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REVIEW

Osteoporosis: Identification, intervention and prevention of fractures

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Osteoporosis may result in fragility fractures with associated significant morbidity. Yet this common skeletal disease, characterised by low bone mass, is often not screened for, and is underdiagnosed and undertreated. Risk assessment (including imminent fracture risk), falls risk, DXA to assess bone mineral density, potential adjuvant calcium and vitamin D, and anti-resorptive agents, are important considerations to prevent fractures. This review highlights the salient points for general practitioners.

Keywords: osteoporosis, bone mineral density, risk assessment, falls assessment, bone densitometry, bisphosphonates, denosumab, teriparatide

Osteoporosis is a common disorder affecting a large proportion of people over 50 years of age. It is frequently present in our patients but often infrequently diagnosed, screened for or treated.

This may partly be because it is a silent disease and remains asymptomatic until a fragility fracture is sustained.[1] However one in three women and one in five men over the age of 50 will sustain an osteoporotic fracture.[2] Fragility fractures are often associated with significant morbidity due to pain with poor quality of life, loss of mobility and independence and increased mortality, especially in patients 70 years and older.[2,3] With an ever increasing life expectancy, the prevalence of fragility fractures can be expected to rise exponentially.[1] It is estimated that by 2050 there will be in excess of 5 million hip fractures globally.[4,5]

The economic burden of these fractures is enormous.[1] Even though there is a high prevalence of osteoporosis globally as well as locally, less than 20% of osteoporotic patients are assessed for fracture risk, screened for osteoporosis or initiated on appropriate secondary prevention including simple calcium or vitamin D supplementation.[2,3] In the first world, a decline in both treatment initiation and adherence rates has been demonstrated.[3,6] Consequently, the incidence of hip fracture is higher than projected in the United States, following more than a decade of decline in hip fracture incidence.[3]

That being said, osteoporosis is a disease that is amenable to both primary and secondary prevention of complications.

Osteoporosis is currently defined by the World Health Organization (WHO) as a systemic skeletal disease characterised by low bone mass (readily measured as bone mineral density [BMD]) and micro-architectural deterioration of bone tissue which is difficult to assess, with a consequent increase in bone fragility, and susceptibility to fracture, which usually involves the wrist, spine, hip, pelvis, ribs or humerus.[7] The vast majority of fragility fractures associated with underlying osteoporosis occur more frequently but not exclusively in those over the age of 50 years.[2] Osteoporosis is a disease that affects both men and women. Men generally suffer from this approximately a decade later on in life than women. In fact, the lifetime risk of osteoporotic fracture in men aged ≥ 50 years is 27% higher than the risk of prostate cancer which is 11.3%.[8,9] In women, it presents earlier due to menopause which results in unbalanced bone remodelling where there is increased bone resorption coupled with decreased bone formation.

Fragility fractures often do not occur in isolation but recur throughout the patient's lifespan as the underlying vulnerability still exists if not identified and treated.[2] Patients presenting with a fragility fracture, including the more innocuous Colle's fracture, warrant careful history and fracture risk assessment which should include BMD assessment, falls risk assessment and screening for secondary causes. Responding to the index fracture will reduce the risk of a second fracture.[3,10]

Risk factors

An important part of the fracture risk assessment is identifying significant underlying risk factors.[10] This may guide the clinician with appropriate further screening as well as risk stratifying. Patients at risk of further fragility fractures can be identified by a number of independent risk factors.[11,12] Age alone is one of the greatest independent risks for fragility fracture.[13] Genetics with a familial history of osteoporosis are a strong predictor especially when a parent has sustained a hip fracture. Other risks include a low body mass index (BMI) which may be an indicator of poor nutrition.[12,14] Inadequate nutrition disrupts the hypothalamic-pituitary-ovarian axis resulting in hypogonadism whilst also directly inhibiting the anabolic phase of bone remodelling.[14] All states of hypogonadism including primary and secondary amenorrhoea, chronic use (longer than two years) of the progesterone-only contraceptive or early menopause are associated with a lower bone mineral content.[15]

