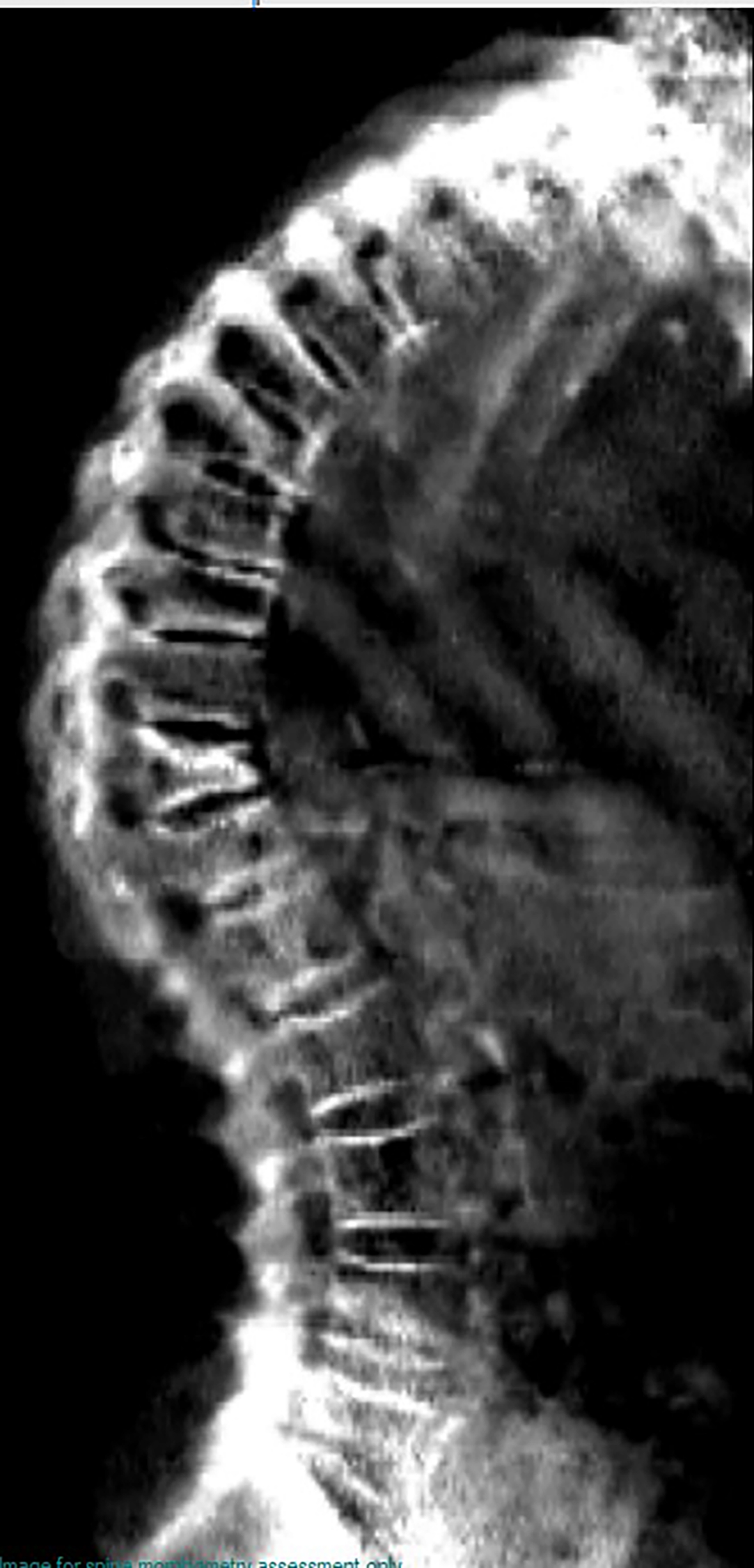
Due to significant advances in osteoporosis management over the last 50 years, including widespread availability of various effective pharmacological therapies, osteoporosis should no longer be considered an inevitable consequence of ageing.

Box 2(insert beside Zoledronate port hip fracture section)

Practice point
The first dose of IV zoledronate is the most important to offer to patients, further doses at annual intervals for 3 years carry additional benefits and should be arranged unless the individual patient circumstances/frailty prevent this. The use of IV zoledronate post hip fracture is advocated by the Scottish Hip fracture audit and by many leading Orthogeriatricians across the UK.

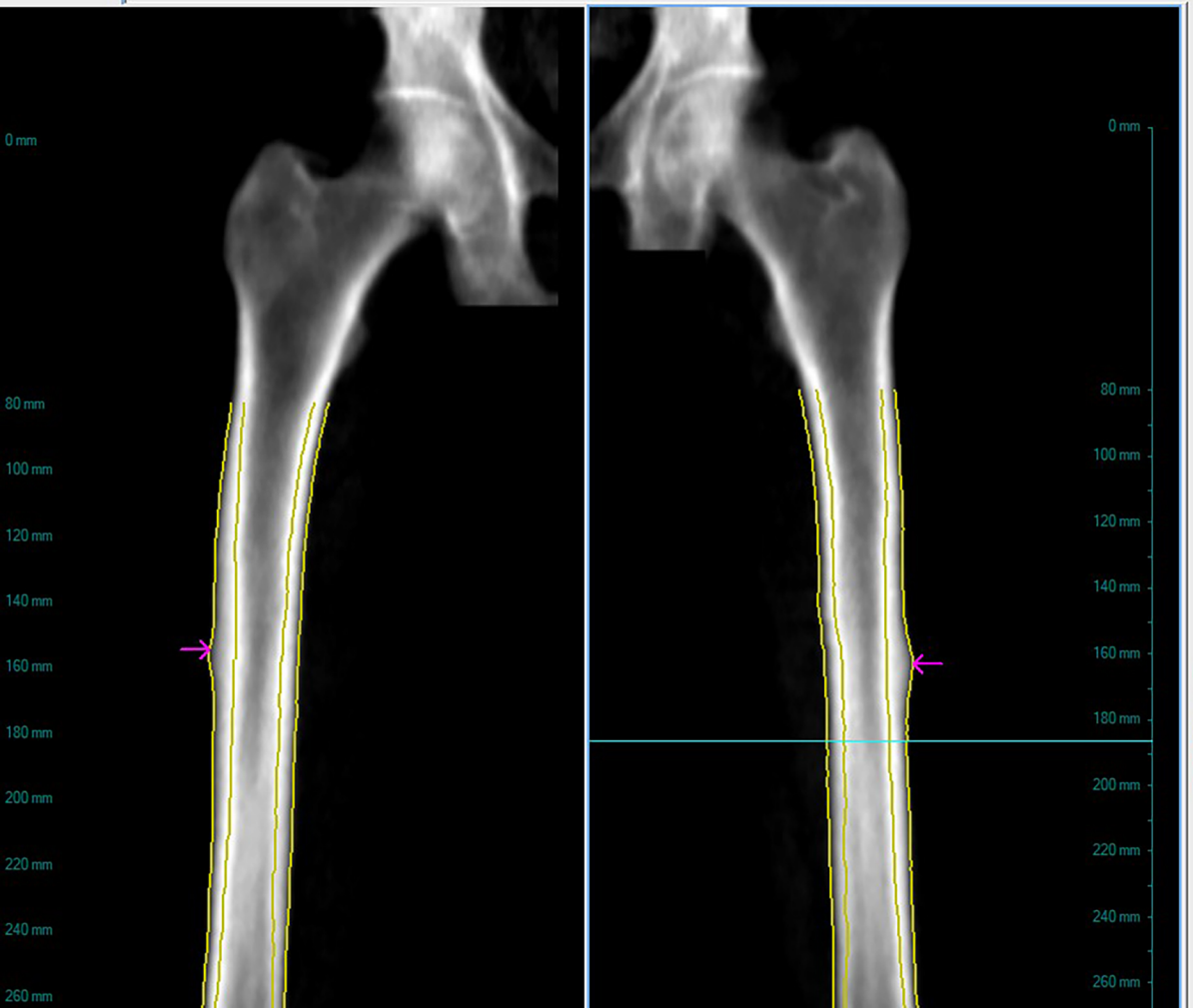
Table 1 Medical condition associated with increased fracture risks

ENDOCRINOLOGY	***RHEUMATOLOGY***	***GASTROENTEROLOGY***	***MEDICATIONS***
Thyrotoxicosis	Rheumatoid Arthritis	Ulcerative Colitis	Glucocorticoids
Hyper and hypoparathyroidim	Ankylosing Spondylitis	Crohn's Disease	Proton Pump Inhibitors
Cushings syndrome and disease	Polymyalgia Rheumatica	Primary Biliary, Alcoholic and Viral Cirrhosis	Enzyme Inducing antiepileptic medications
Hyperprolactinaemia		Malabsorption Syndromes	Aromatase Inhibitors
Early menopause			Gonadotrophin Releasing Hormone Agonists
			Warfarin