Chronic inflammatory diseases also pose a significant risk with these patients being susceptible to increased bone resorption and fracture.[12] This risk is often further emboldened with chronic glucocorticoid therapy. Any patient treated with chronic

glucocorticoids requires active bone health surveillance with lower treatment thresholds than their counterpart standard post-menopausal osteoporosis patients.[2] Glucocorticoid-induced osteoporosis carries a higher risk of fracture for the same BMD T-scores. Cancer patients treated with aromatase inhibitors are another group of vulnerable patients.[2] These patients should be proactively managed with anti-resorptive agents.[2]

Lifestyle, as with most diseases, plays an important role. Clinicians should not neglect to educate, counsel and motivate patients with regards to poor lifestyle habits associated with increased risk, such as smoking, excessive alcohol intake and lack of regular weight-bearing exercise.[12] Poor lifestyle creates what could be referred to as an "unhealthy bone environment", inhibiting healthy balanced bone metabolism and remodelling predisposing to fracture.[12] If cognisant of this bone environment including good nutrition, both primary and secondary prevention can be practised.[14] Adolescent patients are a target group for primary prevention. It is during this phase of life when the most bone mineral content is gained. Ensuring adequate exercise and nutrition in adolescence whilst avoiding bone harmful drugs enables individuals to attain their full skeletal potential which is carried with them throughout adulthood.[14] Up to 60% of the risk of developing future osteoporosis can be explained by the amount of bone mineral content accrued by early adulthood.[16]

Imminent fracture risk

Previous fracture is one of the strongest risk factors for future fracture.[13] The associated risk is highest in the first 6 to 24 months following the fracture.[13] The risk of re-fracture has also been shown to also increase by 5% for each year of age.[13] This, coupled with other risk factors such as falls risk, comorbidities and often other markers of frailty, pose an imminent fracture risk.

Imminent fracture risk refers to the increased risk of a fragility fracture in the near future.[6,13] This provides an important window of opportunity for immediate intervention without delay in secondary prevention.[17,18] Often these patients are stratified as very high risk and may warrant anabolic therapy.[19] The very elderly frail patients should not be denied treatment due to their advanced age as they carry the highest imminent fracture risk.[13,18]

Falls risk

Falls risk is another very important often neglected fracture risk.[13] Falls cannot be ignored and usually occur due to certain mechanisms or physical failures. All patients falling should be assessed for falls risk, especially those with a history of falling.[4,6,20] This would include considering possible underlying causes of poor balance, screening for poor eyesight, inappropriate use of multifocals, possible peripheral neuropathy, B_{12} deficiency or the use of sedatives.[2] Most falls risks are amenable to simple yet effective interventions. Falls interventions should also include supervised balance and strength training as well as an assessment of the living environment for safety modification by the occupational therapists where possible.[2] Falls interventions may appear mundane, however, they have been proven to have a high efficacy in fracture risk reduction and can be practised in a budget-constrained health environment.[2]

Screening and assessment

The use of DXA in assessing BMD and fractures risk is well established and is the most commonly used means of screening for BMD. There is a strong predictive relationship between low T-scores and fracture risk confirming its use as a screening tool, however, it must be noted that not all fractures occur within an osteoporotic range of T-scores.[7] The use of trabecular bone score (TBS) software available for DXA scanning is available and adds further information regarding bone quality. This can be useful especially where there are factors confounding the DXA BMD T-scores. NOFSA have published guidelines for the appropriate use of DXA.[7]

The FRAX® tool is useful in calculating fracture risk.[13,21] This tool can be used where DXA is not always available or where DXA T-scores are not yet within the osteoporotic range but fracture risk is suspected to be high. The FRAX® tool is also used for risk stratification to guide management. This is done through treatment thresholds indicating a need for treatment as well as higher thresholds identifying very high risk patients.

The FRAX® tool now offers an algorithm specific to the demographics of South Africa, dependent on the patient's ethnicity. This allows for access to more accurate and relative risk assessments in the local setting. The tool is free to access and is relatively quick and simple to use; its use should be encouraged by all clinicians. It should be remembered that the FRAX® calculated risk increases as the patient ages and so should be recalculated as time passes.[13,22]

Risk stratifying

Patients that have been assessed for fracture risk and assessed can be further risk stratified according to identified risks, BMD and previous fracture. They may be classified as either low, high risk or very high risk.[23,24] This stratification aids in management decisions with international treatment guidelines trending towards algorithms dependent on these stratifications. Risk stratification can be classified as the following based on these criteria:

Very high fracture risk defined in the patient who has one or more of the following:

- Fracture in the past 12 months
- Multiple fragility fractures
- Fracture whilst on osteoporosis treatment
- Very low T-score < -3.0
- Fracture in a patient exposed to bone toxic therapy, i.e. glucocorticoids
- FRAX® scores of > 30% for a major osteoporotic fracture and > 4.5% for a hip fracture

High fracture risk in the post-menopausal woman with any of the following criteria:

- Prior fragility fracture
- T-score ≤ -2.5
- T-score between -1.0 and -2.5 **and** FRAX® of ≥ 20% for a major osteoporotic fracture or ≥ 3.0% for a hip fracture

Low fracture risk as defined when **all** of the following are true to the patient:

- Age post-menopausal
- No prior fragility fractures
- T-score > -1.0
- FRAX® scores of < 20% for a major osteoporotic fracture and < 3% for a hip fracture

Treatment

It is suggested that calcium and vitamin D be used as adjunct therapy in post-menopausal women at high fracture risk.[25] The benefits of routine calcium supplementation can be a contentious issue. However importantly, most of the major osteoporotic drug trials proving antifracture efficacy of a drug include the adjunct use of calcium where dietary intake was insufficient and vitamin D supplementation where it was found to be insufficient or deficient.[25] Dosages as recommended by NOFSA; 1 000 mg of calcium daily, including dietary contributions, and vitamin D up to 800 iu where deficient.[7,25] There is no evidence to support routine supplementation of vitamin D where levels are already within the sufficient range.

Treatment decisions should be based on the fracture risk of the patient determining appropriate treatment initiation.[23,24] Patients with high fracture risk should be commenced on anti-resorptive therapy as first line.[7,23-25] These drugs include alendronate, risedronate, zoledronic acid and denosumab. Bisphosphonates are most widely used and have the benefit of long-lasting effects in the bone known as "the legacy effect".[16,25-27] This benefit provides for delays and breaks in therapy termed "drug holidays". Drug holidays allow one to negate many of the feared long-term side-effects, such as atypical femur fractures (AFF) and osteonecrosis of the jaw (ONJ).[7,25] However, in patients found to still be at high risk (total hip T-score persisting ≤ -2.5), "drug holidays" are NOT routinely recommended, as treatment benefits still far outweigh the associated possible risks.[5] It was shown that for 1 000 women treated with bisphosphonates for three years, approximately 100 new fragility fractures, including hip fractures, could be prevented at the expense of only 0.08 AFF events.[25] The decision to implement a drug holiday needs to be individualised and the patient counselled regarding the benefits of treatment continuation vs cessation. Patients on a "drug holiday" should be reassessed every two to four years.[25]

There is no preference in agent or route of administration of the bisphosphonates.[25] Denosumab is an alternative therapy to bisphosphonates now registered and available in South Africa, it is administered as a six-monthly subcutaneous injection. It is especially useful for patients with chronic kidney disease with eGFR ≤ 35 ml/min/1.73 m^2 and cancer-associated osteoporosis.[6,25]

Anabolic agents are reserved for patients falling within the very high risk category.[23,24] These drugs increase BMD by increasing bone formation as well as addressing bone quality.[25] In South Africa, we are limited to teriparatide. The anabolic effects are due to the nature in which it is given as pulsed daily doses and limited to an anabolic window.[7,25] The use of teriparatide is limited to one 18–24 month course per lifetime and so should not be used prior to the patient falling into the very high risk group.[7,25] The antifracture effects of teriparatide are realised faster than those of the anti-resorptive agents and so may be a treatment option for those at high imminent fracture risk.[7]

How long to treat?

The current international guidelines follow a "treat to target" approach. This approach advocates regular review with a view to stopping or pausing therapy when the fracture risk is no longer high, defined as DXA T-score of > -2.5 at the hip.[7,25] This allows for the implementation of "drug holidays" but may require a change in therapy when the desired results are not being met. Following the treat-to-target approach allows for better balance between potential treatment benefits and risks.[7,25]

Most importantly, as clinicians facing a growing ageing population, we cannot fail our patients in denying them independence and quality of life as they age. We need to be vigilant in screening and diagnosing osteoporosis and recognising the significance of fragility fractures with an ability to intervene or refer to our colleagues.

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