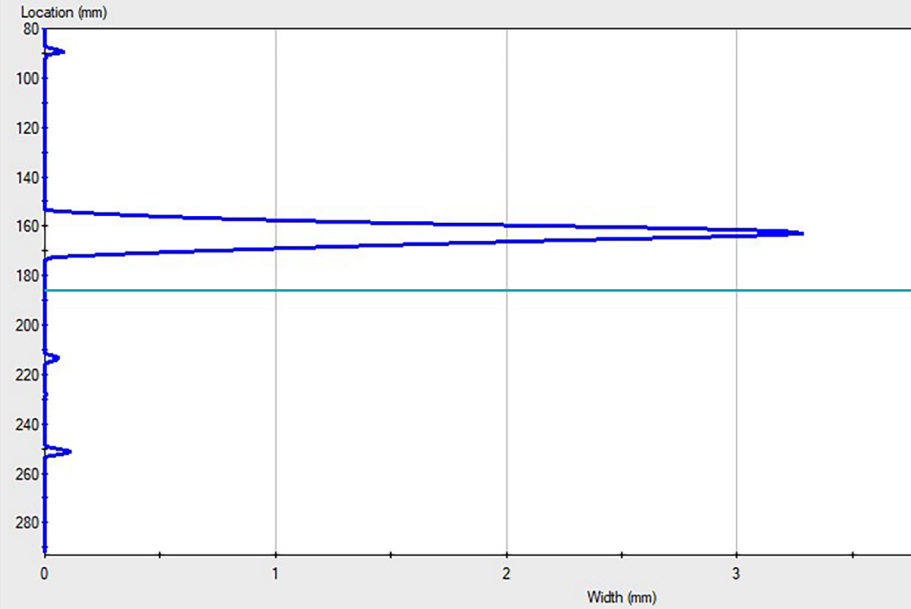


DualFemur

Densitometry | FRAX® | AFF | Information



Beaking Profile

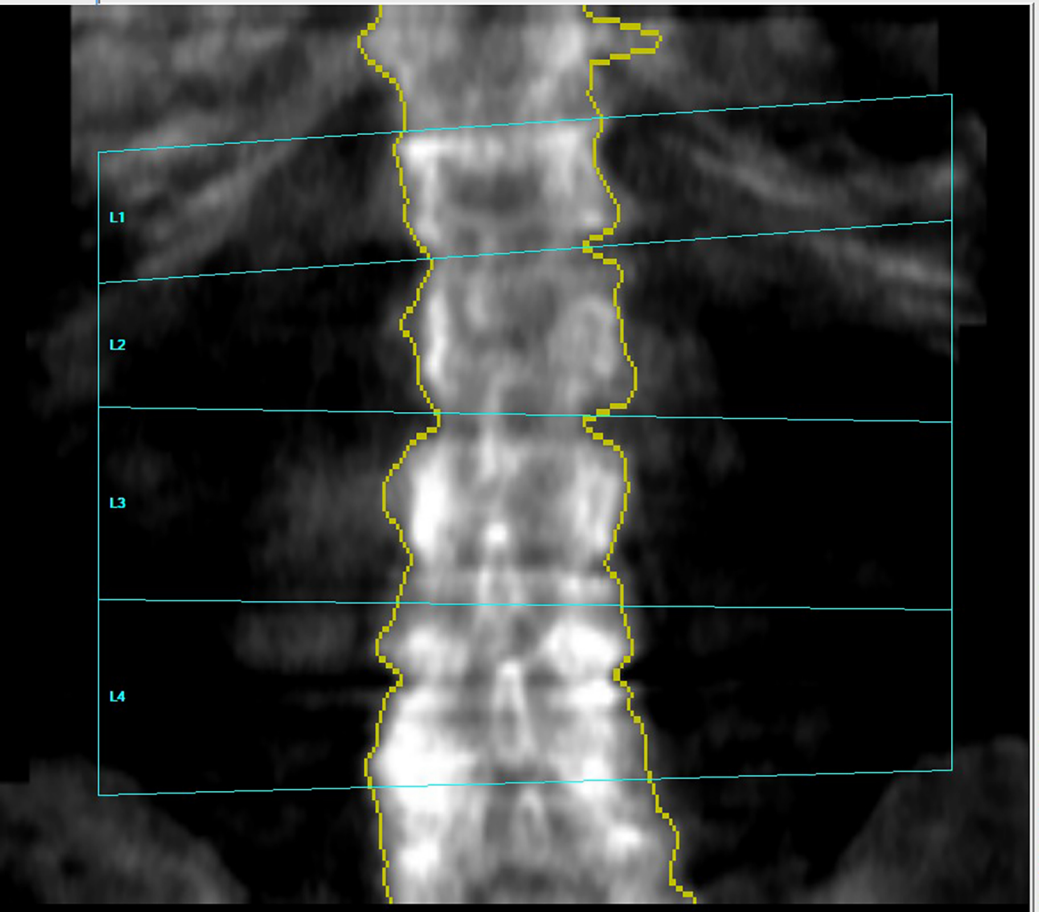


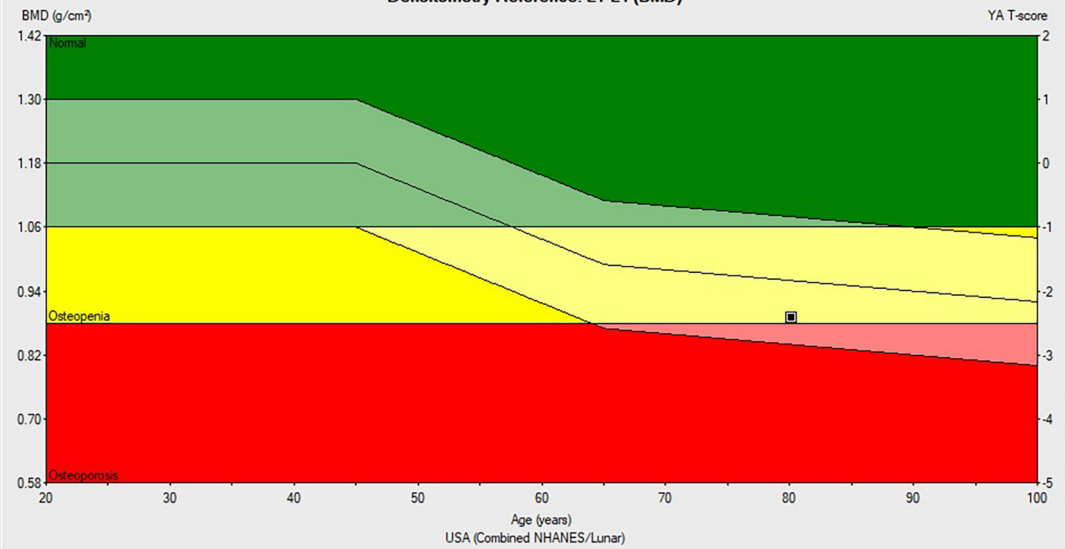
Display: Current Results Value: Beaking Profile

Side	Beaking Index (mm)
Left	3.3

AP Spine

Densitometry | Information





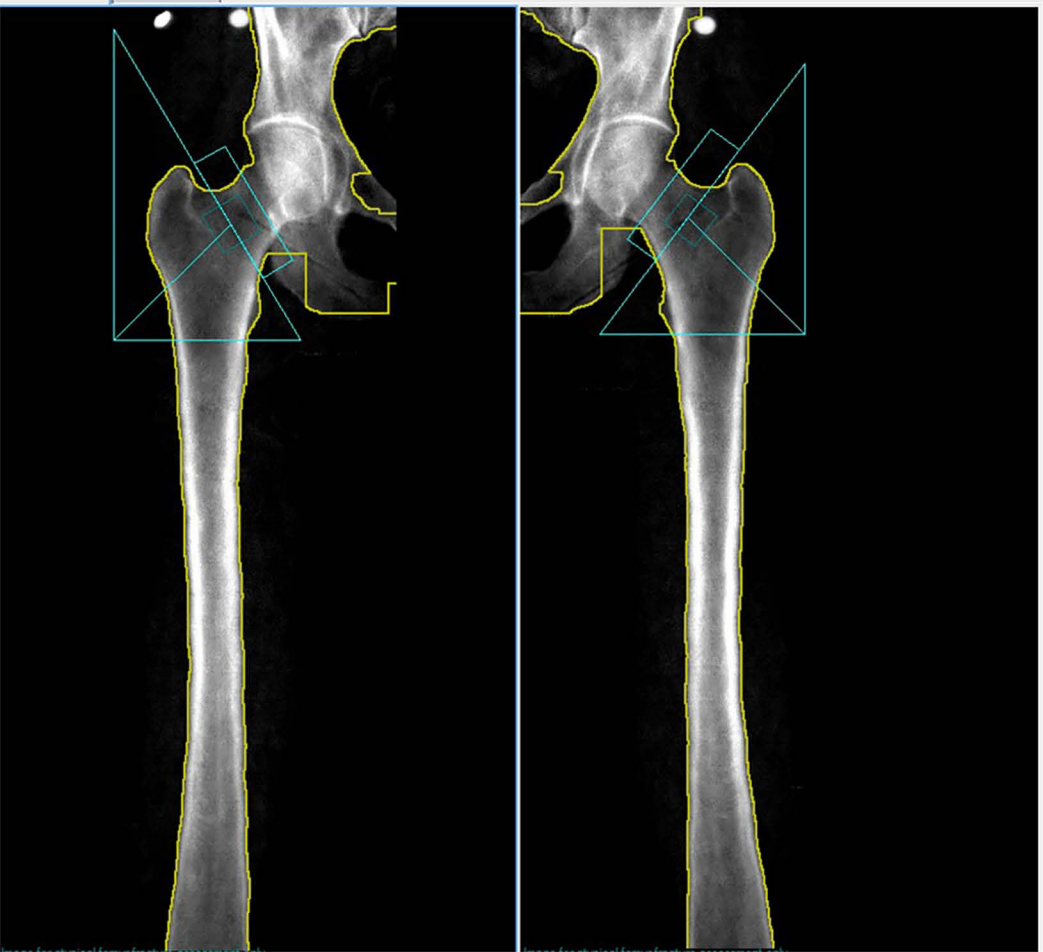
Region: L1-L4

Display: Current Results

Densitometry

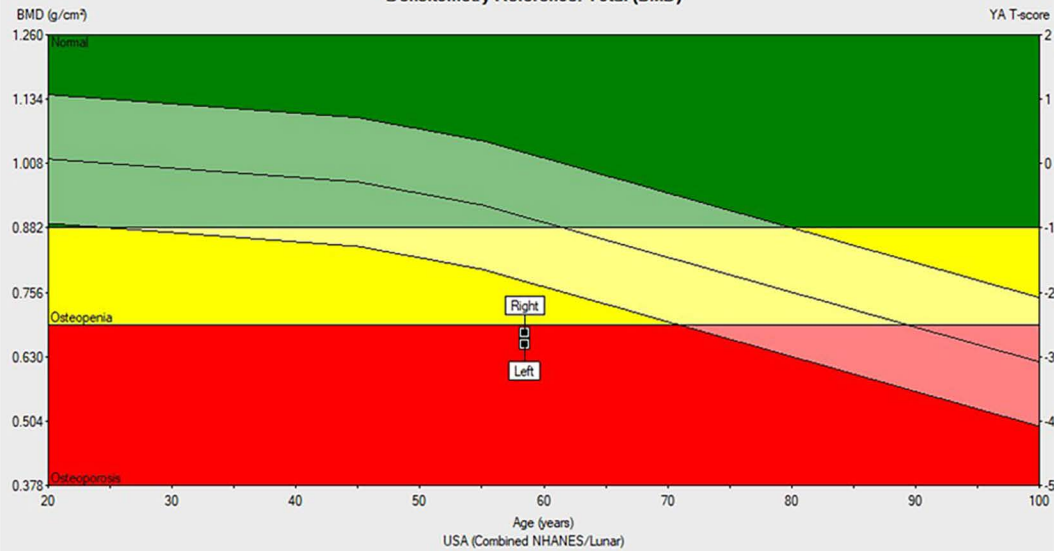
Region	BMD (g/cm²)	YA T-score	AM Z-score	BMC (g)	Area (cm²)
L3	0.921	-2.3	-0.5	11.03	11.97
L4	1.043	-1.3	0.5	14.02	13.44
L1-L2	0.747	-3.5	-1.6	12.89	17.25
L1-L3	0.818	-2.9	-1.1	23.92	29.22
L1-L4	0.889	-2.4	-0.6	37.94	42.67
L2-L3	0.836	-3.0	-1.2	18.13	21.69
L2-L4	0.915	-2.4	-0.5	32.15	35.14

DualFemur | AP Spine



Densitometry | FRAX® | Composition | Composition Trend | AFF | Information

Densitometry Reference: Total (BMD)



Region: Total Mean

Display: Current Results

Densitometry

Region	BMD (g/cm²)	YA T-score	AM Z-score	BMC (g)	Area (cm²)
Shaft Left	0.734	-	-	10.84	14.77
Shaft Right	0.774	-	-	11.03	14.25
Shaft Mean	0.754	-	-	10.94	14.51
Shaft Diff.	0.040	-	-	0.19	0.52
Total Left	0.654	-2.8	-2.0	20.08	30.71
Total Right	0.677	-2.6	-1.8	20.80	30.72
Total Mean	0.666	-2.7	-1.9	20.44	30.71
Total Diff.	0.023	0.2	0.2	0.72	0.00